

# An Integrated Epigenetic and Transcriptomic Analysis Reveals Distinct Tissue-Specific Patterns of DNA Methylation Associated with Atopic Dermatitis

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Epigenetic alterations are increasingly recognized as mechanisms for disease-associated changes in genome function and important risk factors for complex diseases. The epigenome differs between cell types and so far has been characterized in few human tissues only. In order to identify disease-associated DNA methylation differences for atopic dermatitis (AD), we investigated DNA from whole blood, T cells, B cells, as well as lesional and non-lesional epidermis from AD patients and healthy controls. To elicit functional links, we examined epidermal mRNA expression profiles. No genome-wide significant DNA methylation differences between AD cases and controls were observed in whole blood, T cells, and B cells, and, in general, intra-individual differences in DNA methylation were larger than interindividual differences. However, striking methylation differences were observed between lesional epidermis from patients and healthy control epidermis for various CpG sites, which partly correlated with altered transcript levels of genes predominantly relevant for epidermal differentiation and innate immune response. Significant DNA methylation differences were discordant in skin and blood samples, suggesting that blood is not an ideal surrogate for skin tissue. Our pilot study provides preliminary evidence for functionally relevant DNA methylation differences associated with AD, particularly in the epidermis, and represents a starting point for future investigations of epigenetic mechanisms in AD.

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## INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by epidermal barrier dysfunction

and immunological alterations. It is strongly genetically as well as environmentally triggered (Bieber, 2008). Although a number of risk genes for AD have been established in the past years, only 14.4% of the estimated total heritability can be explained so far (Ellinghaus *et al.*, 2013). One additional but potentially underestimated source of this hidden heritability might be represented by epigenetic mechanisms (Johannes *et al.*, 2009).

Epigenetics refers to functionally relevant changes in a chromosome without alterations in the DNA sequence, which critically contributes to phenotypic plasticity. The most widely studied epigenetic mechanism is the cytosine methylation of DNA, which is essential in cell-lineage specification, in the regulation of transcription, and in the maintenance of genome stability (Jones, 2012). Individual DNA methylation patterns are largely established during embryonic development through a highly coordinated process and considered to be relatively stable. Thus, the pre- and perinatal period is a critical window for epigenetic alterations with high sensitivity to environmental exposures affecting many cell types (Martino and Prescott, 2010). However, DNA methylation in part is dynamic, and epidemiological studies on skin and other tissues identified locus- and cell type-specific DNA methylation changes associated with various environmental factors, including chronic exposure to sunlight, asbestos, and

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Abbreviations: AD, atopic dermatitis; AL, AD lesional; AN, AD non-lesional; DET, differentially expressed transcript; DMS, differentially methylated site; FLG, filaggrin; GO, Gene Ontology; NN, control healthy; OAS2, 2'-5'-oligoadenylate synthetase 2; qPCR, quantitative PCR

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tobacco smoke, consumption of alcohol, and use of hair dye (Christensen *et al.*, 2009; Gronniger *et al.*, 2010; Langevin *et al.*, 2011). Therefore, it is likely that DNA methylation serves as an important mediator between the environment and genome regulation also in postnatal life.

So far, epigenetic mechanisms have mostly been studied in cancer, but are increasingly recognized as an important factor influencing the individual risk for complex diseases such as AD or asthma (Miller and Ho, 2008). To our best knowledge, only three studies on AD-specific epigenetic risk factors have been conducted so far. Nakamura *et al.* (2006) reported a significantly reduced expression of DNA methyltransferase 1 (*DNMT1*) in peripheral blood mononuclear cells of AD-affected individuals with high serum IgE levels. DNA methyltransferase 1 is considered to be the key enzyme for maintenance of DNA methylation patterns during cell division, but it also seems to have substantial *de novo* DNA methylation capability and malfunction of this enzyme may lead to modified DNA methylation and consequently skewed expression of AD-related genes. Liang *et al.* (2012) observed hypomethylation of the local high-affinity IgE receptor gamma subunit (*FCER1G*) promoter in monocytes from AD patients to be correlated with increased gene expression. A recent analysis of methylation levels of CpG sites across the *filaggrin* (*FLG*) gene in DNA from peripheral blood of 245 female individuals, 37 of whom had AD ever, showed no significant differences between carriers and noncarriers of *FLG* mutations, but a potential interaction between *FLG* variants and methylation at a single CpG site in the *FLG* gene body (Ziyab *et al.*, 2012). However, the validity and functional relevance of this observation, and the situation in skin, where *FLG* is expressed, are unclear.

In the current epigenome-wide association study, we investigated 28 AD-affected and 29 healthy individuals for methylation changes of DNA derived from lesional (AL) and non-lesional (control healthy (NN)/AD non-lesional (AN) for healthy controls/AD patients) epidermis, whole blood, T cells, and B cells. To explore potential functional links, a genome-wide RNA expression analysis in NN, AL, and AN was implemented, and both data sets were analyzed in an integrated manner. Technical validation of significant DNA methylation and RNA expression array results was performed with the EpiTyper MassARRAY system and quantitative PCR (qPCR), respectively.

## RESULTS

### DNA methylation patterns are highly tissue specific

For methylome analysis, we applied the Human Methylation27 BeadChip in order to capture the methylation status of 27,578 single CpG sites in NN, AL, and AN epidermis, whole blood, T cells, and B cells in a total of 28 AD patients and 29 controls. For details on the study population and biosamples see Table 1.

A principal component analysis of 25,648 autosomal CpG sites in epidermal samples, whole blood, T cells, and B cells showed explicit clustering for the different tissues. Epidermal tissue can be clearly distinguished from the different blood cell types, which closely cluster together (Supplementary Figure S1 online). To determine interindividual and intra-individual

**Table 1. Characteristics of the study cohort**

| Variable                          | Study cohort |                   |
|-----------------------------------|--------------|-------------------|
|                                   | AD (n = 28)  | Controls (n = 29) |
| Female, n (%)                     | 13 (46.4)    | 15 (51.7)         |
| Median age, years (range)         | 38.5 (20–62) | 27 (22–69)        |
| Epidermal methylation data, n (%) |              |                   |
| Lesional                          | 25 (89.3)    | –                 |
| Non-lesional                      | 17 (60.7)    | 28 (96.6)         |
| Epidermal expression data, n (%)  |              |                   |
| Lesional                          | 12 (42.9)    | –                 |
| Non-lesional                      | 7 (25)       | 14 (48.3)         |
| Methylation whole blood, n (%)    | 12 (42.9)    | 13 (44.8)         |
| Methylation B cells, n (%)        | 11 (39.3)    | 12 (41.4)         |
| Methylation T cells, n (%)        | 12 (42.9)    | 13 (44.8)         |

Abbreviation: AD, atopic dermatitis.

DNA methylation differences, we calculated pairwise correlation between individuals of an age- and sex-matched subsample ( $n = 4$ ) across all methylation sites within the same tissue as well as pairwise correlation between different tissues within the same individual (Supplementary Figures S2 and S3 online). We observed stronger correlations within the same tissue between different individuals than between different tissues within the same individual. Thus, our analysis in four different tissues indicates a high tissue-specificity for DNA methylation patterns in accordance with the literature (Illingworth *et al.*, 2008; Varley *et al.*, 2013).

### Differentially methylated CpG sites in epidermal DNA

In the pairwise comparisons of AL/NN ( $n = 25/28$ ), AL/AN ( $n = 16$ ), and AN/NN ( $n = 17/28$ ), we observed 127, 47, and 7 differentially methylated sites (DMSs) reaching a liberal significance threshold of  $P < 0.001$  and a methylation difference of at least 10% ( $|\Delta\beta| > 0.10$ ) (Supplementary Table S1 online). No strong tendency toward hypo- or hypermethylation (47% and 53%, respectively) for disease-associated CpGs could be detected. Functional clustering of the AL/NN-DMS-allocated genes with DAVID (Huang da *et al.*, 2009a, b) revealed a significant (Benjamini Hochberg corrected  $P_{BH} < 2.9 \times 10^{-2}$ ) enrichment of the cellular component terms “integral/intrinsic to plasma membrane” (Gene Ontology (GO): 0031226; 0005887). No significant GO term enrichment could be detected for AL/AN and AN/NN genes. However, six of the AL/AN genes with DMS were grouped to the molecular function term “structural molecule activity” (GO: 0005198), e.g., *desmin* and the epidermal differentiation complex gene *involucrin*, possibly pointing toward an epigenetic influence on the epidermal barrier function related to inflammation.

In all, 11 DMS from the AL/NN analysis reached conservative Bonferroni-corrected genome-wide significance ( $P < 1.9 \times 10^{-6}$ ) and were selected for technical validation using the

**Table 2. Differentially methylated sites between AL and NN**

| CpG        | Chr | Position hg19 | Gene             | CpG location <sup>1</sup> | P value               | Median <sub>meth</sub> (AL) | Median <sub>meth</sub> (NN) | Median <sub>meth</sub> difference | GO term (b.p., m.f., c.c.)                                                                                                                                                                   |
|------------|-----|---------------|------------------|---------------------------|-----------------------|-----------------------------|-----------------------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| cg06641366 | 1   | 90097604      | <i>LRRC8C</i>    | CGI N shore               | $3.49 \times 10^{-8}$ | 0.775                       | 0.334                       | 0.441                             | Integral to membrane (c.c.), endoplasmic reticulum membrane (c.c.)                                                                                                                           |
| cg08823182 | 1   | 153514482     | <i>S100A5</i>    | Promoter                  | $7.19 \times 10^{-6}$ | 0.566                       | 0.341                       | 0.225                             | Protein homodimerization activity (m.f.), calcium/copper/zinc ion binding (m.f.), nucleus (c.c.)                                                                                             |
| cg20839149 | 1   | 156786601     | <i>SH2D2A</i>    | CGI S shelf               | $2.14 \times 10^{-6}$ | 0.138                       | 0.434                       | −0.296                            | Cell differentiation/proliferation (b.p.), signal transduction (b.p.), SH3 domain binding (m.f.), cytoplasm (c.c.)                                                                           |
| cg18119407 | 2   | 201980504     | <i>CFLAR</i>     | CGI N shore               | $1.86 \times 10^{-6}$ | 0.300                       | 0.512                       | −0.212                            | Regulation of apoptotic/necroptotic process (b.p.), positive regulation of IκB kinase/NF-κB cascade (b.p.), cytoplasm (c.c.)                                                                 |
| cg20287234 | 2   | 231789465     | <i>GPR55</i>     | Intronic                  | $1.80 \times 10^{-6}$ | 0.231                       | 0.536                       | −0.305                            | G-protein coupled receptor signaling pathway (b.p.), positive regulation of ERK1/ERK2 cascade/Rho protein signal transduction (b.p.), plasma membrane (c.c.)                                 |
| cg14706739 | 8   | 21916355      | <i>EPB49</i>     | CGI S shore               | $3.90 \times 10^{-7}$ | 0.684                       | 0.518                       | 0.166                             | Cytoskeleton organization (b.p.), actin binding (m.f.), cellular response to calcium ion (b.p.)                                                                                              |
| cg25511807 | 11  | 102401438     | <i>MMP7</i>      | Exonic                    | $1.38 \times 10^{-6}$ | 0.204                       | 0.443                       | −0.239                            | Extracellular matrix organization (b.p.), regulation of cell proliferation (b.p.), antibacterial peptide secretion (b.p.), metalloendopeptidase activity (m.f.), extracellular region (c.c.) |
| cg13435792 | 12  | 15092434      | <i>ERP27</i>     | Promoter                  | $6.30 \times 10^{-6}$ | 0.437                       | 0.701                       | −0.263                            | Endoplasmic reticulum lumen (c.c.)                                                                                                                                                           |
| cg22131172 | 13  | 111522865     | <i>LOC283487</i> | Promoter                  | $1.33 \times 10^{-6}$ | 0.175                       | 0.365                       | −0.190                            | —                                                                                                                                                                                            |

Abbreviations: AL, AD lesional; b.p., biological process; c.c., cellular component; CGI, CpG island; Chr, chromosome; ERK, extracellular signal-regulated kinase; GO, Gene Ontology; m.f., molecular function; NN, control healthy. Sorted by chromosome.

<sup>1</sup>In relation to gene, GO terms are b.p., m.f., c.c..

Sequenom EpiTyper. In addition, we selected two CpGs with *P*-values marginally below the Bonferroni threshold ( $P < 3.0 \times 10^{-6}$ ) and  $|\Delta\beta| > 0.10$ , as well as three CpGs with a  $|\Delta\beta| > 0.20$  and a *P*-value of  $< 10^{-5}$  between AL and NN for validation. Thus, a total of 16 CpGs were reanalyzed in-depth with the Sequenom EpiTyper approach. Nine CpGs could be validated, showing a significant association (Bonferroni-corrected significance threshold  $P = 0.003$ ) with AD as well as a high correlation between methylation values as measured by the two different methods (Supplementary Table S2 online).

CpGs located within or next to the genes *CFLAR*, *GPR55*, *MMP7*, *LOC283487*, *SH2D2A*, and *ERP27* were hypomethylated, whereas CpGs assigned to *LRRC8C*, *S100A5*, and *EPB49* were hypermethylated in AD patients (Table 2). The strongest association ( $P = 3.49 \times 10^{-8}$ ) and the maximum difference in methylation ( $\Delta\beta = 0.44$ ) was observed for cg06641366 located within a CpG island N shore in the promoter region of *LRRC8C*. All EpiTyper assays were designed in order to allow us regional finemapping of additional CpG sites within a region of 300–400 bp around the associated CG dinucleotide. For three of the identified loci (*LRRC8C*, *GPR55*, *MMP7*), >85% of fine-mapped CpGs revealed significant associations. All analyzed CpGs in the promoter region of the gene *LRRC8C*

and within exon 1 of *MMP7*, and 12 of 14 CpGs within intron 1 of *GPR55* showed *P*-values  $< 0.003$ , whereas in the remaining loci (*S100A5*, *CFLAR*, *EPB49*, *LOC283487*, *SH2D2A*, *ERP27*) only the CpG identified in the screen or one or two directly neighboring CpG sites were associated. Associated CpGs within a certain locus showed broad ranges of median methylation differences of 9–60% between AL and NN (Supplementary Figure S6 online; Supplementary Table S2 online).

Two of the significantly associated sites (*LRRC8C* and *EPB49*) in AL versus NN additionally showed a nominal association ( $P < 10^{-3}$ ,  $\Delta\beta = 0.20$ , and  $\Delta\beta = 0.13$ , respectively) between AL and AN (Supplementary Figure S4 online), whereas no association was seen for AN versus NN ( $P_{LRRC8C} = 0.7225$ ,  $P_{EPB49} = 0.7508$ ). Both associations could be technically validated ( $P = 0.00083$ ,  $\Delta\beta = 0.33$  and  $P = 0.0011$ ,  $\Delta\beta = 0.26$ , respectively, Supplementary Table S2 online), and the fine mapping showed an additionally associated neighboring CpG for *LRRC8C* ( $P = 0.00018$ ,  $\Delta\beta = 0.35$ ). In contrast, a single CpG site assigned to the gene *ERP27* showed clear methylation differences with nominal significance ( $P < 10^{-3}$ ) for AL ( $\Delta\beta = -0.26$ ,  $P = 6.3 \times 10^{-6}$ ) and for AN ( $\Delta\beta = -0.20$ ,  $P = 8.02 \times 10^{-4}$ ) compared with those in NN, but not between AL and AN within cases ( $P = 0.16$ ),

suggesting AD-specific relevance. Technical validation with the EpiTyper in AN versus NN showed a  $\Delta\beta$  of  $-0.39$ , but no significant association ( $P=0.006$ ) for this CG dinucleotide.

We did not find any genome-wide significant median methylation differences  $\geq 10\%$  between cases and controls in DNA from whole blood, T cells, and B cells nor between AN and NN ( $P>1.0 \times 10^{-4}$ ) or AL and AN ( $P>3.0 \times 10^{-6}$ ).

A *FLG* mutation (R501X, 2282del4) stratified analysis for our top DMS did not reveal significant differences between carriers and noncarriers. Further, we did not observe significant methylation differences of CpGs within *FLG* in any of the tissues investigated.

Similarly, apart from hypomethylation of a site mapping to *IL23A* ( $\Delta\beta = -0.129$ ,  $P=0.00097$ ) in AL/NN, which, however, did not correlate to any expression change, no DMS significantly associated with AD located in genetic susceptibility loci for psoriasis, AD, and asthma identified through GWAS could be detected in any of the tissues (Supplementary Table S3 online).

#### Differentially expressed epidermal mRNA

Genome-wide mRNA expression analysis using the HumanHT-12v3 Expression BeadChip, which measures the expression of  $>25,000$  coding and noncoding transcripts with  $>48,000$  probes, revealed a total of 10,419 transcripts to be expressed in the epidermis. In the pairwise comparisons of AL/NN ( $n=12/14$ ), AL/AN ( $n=6$ ), and AN/NN ( $n=7/14$ ), 132, 90, and 398 transcripts showed suggestive evidence for differential expression ( $P<0.001$ , fold change  $>1.3$ ). Functional enrichment analysis with DAVID presented a strongly significant ( $P_{BH}<10^{-4}$ ) enrichment of gene transcripts for various GO terms related to epidermal differentiation within the AL/NN analysis (Supplementary Table S4 online).

Seven transcripts showed genome-wide significant expression differences ( $P<4.8 \times 10^{-6}$ ) between AL and NN, and four additional transcripts between AN and NN (Supplementary Table S5 online). Some of these transcripts are involved in innate immune response, but we also detected transcripts from genes with structural functions, e.g., late cornified envelope genes located within the epidermal differentiation complex.

#### Correlation of DNA methylation and mRNA expression in epidermis

Across individual epidermal specimens with DNA methylation as well as expression data available, we analyzed correlations between DMS defined as  $|\Delta\beta|>0.1$  and  $P<0.05$  and differentially expressed transcripts (DETs) defined as fold change  $>1.3$  and  $P<0.05$  located *in-cis* within a 200-kb distance from the DMS. In the comparison of AL/NN, AL/AN, and AN/NN, we observed 47, 2, and 10 DMS/DET pairs showing  $P<0.01$  and a correlation of at least  $|r|>0.5$  (Table 3). We did not see any significant functional enrichment for correlated DETs in the AL/AN and AN/NN analysis, whereas a large proportion ( $>25\%$ ) of correlated transcripts from AL/NN comparison relates to *S100A* genes located within the epidermal differentiation complex and to genes encoding keratins located within the keratin clusters. Accordingly, a functional

analysis performed with DAVID in order to identify common functional characteristics of correlated DETs showed a clear enrichment of gene transcripts annotated to the cellular component terms “keratin filament” ( $P_{BH}=2.4E-2$ , GO:0045095), “intermediate filament cytoskeleton” ( $P_{BH}=2.6E-2$ , GO:0045111), and “intermediate filament” ( $P_{BH}=4.7E-2$ , GO:0005882; Figure 1). In addition, we observed differential methylation of a CpG site within *OAS2* (2'-5'-oligoadenylate synthetase 2), which was correlated with expression levels of *OAS1*, *OAS2*, and *OAS3*.

From nine selected DMS/DET pairs fulfilling the more stringent *in-cis* definition of  $\pm 50$  kb, we successfully validated AD-associated DNA methylation and RNA expression changes as well as correlation for the six DMS/DET combinations *KRT6A/KRT6A*, *KRT6A/KRT6B*, *IFI27/IFI27*, *OAS2/OAS2*, *GDPD3/GDPD3*, and *S100A5/S100A2* with the EpiTYPER and qPCR (Supplementary Table S6 online).

Strong *in-trans* correlation was found for cg06641366 (*LRRC8C*) methylation with mRNA expression of *CD36* (7q31.11;  $r=0.842$ ,  $P=2.08 \times 10^{-6}$ ), which showed differential expression in AL and NN (Supplementary Figure S5 online), as well as cg14706739 (*EPB49*) methylation with *LCE3D* and *IFI27* mRNA expression ( $r=0.821$ ,  $P=2.37 \times 10^{-6}$ ;  $r=0.823$ ,  $P=2.27 \times 10^{-6}$ ), which are located on 1q21.3 and 14q32.12, respectively (Supplementary Table S6 online).

#### DISCUSSION

Here we used a genome-wide approach to study previously unreported DNA methylation and expression patterns in AD.

In our small-scale pilot study across several tissues, intra-individual inter-tissue variation in DNA methylation by far exceeded interindividual variation in any given tissue and confirmed previous findings of a high tissue specificity of DNA methylation (Zhang *et al.*, 2013; Ziller *et al.*, 2013). In particular, epidermis and blood cells appear to have very distinct methylomic profiles. Our analysis further indicates that the key tissue influenced by epigenetic dysregulation in AD may be the skin and that blood does not present an adequate surrogate tissue for epidermis. Using conservative significance thresholds and stringent criteria for methylation degrees, several strong AD-associated differences were observed in the DNA of epidermal specimen, but not in the DNA from blood, T cells, or B cells. The lack of association in the latter may be due to the heterogeneous cell composition of the samples, especially of whole blood, or due to small sample sizes. To rule out bias through inflammatory infiltrates in AL epidermal shaves (Suarez-Farinas *et al.*, 2013), we checked for expression of T cell-specific CD3 genes (*CD3 $\alpha$* , *CD3 $\epsilon$* , and *CD3 $\gamma$*  units). Very low expression levels reaching  $<50\%$  of the minimum magnitude found in blood were detected for CD3 E and D in five epidermal samples (three cases and two controls) only, whereas CD3G could not be detected in any epidermal sample, indicating that “contamination” by infiltrating immune cells was not a major issue.

In the isolated analysis of methylation, the CpGs found to exhibit the strongest AD-associated signatures are located in or near plasma membrane genes, a functionally very divergent group including, e.g., ion channels, signal transducers, and

**Table 3. Significant *in-cis* ( $\pm 200$ kb) correlations between differential DNA methylation ( $\Delta\beta \geq 0.1$ ,  $P < 0.05$ ) and mRNA expression (fold change  $> 1.3$ ,  $P < 0.05$ ) for AL/NN, AN/NN, and AL/AN with  $|r| > 0.5$  and  $P < 0.01$**

| AL versus NN       |     |               |          |                 |                                   |                       |               |     |               |               |             |                               |        |                       |
|--------------------|-----|---------------|----------|-----------------|-----------------------------------|-----------------------|---------------|-----|---------------|---------------|-------------|-------------------------------|--------|-----------------------|
| Methylation        |     |               |          |                 | Expression                        |                       |               |     |               |               |             |                               |        |                       |
| CpG ID             | Chr | Position hg19 | Gene     | CpG location    | Median <sub>meth</sub> difference | P-value               | Transcript ID | Chr | Position hg19 | Gene          | Fold change | P-value                       | r      | P                     |
| In-cis correlation |     |               |          |                 |                                   |                       |               |     |               |               |             |                               |        |                       |
| cg22718139         | 1   | 120311439     | HMGCS2   | Exonic          | 0.175                             | $9.28 \times 10^{-4}$ | ILMN_1815203  | 1   | 120290619     | HMGCS2        | 0.579       | 0.0023                        | -0.658 | $6.39 \times 10^{-4}$ |
| cg08823182         | 1   | 153514482     | S100A5   | Promoter region | 0.225                             | $7.19 \times 10^{-6}$ | ILMN_1729801  | 1   | 153362508     | S100A8        | 8.367       | $3.73 \times 10^{-4}$         | 0.808  | $3.39\text{E-}06$     |
| cg08823182         | 1   | 153514482     | S100A5   | Promoter region | 0.225                             | $7.19 \times 10^{-6}$ | ILMN_1750974  | 1   | 153330330     | S100A9        | 14.031      | $2.29 \times 10^{-4}$         | 0.802  | $4.30 \times 10^{-6}$ |
| cg08823182         | 1   | 153514482     | S100A5   | Promoter region | 0.225                             | $7.19 \times 10^{-6}$ | ILMN_1757351  | 1   | 153430220     | S100A7        | 9.802       | $2.98 \times 10^{-4}$         | 0.705  | $1.77 \times 10^{-4}$ |
| cg08823182         | 1   | 153514482     | S100A5   | Promoter region | 0.225                             | $7.19 \times 10^{-6}$ | ILMN_1673191  | 1   | 153388945     | S100A7A       | 6.225       | 0.0282                        | 0.592  | 0.0028                |
| cg08823182         | 1   | 153514482     | S100A5   | Promoter region | 0.225                             | $7.19 \times 10^{-6}$ | ILMN_1725852  | 1   | 153533584     | S100A2        | 1.731       | 0.0128                        | 0.553  | 0.0058                |
| cg00626119         | 1   | 156785288     | NTRK1    | CGI S shore     | -0.110                            | 0.0010                | ILMN_1732154  | 1   | 156611182     | BCAN          | 0.615       | 0.0021                        | 0.603  | 0.0018                |
| cg20839149         | 1   | 156786601     | SH2D2A   | CGI S shelf     | -0.296                            | $2.14 \times 10^{-6}$ | ILMN_1732154  | 1   | 156611182     | BCAN          | 0.615       | 0.0021                        | 0.592  | 0.0023                |
| cg02694395         | 1   | 171283893     | FMO4     | Intronic        | 0.119                             | $9.02 \times 10^{-4}$ | ILMN_1732158  | 1   | 171154347     | FMO2          | 1.373       | 0.0488                        | 0.652  | $7.42 \times 10^{-4}$ |
| cg26203861         | 1   | 201858661     | TMEM58   | Exonic          | 0.118                             | $5.79 \times 10^{-5}$ | ILMN_1769201  | 1   | 201980498     | RP11-510N19.5 | 1.351       | 0.0068                        | 0.565  | 0.0046                |
| cg20848130         | 1   | 228337776     | GJA12    | Intronic        | 0.107                             | 0.0083                | ILMN_1790202  | 1   | 228288427     | C1orf35       | 0.635       | 0.0064                        | -0.542 | 0.0070                |
| cg10635061         | 2   | 106055006     | FHL2     | Exonic          | 0.256                             | $1.65 \times 10^{-5}$ | ILMN_2355831  | 2   | 105974169     | FHL2          | 1.510       | 0.0254                        | 0.528  | 0.0089                |
| cg26523005         | 3   | 42947267      | ZNF662   | CGI N shore     | 0.105                             | $1.47 \times 10^{-6}$ | ILMN_1763127  | 3   | 42846244      | CCBP2         | 1.899       | 0.0348                        | 0.710  | $1.51 \times 10^{-4}$ |
| cg26523005         | 3   | 42947267      | ZNF662   | CGI N shore     | 0.105                             | $1.47 \times 10^{-6}$ | ILMN_2230016  | 3   | 42798669      | HIGD1A        | 1.349       | 0.0130                        | 0.522  | 0.0098                |
| cg10525372         | 6   | 112375333     | WSP3     | Exonic          | -0.113                            | 0.0075                | ILMN_1712360  | 6   | 112375275     | WSP3          | 1.450       | 0.0398                        | -0.700 | $2.07 \times 10^{-4}$ |
| cg14706739         | 8   | 21916355      | EPB49    | CGI S shore     | 0.166                             | $3.90 \times 10^{-7}$ | ILMN_1737162  | 8   | 22004338      | LG3           | 0.711       | 0.0309                        | -0.622 | 0.0012                |
| cg15537850         | 8   | 144661051     | NAPRT1   | CGI S shore     | -0.166                            | 0.0023                | ILMN_1702389  | 8   | 144519825     | ZC3H3         | 0.761       | $4.50 \times 10^{-4}$         | 0.565  | 0.0040                |
| cg13351583         | 9   | 91793648      | SHC3     | CGI S shore     | -0.145                            | $6.48 \times 10^{-4}$ | ILMN_1756326  | 9   | 91926113      | CKS2          | 1.377       | 0.0148                        | -0.536 | 0.0078                |
| cg04126866         | 10  | 85932763      | C10orf99 | Promoter region | -0.105                            | 0.0053                | ILMN_1802192  | 10  | 85933494      | C10orf99      | 5.658       | $3.00 \times 10^{-4}$         | -0.685 | $3.16 \times 10^{-4}$ |
| cg03245641         | 11  | 64703415      | GPHA2    | Promoter region | 0.205                             | $1.59 \times 10^{-4}$ | ILMN_2077094  | 11  | 64856796      | VPS51         | 0.663       | 0.0174                        | -0.636 | $8.47 \times 10^{-4}$ |
| cg06539449         | 11  | 69461008      | CCND1    | CGI N shore     | 0.106                             | $3.26 \times 10^{-4}$ | ILMN_1688480  | 11  | 69455855      | CCND1         | 0.417       | $5.72\text{e} \times 10^{-4}$ | -0.557 | 0.0054                |
| cg19220825         | 12  | 50353951      | AQP5     | CGI N shore     | -0.116                            | $3.91 \times 10^{-4}$ | ILMN_2208495  | 12  | 50523575      | CERS5         | 0.696       | 0.0027                        | 0.539  | 0.0073                |
| cg00213044         | 12  | 52886438      | KRT6A    | Intronic        | -0.119                            | $2.97 \times 10^{-4}$ | ILMN_1801428  | 12  | 53083410      | KRT77         | 0.152       | $6.83 \times 10^{-4}$         | 0.679  | $3.73 \times 10^{-4}$ |
| cg00213044         | 12  | 52886438      | KRT6A    | Intronic        | -0.119                            | $2.97 \times 10^{-4}$ | ILMN_1721354  | 12  | 52840435      | KRT6B         | 14.217      | $1.25 \times 10^{-4}$         | -0.555 | 0.0056                |
| cg00213044         | 12  | 52886438      | KRT6A    | Intronic        | -0.119                            | $2.97 \times 10^{-4}$ | ILMN_2219002  | 12  | 52880958      | KRT6A         | 22.890      | $7.54 \times 10^{-6}$         | -0.535 | 0.0079                |
| cg06494782         | 12  | 52995446      | KRT72    | CGI S shore     | 0.103                             | 0.0327                | ILMN_2219002  | 12  | 52880958      | KRT6A         | 22.890      | $7.54 \times 10^{-6}$         | 0.643  | $9.32 \times 10^{-4}$ |
| cg06494782         | 12  | 52995446      | KRT72    | CGI S shore     | 0.103                             | 0.0327                | ILMN_1801428  | 12  | 53083410      | KRT77         | 0.152       | $6.83 \times 10^{-4}$         | -0.641 | 0.0010                |
| cg06494782         | 12  | 52995446      | KRT72    | CGI S shore     | 0.103                             | 0.0327                | ILMN_1754576  | 12  | 52862300      | KRT6C         | 33.533      | $4.64 \times 10^{-4}$         | 0.560  | 0.0044                |

Table 3 continued on following page

Table 3. (Continued)

Table 3. (Continued)

| AL versus NN       |     |               |           |                 |                                   |                       |               |     |               |          |             |                       |        |                       |
|--------------------|-----|---------------|-----------|-----------------|-----------------------------------|-----------------------|---------------|-----|---------------|----------|-------------|-----------------------|--------|-----------------------|
| Methylation        |     |               |           |                 |                                   | Expression            |               |     |               |          |             |                       |        |                       |
| CpG ID             | Chr | Position hg19 | Gene      | CpG location    | Median <sub>meth</sub> difference | P-value               | Transcript ID | Chr | Position hg19 | Gene     | Fold change | P-value               | r      | P                     |
| In-cis correlation |     |               |           |                 |                                   |                       |               |     |               |          |             |                       |        |                       |
| cg06494782         | 12  | 52995446      | KRT72     | CGI S shore     | 0.103                             | 0.0327                | ILMN_1669820  | 12  | 52840435      | KRT6B    | 6.559       | 0.0083                | 0.550  | 0.0060                |
| cg23696712         | 12  | 53228141      | KRT6L     | Promoter region | 0.152                             | $2.57 \times 10^{-5}$ | ILMN_1801428  | 12  | 53083410      | KRT77    | 0.152       | $6.83 \times 10^{-4}$ | -0.753 | $3.46 \times 10^{-5}$ |
| cg23841186         | 12  | 53492662      | SOAT2     | CGI S shore     | -0.163                            | 0.0017                | ILMN_1669362  | 12  | 53491220      | IGFBP6   | 1.959       | 0.0025                | -0.581 | 0.0030                |
| cg23841186         | 12  | 53492662      | SOAT2     | CGI S shore     | -0.163                            | 0.0017                | ILMN_1661799  | 12  | 53535837      | HIGD1A1  | 1.767       | 0.0037                | -0.517 | 0.0098                |
| cg20870559         | 12  | 113416518     | OAS2      | Exonic          | -0.241                            | 0.0010                | ILMN_1674063  | 12  | 113416200     | OAS2     | 3.705       | 3.29E-06              | -0.741 | $5.47 \times 10^{-5}$ |
| cg20870559         | 12  | 113416518     | OAS2      | Exonic          | -0.241                            | 0.0010                | ILMN_1745397  | 12  | 113376157     | OAS3     | 1.770       | 9.35E-05              | -0.738 | $6.00 \times 10^{-5}$ |
| cg20870559         | 12  | 113416518     | OAS2      | Exonic          | -0.241                            | 0.0010                | ILMN_2410826  | 12  | 113344582     | OAS1     | 1.483       | 2.05E-06              | -0.561 | 0.0050                |
| cg20161089         | 14  | 94577514      | IFI27     | Intronic        | -0.222                            | 0.0196                | ILMN_2058782  | 14  | 94571182      | IFI27    | 9.888       | $6.16 \times 10^{-6}$ | -0.797 | $5.17 \times 10^{-6}$ |
| cg14370448         | 16  | 30103978      | TBX6      | CGI S shore     | -0.180                            | 0.0018                | ILMN_1774901  | 16  | 30116131      | GDPD3    | 1.746       | 0.0110                | -0.562 | 0.0043                |
| cg03297731         | 16  | 30124293      | GDPD3     | Intronic        | -0.109                            | $8.23 \times 10^{-6}$ | ILMN_1774901  | 16  | 30116131      | GDPD3    | 1.746       | 0.0110                | -0.564 | 0.0047                |
| cg07634706         | 16  | 57438524      | CCL17     | Promoter region | 0.101                             | 0.0290                | ILMN_1787673  | 16  | 57290004      | PLLP     | 0.468       | 0.0412                | -0.589 | 0.0030                |
| cg02992647         | 17  | 36004446      | DDX52     | CGI S shore     | 0.139                             | 0.0033                | ILMN_1666546  | 17  | 35849937      | DUSP14   | 1.470       | 0.0020                | 0.567  | 0.0038                |
| cg26499286         | 17  | 39472498      | KRTAP17-1 | Promoter region | -0.194                            | $1.04 \times 10^{-5}$ | ILMN_1770228  | 17  | 39533902      | KRT34    | 1.421       | 0.0493                | -0.555 | 0.0056                |
| cg14870271         | 17  | 76976010      | LGALS3BP  | Exonic          | -0.130                            | 0.0200                | ILMN_1659688  | 17  | 76967320      | LGALS3BP | 1.655       | 0.0129                | -0.601 | 0.0023                |
| cg10533434         | 18  | 61329226      | SERPINB3  | Promoter region | -0.208                            | 0.0111                | ILMN_1703855  | 18  | 61322431      | SERPINB3 | 5.352       | 0.0019                | -0.580 | 0.0035                |
| cg13943564         | 18  | 61555117      | SERPINB2  | Intronic        | 0.198                             | 0.0093                | ILMN_2397028  | 18  | 61637159      | SERPINB8 | 1.424       | $3.85 \times 10^{-4}$ | 0.525  | 0.0093                |
| cg24477567         | 19  | 11495295      | EPOR      | CGI S shore     | 0.161                             | $4.00 \times 10^{-4}$ | ILMN_2078599  | 19  | 11685475      | ACP5     | 1.915       | $4.95 \times 10^{-4}$ | 0.717  | $1.25 \times 10^{-4}$ |
| cg19103704         | 19  | 40440963      | FCGBP     | Promoter region | -0.185                            | 0.0170                | ILMN_1719205  | 19  | 40325094      | FBL      | 0.706       | 0.0017                | 0.537  | 0.0077                |
| cg15937958         | 19  | 42947133      | UNQ473    | Exonic          | -0.129                            | $7.61 \times 10^{-5}$ | ILMN_1803838  | 19  | 42891173      | CNFN     | 2.108       | $1.04 \times 10^{-4}$ | -0.561 | 0.0044                |
| AN versus NN       |     |               |           |                 |                                   |                       |               |     |               |          |             |                       |        |                       |
| Methylation        |     |               |           |                 |                                   | Expression            |               |     |               |          |             |                       |        |                       |
| CpG ID             | Chr | Position hg19 | Gene      | CpG location    | Median <sub>meth</sub> difference | P-value               | Transcript ID | Chr | Position hg19 | Gene     | Fold change | P-value               | r      | P                     |
| cg01550148         | 5   | 134735544     | H2AFY     | CGI S shore     | 0.107                             | $8.81 \times 10^{-4}$ | ILMN_1746171  | 5   | 134669590     | H2AFY    | 1.32        | 0.0284                | 0.598  | 0.0088                |
| cg25802093         | 10  | 22634038      | SPAG6     | CG island       | 0.138                             | 0.0036                | ILMN_1700915  | 10  | 22610140      | BMI1     | 1.43        | 0.0014                | 0.668  | 0.0032                |
| cg08965235         | 11  | 65325158      | LTBP3     | CG island       | 0.101                             | 0.0324                | ILMN_1804117  | 11  | 65338153      | SSSCA1   | 0.66        | 0.0017                | 0.622  | 0.0070                |
| cg00350296         | 11  | 66084841      | CD248     | CGI S shore     | 0.115                             | 0.0076                | ILMN_2398432  | 11  | 66104804      | BRMS1    | 0.66        | $1.52 \times 10^{-4}$ | 0.618  | 0.0074                |
| cg00350296         | 11  | 66084841      | CD248     | CGI S shore     | 0.115                             | 0.0076                | ILMN_1664030  | 11  | 66036004      | RAB1B    | 0.68        | 0.0021                | 0.668  | 0.0032                |
| cg09816471         | 16  | 11761860      | SNN       | CG island       | 0.156                             | 0.0027                | ILMN_1723729  | 16  | 11929056      | RSL1D1   | 0.68        | 0.0161                | 0.814  | $4.39 \times 10^{-5}$ |

Table 3 continued on following page

Table 3. (Continued)

| AN versus NN |     |               |          |              |                                   |                       |               |     |               |          |             |                       |       |                       |
|--------------|-----|---------------|----------|--------------|-----------------------------------|-----------------------|---------------|-----|---------------|----------|-------------|-----------------------|-------|-----------------------|
| Methylation  |     |               |          |              |                                   | Expression            |               |     |               |          |             |                       |       |                       |
| CpG ID       | Chr | Position hg19 | Gene     | CpG location | Median <sub>meth</sub> difference | P-value               | Transcript ID | Chr | Position hg19 | Gene     | Fold change | P-value               | r     | P                     |
| cg16791686   | 19  | 48249014      | GLTSCR2  | CG island    | -0.115                            | 0.0185                | ILMN_1703565  | 19  | 48248793      | GLTSCR2  | 0.74        | 0.0116                | 0.600 | 0.0099                |
| cg08260891   | 20  | 44518802      | CTSA     | CGI N shore  | 0.170                             | 0.0460                | ILMN_1719286  | 20  | 44519683      | CTSA     | 0.69        | 0.0456                | 0.645 | 0.0048                |
| cg08260891   | 20  | 44518802      | CTSA     | CGI N shore  | 0.170                             | 0.0460                | ILMN_1773389  | 20  | 44527399      | PLTP     | 0.58        | 0.0196                | 0.783 | $1.81 \times 10^{-4}$ |
| cg19067730   | 20  | 44518824      | CTSA     | CGI N shore  | 0.100                             | 0.0401                | ILMN_1773389  | 20  | 44527399      | PLTP     | 0.58        | 0.0196                | 0.606 | 0.0090                |
| AL versus AN |     |               |          |              |                                   |                       |               |     |               |          |             |                       |       |                       |
| Methylation  |     |               |          |              |                                   | Expression            |               |     |               |          |             |                       |       |                       |
| CpG ID       | Chr | Position hg19 | Gene     | CpG location | Median <sub>meth</sub> difference | P-value               | Transcript ID | Chr | Position hg19 | Gene     | Fold change | P-value               | r     | P                     |
| cg01568736   | 18  | 61441730      | SERPINB7 | Intronic     | 0.149                             | 0.0055                | ILMN_1703855  | 18  | 61322431      | SERPINB3 | 7.32        | $8.85 \times 10^{-4}$ | 0.905 | 0.0046                |
| cg23185262   | 21  | 45137544      | PDXK     | CGI N shore  | 0.105                             | $8.58 \times 10^{-4}$ | ILMN_1761797  | 21  | 45192393      | CSTB     | 2.39        | 0.0072                | 0.874 | 0.0045                |

Abbreviations: AL, AD lesional; AN, AD non-lesional; CGI, CpG island; Chr, chromosome; NN, control healthy.

Abbreviations: AL, AD lesional; AN, AD non-lesional; CGI, CpG island; Chr, chromosome; NN, control healthy.

structural proteins. “Fine mapping” of these loci often revealed further DMS within 400bp around the initial CpG to be associated with AD. Further, in contrast to common assumptions (Barrera and Peinado, 2012), methylation patterns across neighboring CpGs within a certain region were not always consistent (Supplementary Figure S6 online). Methylation patterns were not associated with *FLG* genotypes, and there were no DMS within the *FLG* gene, indicating that *FLG* is not the subject of epigenetic regulation in AD.

Relevant correlations of DNA methylation and RNA expression were mainly restricted to the AL/NN analysis, but high numbers of transcripts exhibiting expression changes between AL/AN and AN/NN indicate disease-associated differences between uninvolved, involved, and healthy epidermis, which, however, might be regulated by mechanisms other than DNA methylation. An integrated analysis of both DNA methylation and mRNA expression data from epidermal specimen revealed several sites differently methylated between cases and controls, which were correlated with altered expression levels of transcripts in *cis*. In addition, we observed some *trans* effects. Although we acknowledge that these must be interpreted with great caution, there is increasing evidence for the existence of interchromosomal regulatory mechanisms between DNA methylation and gene expression (van Eijk *et al.*, 2012). Most CpG/transcript pairs displayed an inverse correlation, i.e., higher methylation levels were associated with lower expression and vice versa, which is commonly observed in CpG islands close to transcription start sites where DNA methylation is associated with long-term silencing of the according gene. However, we also observed positive correlations, which is in line with results from other studies, in particular on sites outside of CpG islands or within gene bodies (Jones, 1999; Gibbs *et al.*, 2010; Bell *et al.*, 2011).

The majority (>25%) of correlated transcripts from the AL/NN comparison mapped to *S100A* genes located within the epidermal differentiation complex or to genes encoding keratins located within the keratin clusters. S100 proteins are known to be key players in epidermal inflammatory processes with multiple functions including regulation of keratinocyte proliferation and maturation, antimicrobial defense, and self-danger signaling (Halawi *et al.*, 2013). Keratins belong to a family of epithelial cytoskeleton proteins and in general are important for the structural integrity of epithelial tissue. Apart from their mechanical roles, some keratins are also involved in intracellular signaling pathways (Moll *et al.*, 2008).

Our analysis confirms the known overexpression of S100A2, A7, A8, A9, and A15 (alias S100A7A) in lesional skin of AD patients (Suigura *et al.*, 2005; Wolf *et al.*, 2007; Gläser *et al.*, 2009; Harder *et al.*, 2010), and this expression change was correlated with DNA hypermethylation of a single CpG within *S100A5*, indicating a potential coregulatory mechanism through methylation. S100A8 and S100A9 are frequently coexpressed and preferentially form heterodimers with each other. Both proteins are stress-induced and overexpressed after epidermal injury (reviewed in: Kerkhoff *et al.*, 2012). S100A7 and S100A15, which are overexpressed in psoriasis, exert antimicrobial activity and act as amplifiers of inflammation through their chemotactic activity and the

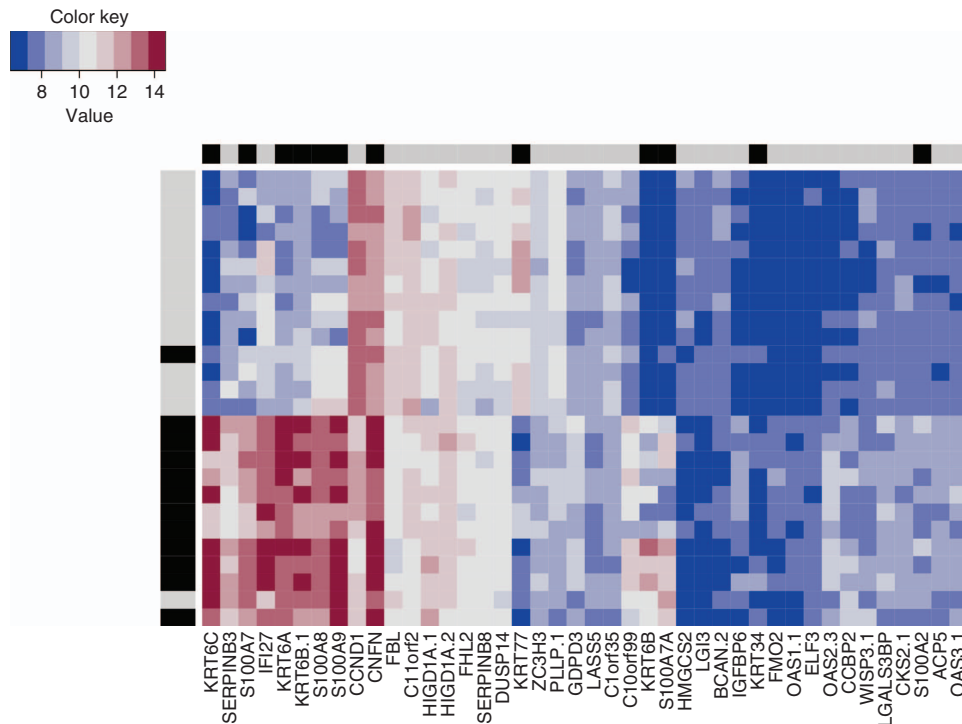


**Figure 1. Heat map showing *in-cis* regulated mRNA expression in AD lesional (AL) versus control healthy (NN).** The left column indicates cases in black and controls in gray. The bar on top indicates genes in black, which are involved in terminal differentiation.

induction of immunotropic cytokine expression in keratinocytes (Wolf *et al.*, 2011; Hegyi *et al.*, 2012).

Similarly, our observations confirm increased levels of *KRT6A* and *KRT6B* mRNA in AL skin (Sugiura *et al.*, 2005; Jarzab *et al.*, 2010). This overexpression of both *KRT6A* and *KRT6B* mRNA (AL versus NN:  $P_{KRT6A:expr} = 7.54 \times 10^{-6}$ ,  $P_{KRT6B.1:expr} = 1.25 \times 10^{-4}$ ; AL versus AN:  $P_{KRT6A:expr} = 0.0038$ ,  $P_{KRT6B.1:expr} = 0.0004$ ) was correlated with decreased methylation of a single CpG in *KRT6A*. Both keratins belong to the group of so-called alternative pathway keratins. This alternative keratinization pathway is supposed to provide a physiological response if rapid epidermal regeneration processes are needed, e.g., in epidermal wound healing after injury (Takahashi *et al.*, 1995). Mutations in *KRT6A* and *KRT6B* cause pachyonychia congenita, a rare autosomal dominant skin disorder characterized by cytolysis and hyperkeratosis (McLean *et al.*, 2011).

Differential single CpG methylation coupled with altered co-expression was also observed for *OAS1*, *OAS2*, and *OAS3*, which belong to a family of proteins regulated by IFN and are involved in the innate immune response to viral infection (Bin *et al.*, 2011). Further, methylation levels at a CpG (cg06641366) located near *LRRC8C* (1p22.2) revealed a strong positive correlation ( $r = 0.84$ ,  $P_{corr} = 2.08 \times 10^{-6}$ ) with expression probes in *trans* for *CD36* (7q21.11). *CD36* has been shown to be upregulated upon skin barrier disruption (Schmuth *et al.*, 2005) and in inflammatory skin disorders (Westergaard *et al.*, 2001, 2003; Fujimoto *et al.*, 2010), to mediate the secretion and processing of epidermal lipoproteins (Schmuth *et al.*, 2005) and to influence terminal keratinocyte differentiation (Westergaard *et al.*, 2003).

Together, these findings indicate altered methylation and expression of genes important for keratinocyte differentiation, proliferation, and innate immune response in lesional epidermis of AD patients.

Our study on AD yielded a lower number of DMS as compared with a previous epigenome-wide association study on psoriasis skin (Roberson *et al.*, 2011). Apart from differences in study design, this might reflect a higher degree of heterogeneity in terms of disease phenotype and pathophysiology. However, it is noteworthy that from the top 50 DMS reported for lesional psoriatic versus healthy control skin (Roberson *et al.*, 2011) a total of 19 CpGs showed significant and analogous differential methylation in lesional AD versus healthy control epidermis (Supplementary Table S7 online). For example, as for psoriasis, we observed a hypomethylation of the CG dinucleotide cg20161089 in *IFI27* and adjacent sites, which was accompanied by significantly increased mRNA expression in AL as compared to NN (Supplementary Figure S7 online and Supplementary Table S8 online). *IFI27* belongs to the family of IFN-stimulated genes, which mediate antiviral effects (Schoggins and Rice, 2011). It is upregulated in psoriatic skin and is supposed to be involved in keratinocyte hyperproliferation in skin cancer, psoriasis, and chronic eczema (Suomela *et al.*, 2004).

These findings support the results from genetic association studies, which indicate the presence of shared risk loci between AD and psoriasis (Weidinger *et al.*, 2013).

Our study suffers from several limitations, such as small sample sizes, lack of independent replication, and application of low coverage platforms. Further, although an in-silico mQTL analysis in blood from a large population-based cohort

did not observe any single-nucleotide polymorphism association with methylation levels at our top DMS within a distance of 500 kb (Petersen *et al.*, 2013), we cannot fully exclude influences of low-prevalent genetic variations in the epidermis and the context of AD. However, the tissue specificity and the lack of “outliers” for methylation levels at the sites we report render this possibility very unlikely. It should also be noted that our results do not allow conclusions on whether the DNA methylation changes between AD and healthy epidermis are a marker of predisposing causal mechanisms or mediators of causal environmental influences or simply a consequence of the disease or disease-associated features.

Finally, advanced studies will have to investigate the detailed functional consequences of aberrant methylation at the sites we report.

However, we feel that, at large, our approach provides evidence for functionally relevant differences in DNA methylation, in particular in the epidermis, which are associated with AD, and that it represents a starting point in the field of epigenetic epidemiology in complex skin diseases.

## **MATERIALS AND METHODS**

### **Study cohort and sample preparation**

The study was conducted according to the Declaration of Helsinki Principles and after written informed patient consent in accordance with local ethical committee approval. In all, 28 patients suffering from dermatologist-diagnosed AD and 29 healthy volunteers without a self-reported history of atopic diseases (asthma, AD, rhinitis) were recruited through Dermatology Departments at University Hospitals in Munich and Bonn. All patients suffered from moderate to severe early-onset persistent disease, received no systemic treatment at the time of sampling, and skin lesions chosen for biopsy had not been treated topically for at least 48 hours. Epidermal shaves of approximately 36 mm<sup>2</sup> from lesional and non-lesional skin (patients) and from healthy skin (controls) were taken and immediately stored in PAXgene Tissue Tubes (Qiagen, Hilden, Germany) at –80 °C until further processing. DNA and RNA were extracted with the QIAamp DNA Mini Kit (Tissue Protocol; Qiagen) and the PAXgene Tissue RNA Kit (Qiagen), respectively.

Whole blood samples were taken for DNA extraction and for isolation of CD4<sup>+</sup> T cells and B cells. After peripheral blood mononuclear cell isolation by density gradient centrifugation (Ficoll-Paque), both cell types were purified by negative selection using the MACS CD4<sup>+</sup> T-Cell Isolation Kit and the MACS B Cell Isolation Kit II (Miltenyi Biotec, Bergisch Gladbach, Germany). Approximately 1 × 10<sup>7</sup> cells were resuspended in 200 µl phosphate-buffered saline and stored in liquid nitrogen until DNA was extracted with the QIAamp DNA Mini Kit (Blood or Body Fluid Spin Protocol, Qiagen). A 9-ml EDTA tube of peripheral blood was subjected to DNA isolation using a slightly modified protocol based on the study by Miller *et al.* (1988).

All protocols for storage and isolation of nucleic acids as well as for purification of T cells and B cells were applied following the manufacturer's instructions (Qiagen and Miltenyi Biotec).

DNA and RNA qualities were assessed on a 0.8% agarose gel after electrophoresis and a NanoDrop 8000 (Thermo Fisher Scientific, Schwerte, Germany) or with the RNA 6000 Nano Kit on the Bioanalyzer 2100 (Agilent Technologies, Böblingen, Germany). Only DNA samples providing a compact band ≥20.000 bp and an OD

ratio 260/280 of ≥1.7, and RNA samples with a RNA integrity number ≥6 and an OD ratio 260/280 of ≥1.9 were subjected to downstream analysis.

### **Infinium 27K methylation assay**

DNA methylation status for the different tissue samples was determined using the Infinium Human Methylation27 BeadChip (Illumina, San Diego, CA). In brief, genomic DNA (700 ng) from each sample was bisulfite converted with the EZ DNA Methylation or the EZ-96 DNA Methylation Kit (Zymo Research, Irvine, CA). A 250 ng quantity of converted DNA was subjected to the Illumina Infinium methylation assay and hybridized on BeadChips. Raw data processing and initial quality visualization were performed with the Illumina GenomeStudio (version 2011.1) Methylation Module software (version 1.9.0, Illumina). For data normalization, we used the pipeline described in the study by Touleimat and Tost (2012) adapted for the Illumina 27k Methylation Chip with default parameter settings. In brief, after excluding samples with more than 20% of bad quality probes (detection *P*-value < 0.01) and CpG sites (*n* = 846) in close proximity (50 bp) to common single-nucleotide polymorphisms (source: 1 kg.eur.hg19), for each chip background level correction and color bias adjustment were performed using the Bioconductor lumi package (Du *et al.*, 2008). Normalization between samples was applied by building categories using the “relation to CpG-island” information (i.e., south shore, south shelf, north shore, north shelf, and distant) from the Illumina annotation file. For statistical analysis, 25,648 *β*-values with a detection *P*-value < 0.01 were considered.

### **HumanHT-12 Expression BeadChip**

Whole-genome expression profiles for AL, AN, and NN samples were generated with the Illumina HumanHT-12 v3 Expression BeadChip (Illumina). RNA amounting to 500 ng was first reverse transcribed into complementary DNA. After second strand synthesis and purification of cDNA, *in vitro* transcription into cRNA and biotin-UTP labeling were performed using the Illumina TotalPrep-96 RNA Amplification Kit (Ambion, Life Technologies, Carlsbad, CA). RNA amounting to 3000 ng was hybridized to the Illumina HumanHT-12 v3 Expression BeadChip. Chips were washed, detected, and scanned according to the manufacturer's instructions. Data collection and visualization were performed with the Illumina GenomeStudio 2011.1 Gene Expression Module software.

### **Sequenom EpiTyper assay**

Sequenom matrix-assisted laser desorption/ionization–time-of-flight EpiTyper assay (Sequenom, San Diego, CA) was used for technical validation and fine mapping of 24 single CpGs at 23 different genomic loci as selected from the screen. Assays were designed with the EpiDesigner BETA software (<http://www.epidesigner.com/>) as provided by Sequenom. All assays were designed so as to cover all 24 CpGs identified in the screen and a maximum of CpGs within an approximately 400 bp region. Primer sequences for bisulfite-treated genomic DNA can be found in Supplementary Table S9 online.

A 700-ng quantity of genomic DNA from each sample was bisulfite converted with the EZ DNA Methylation Kit (Zymo Research) according to the manufacturer's recommendations. Quantitative methylation measurement was carried out by matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry using the EpiTYPER Mass-ARRAY (Sequenom) as previously described (Ehrich *et al.*, 2005).

Quality control for the EpiTyper assay included double measurement of amplicon 2 containing six CpG sites in all samples, which showed high concordance. Testing of bisulfite conversion rates was applied using the bioconductor package MassArray (Thompson *et al.*, 2009). Samples showing a conversion rate <80% were excluded from analysis. Analysis of DNA methylation standards of 0%, 25%, 50%, and 100% yielded a good calibration line (Supplementary Figure S8 online). For person- and CpG-wise call rate, a threshold of 80% was applied.

Technical validation with the EpiTyper was conducted in 21 AL, 10 AN, and 24 NN samples, from whom DNA was still available.

### Reverse-transcriptase-qPCR

For technical validation of mRNA expression differences of selected genes qPCR was applied. The same RNA samples used for the Human HT-12 Expression BeadChip were reverse transcribed and subjected to qPCR using a StepOne Real-Time PCR System (Applied Biosystem, Carlsbad, CA) as described previously (Roth *et al.*, 2013). The specific primer sequences for the different genes can be found in Supplementary Table S10 online. Standard curves were generated for each primer set using serial dilutions of complementary DNA. Relative mRNA expression levels were normalized to expression of the housekeeping genes, *human acidic ribosomal protein (hARP)* and *ribosomal protein L38 (RP38)*. Both standardized measurements were used to compare 10 AL with 12 NN as well as 9 AL/AN pairs using the nonparametric Wilcoxon signed rank test and the paired *t*-test.

We found strong concordance between HT-12 expression measurement and qPCR except for *TBX6*, *CD248*, and *CCND1* (Supplementary Table S11 online). Moreover, the five most strongly altered mRNA expression levels on the HT-12 chip exhibited similar *P*-values in the qPCR with the same direction of expression differences between AL and NN.

### Statistical analysis

Quality of preprocessed data,  $\beta$ -values, with the pipeline described in the study by Touleimat and Tost (2012) was assessed by multidimensional scaling plots clustering samples by tissue and sex.  $\beta$ -Values represent the ratio of the intensity of the methylated bead type of the combined locus intensity and are intuitively interpreted. DNA methylation data were normalized within and between chips using quantile normalization.

In addition, we used two standard DNAs from a control sample (blood, epidermal sheet) for assessing the experiment's reliability. Pearson correlation across all CpGs was high ( $r > 0.98$ ). Finally,  $\beta$ -values of the replicated sample were averaged for differential DNA methylation analysis assessed using median regression adjusted for age and sex implemented in the quantreg package (Koenker, 2012). As the biological impact of small changes in DNA methylation on gene expression is unknown, we decided to use a threshold of 10% median methylation difference between sample groups in order to assure functional relevance. For multiple testing adjustment, the Bonferroni or false discovery rate method (Benjamini and Hochberg, 1995) was applied.

For expression analysis, the raw data were exported from the Illumina "GenomeStudio" Software to R. The data were converted into logarithmic scores and normalized using the quantiles method (Du *et al.*, 2008). Differences in expression levels between cases and controls were compared using linear regression models that were adjusted for age and sex.

For comparison of DNA methylation and expression data within the same individual, the *t*-test for paired samples was applied.

Functional integration was assessed by *in-cis* correlation of significant DMS and DETs within a 200-kb interval between probes using thresholds of spearman correlation  $|r| > 0.5$ ,  $P < 0.01$ . For *in-trans* correlation of significant DMS and DETs, we required a more stringent rank correlation of  $|r| > 0.8$  and considered only significantly differentially expressed genes below a Bonferroni threshold of  $1.5 \times 10^{-5}$ .

Functional enrichment analyses were performed with DAVID (Huang da *et al.*, 2009a, b) using the following settings: uploaded gene lists displayed the official gene symbol; annotations were limited to *Homo sapiens*; DAVID default *Homo sapiens* whole-genome background and pre-built Illumina HumanHT-12\_V3 array background were used for clustering of DMS and DET gene annotations. We display Benjamini-Hochberg corrected *P*-values ( $P_{BH}$ ).

### CONFLICT OF INTEREST

The authors state no conflict of interest.

### ACKNOWLEDGMENTS

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### SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/jid>

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## SUPPLEMENTARY MATERIAL

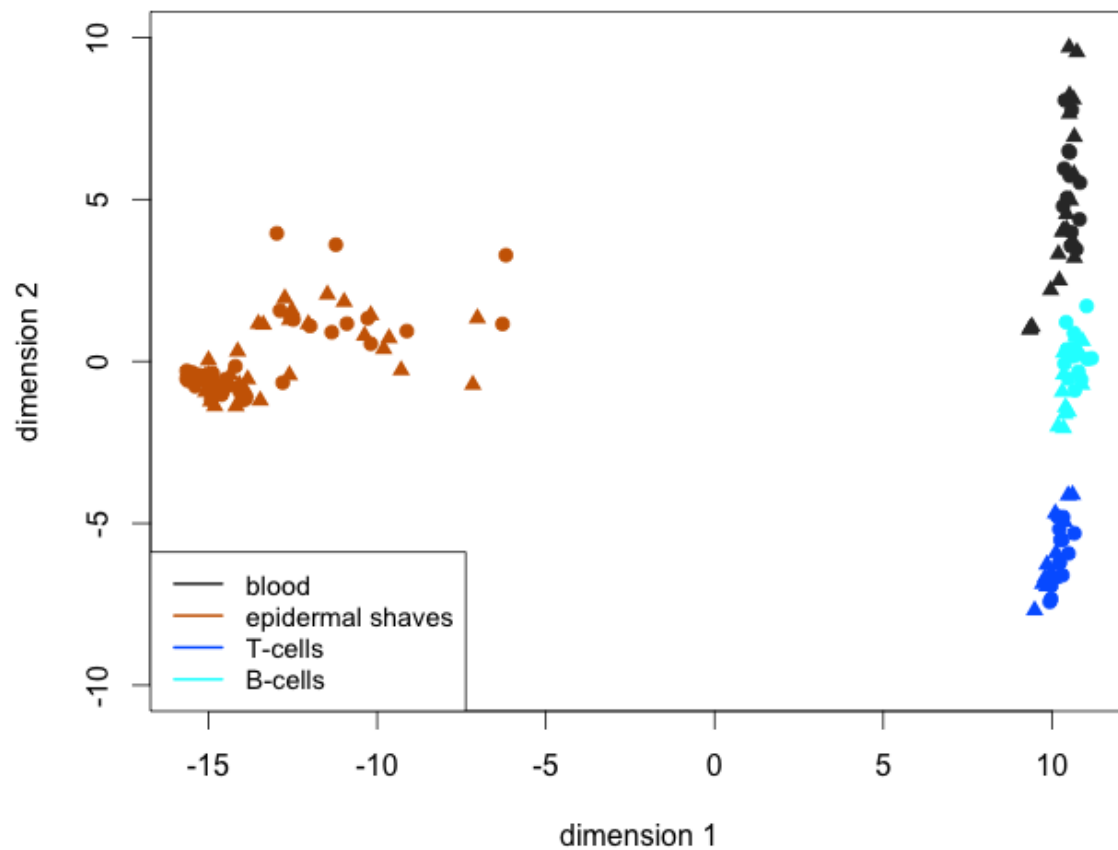
### **An integrated epigenetic and transcriptomic analysis reveals distinct tissue-specific patterns of DNA methylation associated with atopic dermatitis**

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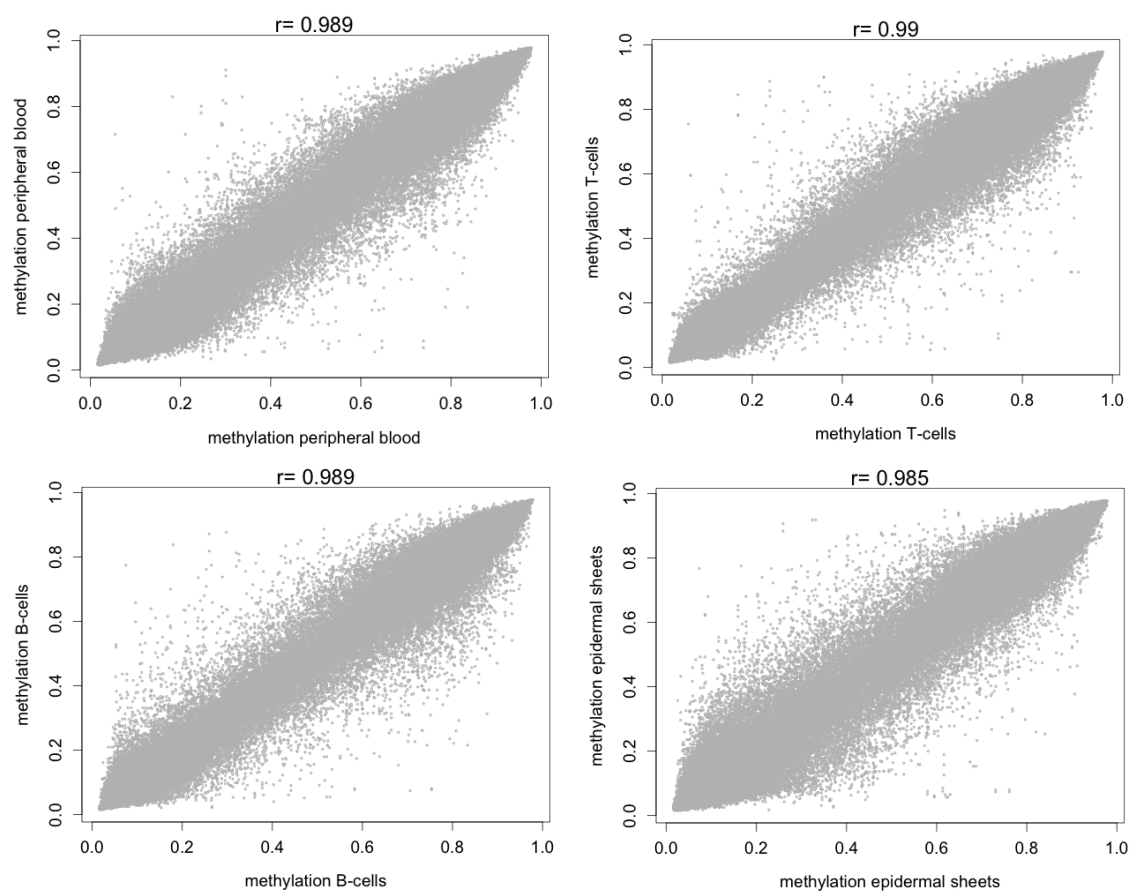
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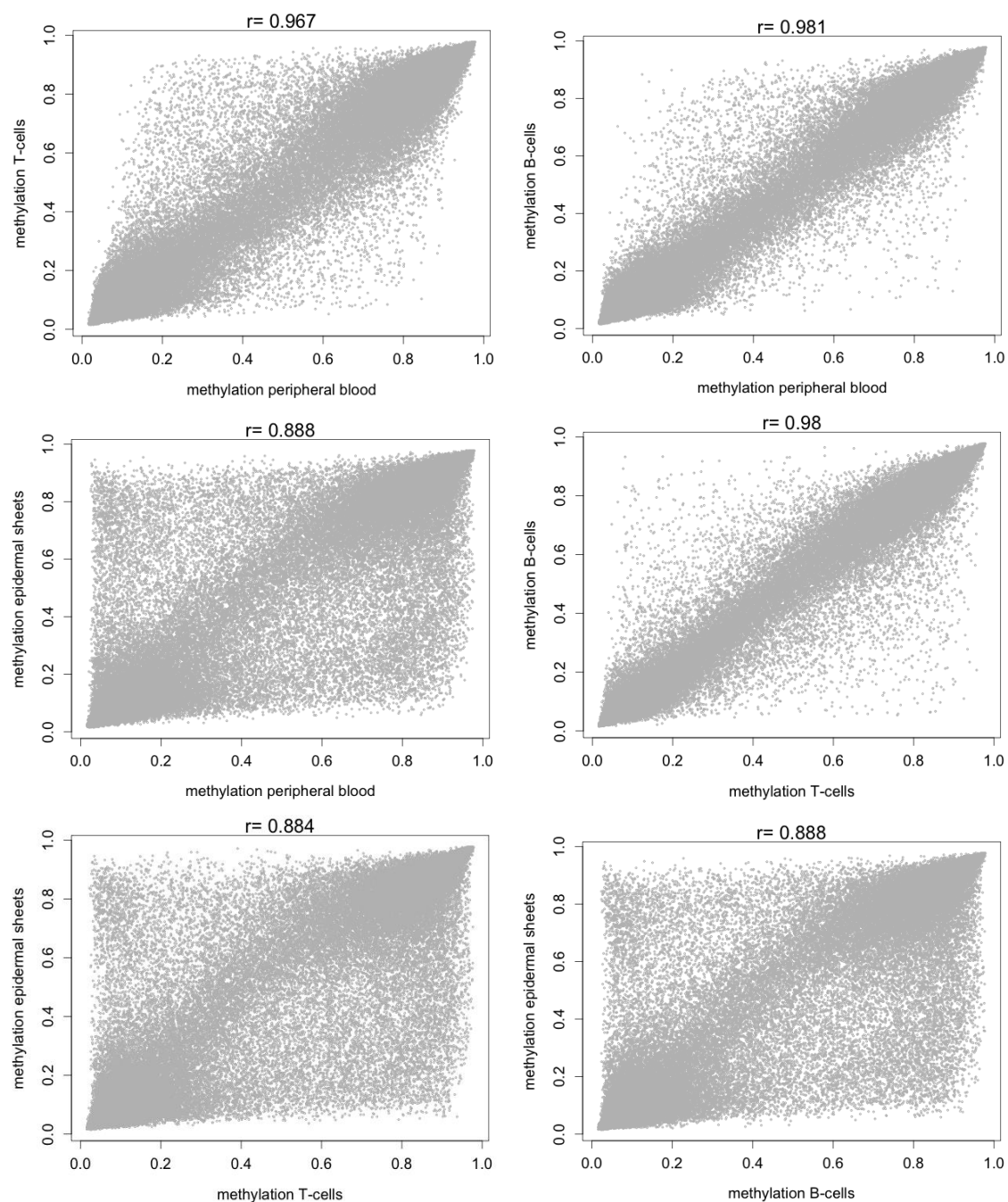
**Supplementary Figure S1:** Principal Component Analysis (PCA) of 25,648 autosomal CpG sites in the entire study cohort. The figure shows a complete separation of blood cells (whole blood, T-cells, B-cells) from epidermal tissues as well as a pronounced subclustering of the different blood cells. Females are symbolized by solid circles and males by triangles.



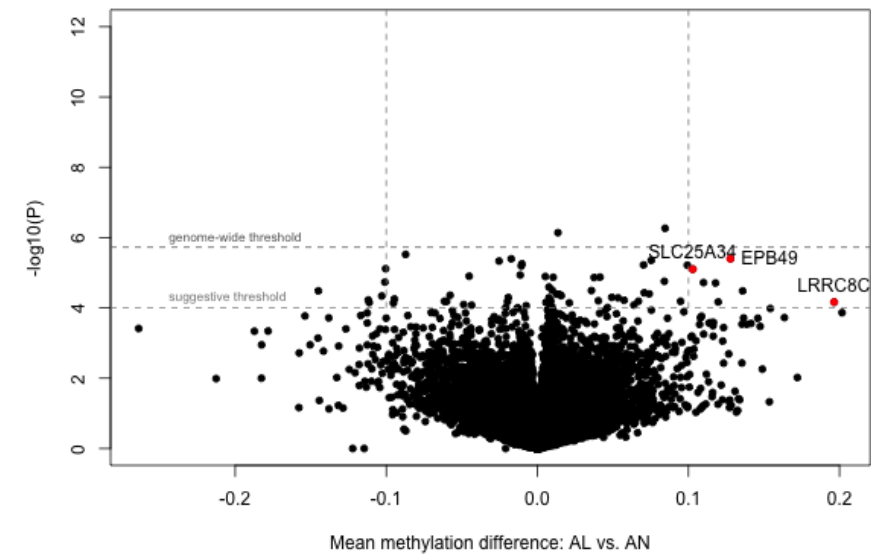
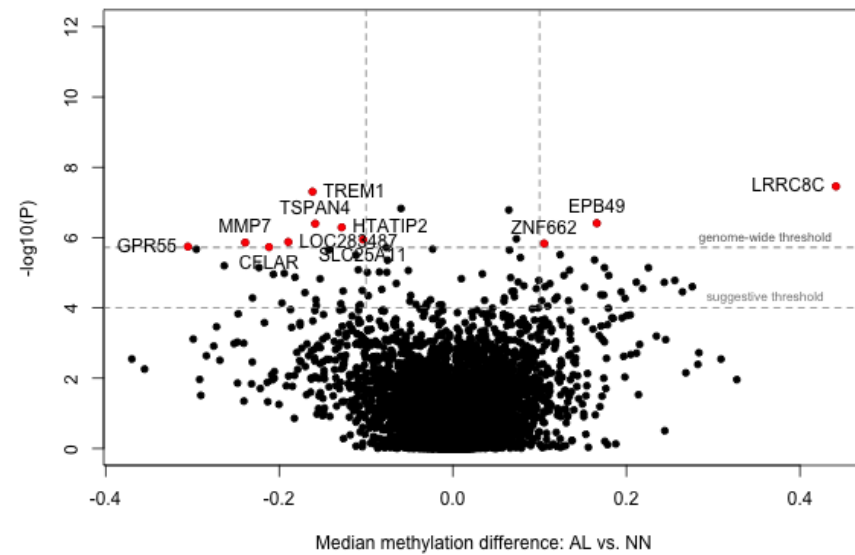
**Supplementary Figure S2:** Interindividual correlation of all CpG-sites within the same tissue of 2 representative cases-control pairs matched for age and sex. Each CpG site of each individual is plotted against each CpG site of all other individuals.



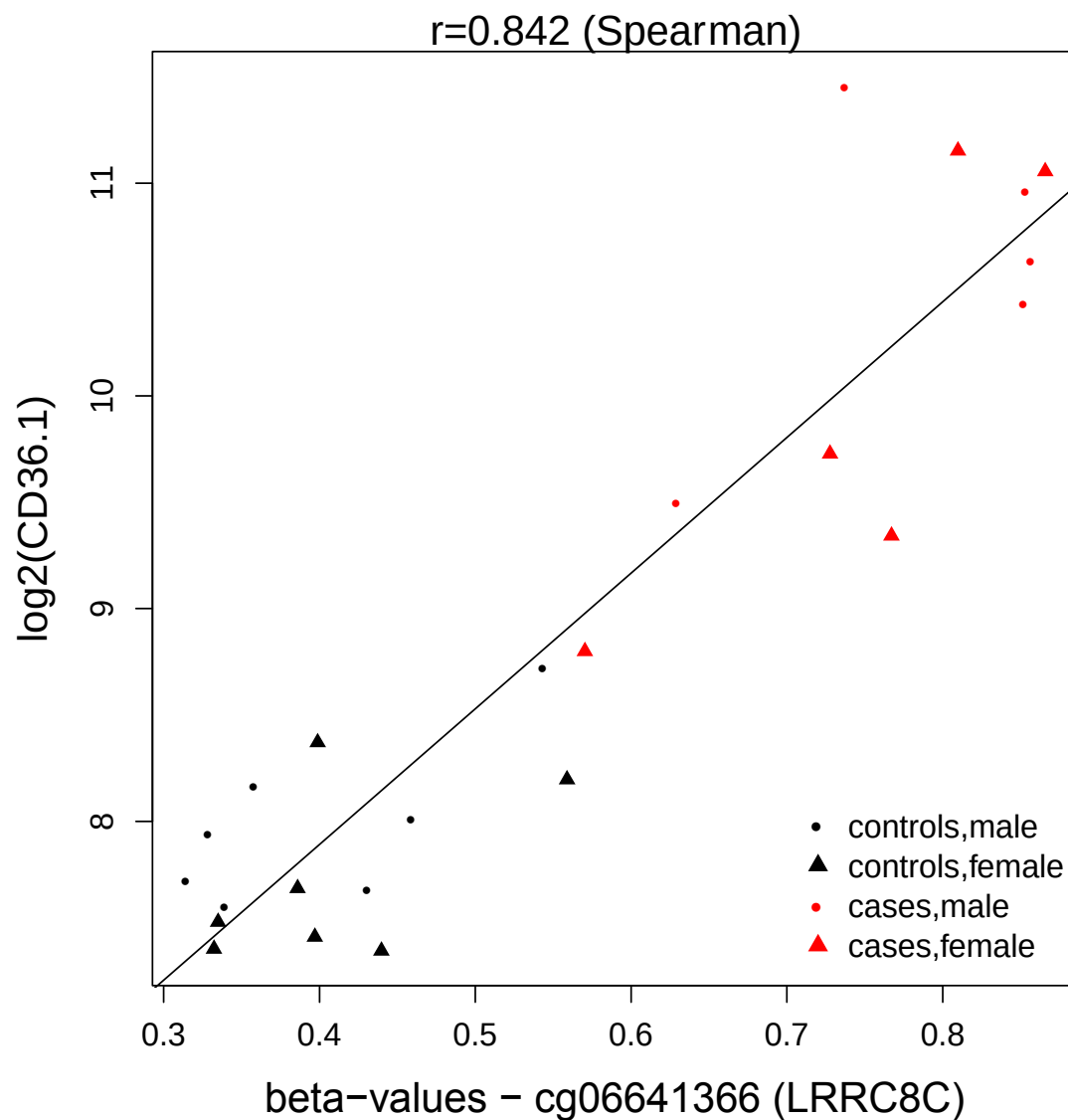
**Supplementary Figure S3:** Intraindividual correlation of all CpG-sites between tissues of 2 representative cases-control pairs matched for age and sex .



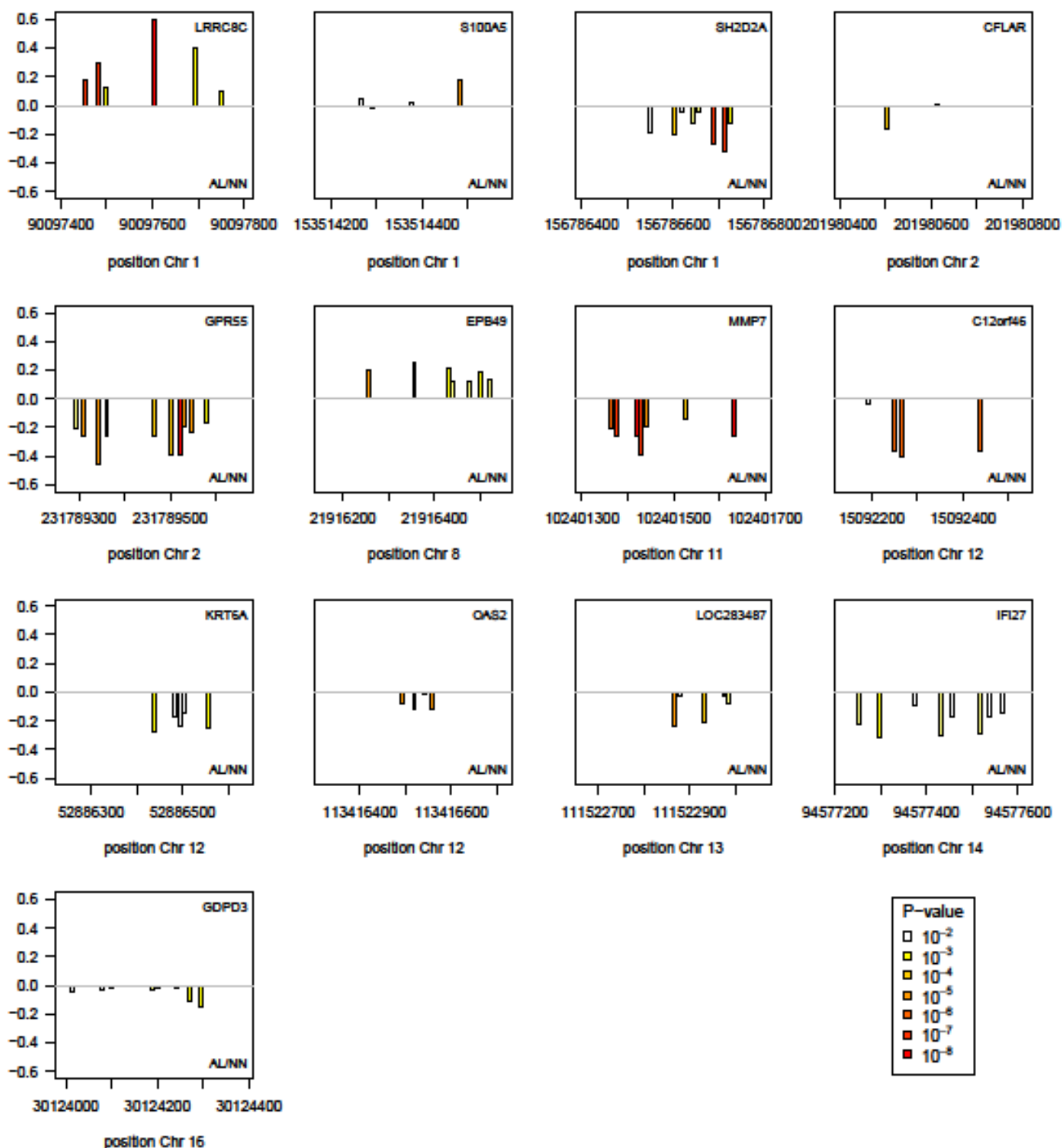
**Supplementary Figure S4:** Volcano plot of  $-\log_{10}(\text{P-value})$  against methylation differences of AL vs. NN (left) and AL vs. AN (right). 11 genome-wide significant differentially methylated CpG sites could be detected with  $|\Delta\beta| > 0.1$  in AL vs. NN. Three differentially methylated CpG sites in AL vs. AN showed suggestive significant results, however only *LRRC8C* and *EPB49* could be technically validated. Genome-wide and suggestive significant CpGs are indicated in red.



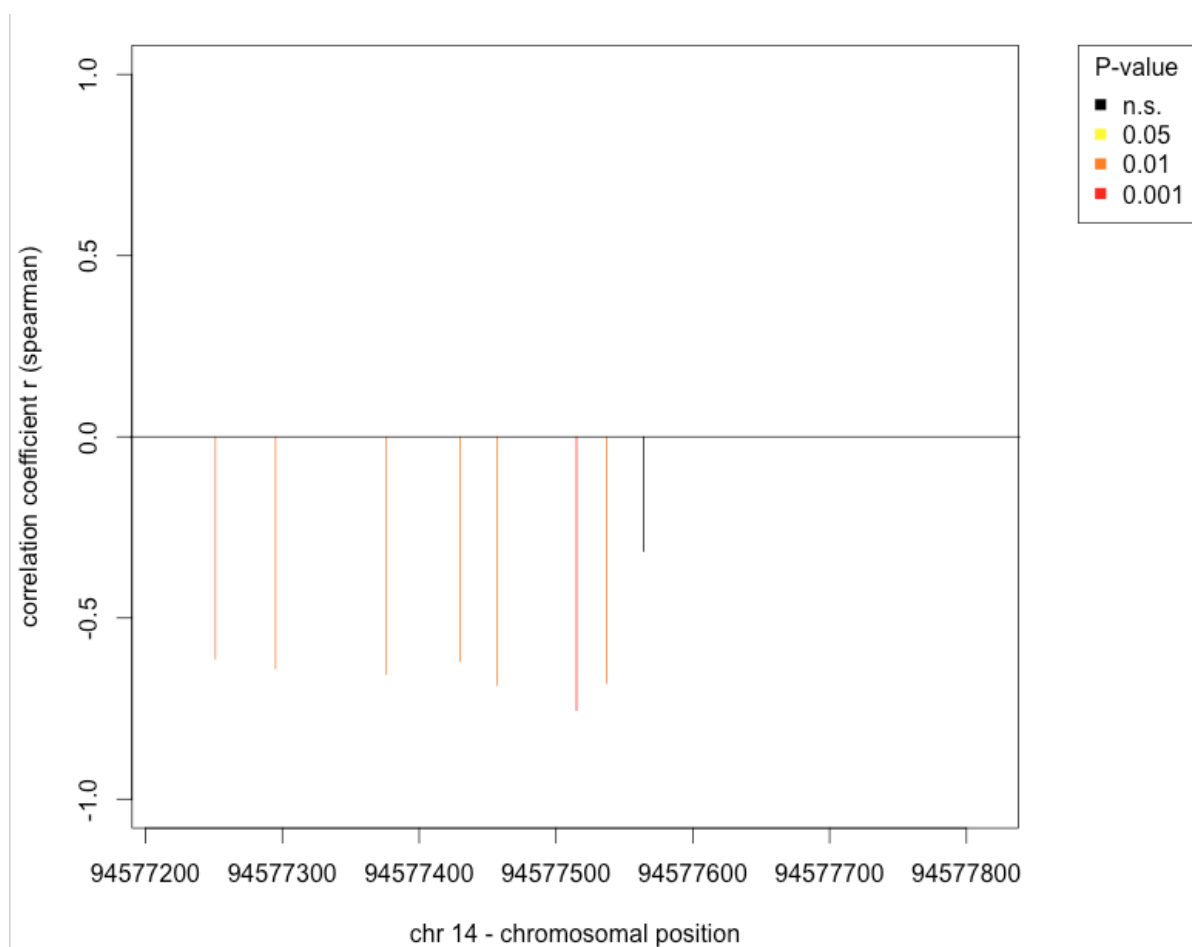
**Supplementary Figure S5:** Correlation of CpG site cg06641366 (*LRRC8C*, 1p22.2) with in trans expression levels of *CD36* (7q21.11). Displayed are CpG  $\beta$ -values on the X-axis vs.  $\log_2$  mRNA-expression levels on the Y-axis. AD cases are colored in red and controls in black. Females are symbolized by solid circles and males by triangles.



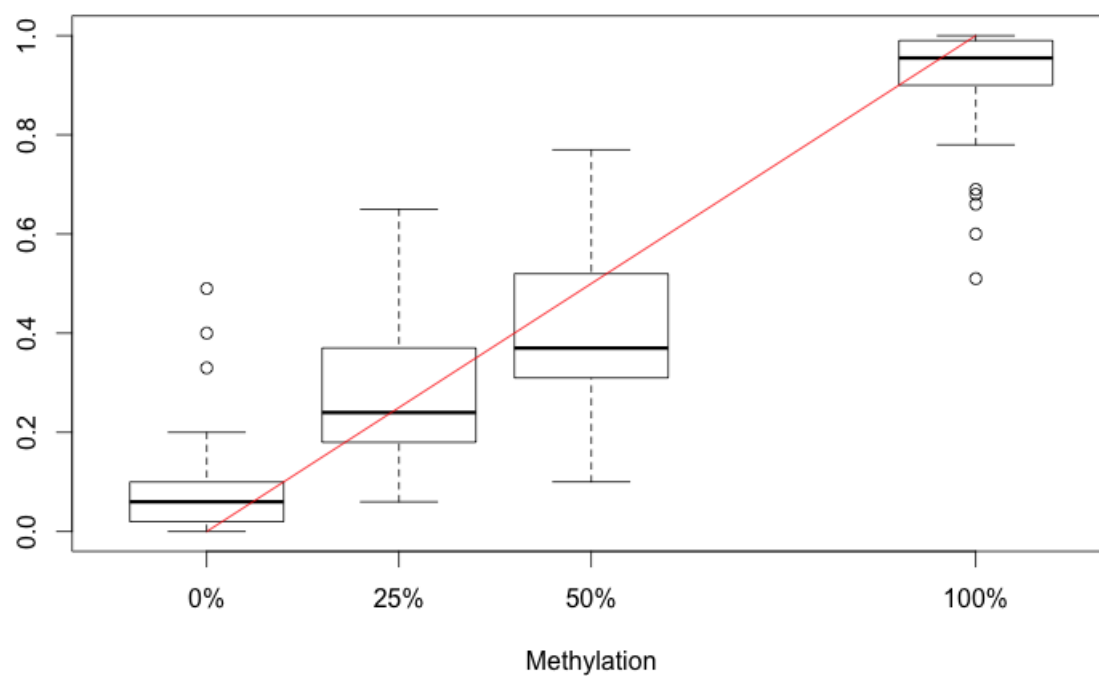
**Supplementary Figure S6:** Fine mapping of validated DMS from methylation and correlation analysis within AL/NN. Each bar represents a single Cpg site, with the bar height indicating the methylation difference in AL when compared to NN, and the bar colour indicating the P value for association with AD. The x axis shows the chromosomal position.



**Supplementary Figure S7:** Correlation of *IFI27* CpG methylation from the EpiTyper analysis with *IFI27* mRNA expression from the RT qPCR approach. Color code reflects strength of association and line length indicate strength of correlation.



**Supplementary Figure S8:** Calibration line of standard DNA with 0%, 25%, 50% and 100% methylation.



**Supplementary Table S1:** Differentially methylated sites (DMS) with  $P < 0.001$  and a median methylation difference  $|\Delta\beta| > 0.10$  in AL/NN, AN/NN and AL/AN analysis. Significantly enriched (P Benjamini & Hochberg  $< 0.05$ ) GO-terms are indicated. Enrichment analysis was performed with DAVID (Huang da et al., 2009a, b).

| AL vs. NN  |     |               |        |              |                   |                       |                                                                     |
|------------|-----|---------------|--------|--------------|-------------------|-----------------------|---------------------------------------------------------------------|
| CpG ID     | Chr | Position hg19 | Gene   | CpG-location | Median difference | P-value               | GO-term                                                             |
| cg18212039 | 1   | 26346812      | EXTL1  |              | 0.103             | $7.51 \times 10^{-4}$ | -                                                                   |
| cg21093060 | 1   | 32644693      | TXLNA  | CGI N Shore  | 0.183             | $1.91 \times 10^{-4}$ | -                                                                   |
| cg09914444 | 1   | 46972183      | DMBX1  |              | -0.272            | $3.44 \times 10^{-4}$ | -                                                                   |
| cg06641366 | 1   | 90097604      | LRRC8C | CGI N Shore  | 0.441             | $3.49 \times 10^{-8}$ | -                                                                   |
| cg22718139 | 1   | 120311439     | HMGCS2 |              | 0.175             | $9.28 \times 10^{-4}$ | -                                                                   |
| cg08823182 | 1   | 153514482     | S100A5 |              | 0.225             | $7.19 \times 10^{-6}$ | -                                                                   |
| cg00626119 | 1   | 156785288     | NTRK1  | CGI S Shore  | -0.110            | 0.0010                | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg20839149 | 1   | 156786601     | SH2D2A | CGI S Shelf  | -0.296            | $2.14 \times 10^{-6}$ | -                                                                   |
| cg12499211 | 1   | 156786643     | SH2D2A | CGI S Shelf  | -0.223            | $7.14 \times 10^{-6}$ | -                                                                   |
| cg10636246 | 1   | 159046973     | AIM2   |              | -0.197            | $7.27 \times 10^{-5}$ | -                                                                   |
| cg02694395 | 1   | 171283893     | FMO4   |              | 0.119             | $9.02 \times 10^{-4}$ | -                                                                   |
| cg10861599 | 1   | 173176523     | TNFSF4 |              | -0.157            | $8.51 \times 10^{-5}$ | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg26203861 | 1   | 201858661     | TMEM58 |              | 0.118             | $5.79 \times 10^{-5}$ | -                                                                   |
| cg23901896 | 1   | 201976446     | ELF3   |              | 0.124             | $3.06 \times 10^{-6}$ | -                                                                   |
| cg23829949 | 1   | 244214679     | ZNF238 | CGI S Shore  | 0.244             | $1.88 \times 10^{-5}$ | -                                                                   |
| cg27223827 | 2   | 106054920     | FHL2   |              | 0.219             | $2.82 \times 10^{-5}$ | -                                                                   |
| cg10635061 | 2   | 106055006     | FHL2   |              | 0.256             | $1.65 \times 10^{-5}$ | -                                                                   |
| cg18119407 | 2   | 201980504     | CFLAR  | CGI N Shore  | -0.212            | $1.86 \times 10^{-6}$ | -                                                                   |
| cg04098585 | 2   | 204571215     | CD28   |              | -0.130            | $1.16 \times 10^{-4}$ | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg18328334 | 2   | 218808652     | TNS1   |              | 0.194             | $3.51 \times 10^{-5}$ | -                                                                   |

| AL vs. NN  |     |               |          |              |                   |                       |                                                                     |
|------------|-----|---------------|----------|--------------|-------------------|-----------------------|---------------------------------------------------------------------|
| CpG ID     | Chr | Position hg19 | Gene     | CpG-location | Median difference | P-value               | GO-term                                                             |
| cg20287234 | 2   | 231789465     | GPR55    |              | -0.305            | 1.80x10 <sup>-6</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg01447817 | 2   | 241630251     | AQP12A   |              | -0.112            | 3.11x10 <sup>-6</sup> | -                                                                   |
| cg20916523 | 3   | 10184584      | VHL      | CGI S Shore  | -0.217            | 2.63x10 <sup>-4</sup> | -                                                                   |
| cg05446471 | 3   | 13522740      | HDAC11   | CGI S Shore  | 0.178             | 3.01x10 <sup>-4</sup> | -                                                                   |
| cg12413566 | 3   | 39235366      | CMYA1    |              | -0.110            | 5.47x10 <sup>-4</sup> | -                                                                   |
| cg22917487 | 3   | 39322103      | CX3CR1   |              | 0.174             | 4.30x10 <sup>-5</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg26523005 | 3   | 42947267      | ZNF662   | CGI N Shore  | 0.105             | 1.47x10 <sup>-6</sup> | -                                                                   |
| cg12069042 | 3   | 48466700      | PLXNB1   | CGI N Shelf  | 0.106             | 2.08x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg10135708 | 3   | 48601117      | UCN2     |              | 0.110             | 2.79x10 <sup>-4</sup> | -                                                                   |
| cg13585240 | 3   | 48959375      | ARIH2    | CGI S Shelf  | -0.108            | 8.79x10 <sup>-5</sup> | -                                                                   |
| cg20804821 | 3   | 51988454      | GPR62    |              | -0.126            | 3.31x10 <sup>-5</sup> | -                                                                   |
| cg18328933 | 3   | 52008538      | ABHD14A  | CGI N Shore  | 0.106             | 2.50x10 <sup>-5</sup> | -                                                                   |
| cg20114394 | 3   | 120170441     | FSTL1    | CG Island    | 0.153             | 2.38x10 <sup>-4</sup> | -                                                                   |
| cg10523671 | 3   | 121612956     | SLC15A2  |              | 0.179             | 1.02x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg05781767 | 3   | 127347362     | PODXL2   | CGI N Shore  | 0.133             | 6.22x10 <sup>-5</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg08124030 | 3   | 149095283     | TM4SF1   |              | -0.161            | 2.35x10 <sup>-4</sup> | -                                                                   |
| cg17795586 | 3   | 151047735     | P2RY13   |              | 0.135             | 5.30x10 <sup>-4</sup> | -                                                                   |
| cg12894629 | 3   | 195942717     | OSTalpha |              | 0.172             | 7.78x10 <sup>-4</sup> | -                                                                   |
| cg22672790 | 5   | 161112787     | GABRA6   |              | -0.105            | 9.14x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg03355526 | 5   | 178368415     | ZNF454   | CG Island    | 0.136             | 7.94x10 <sup>-4</sup> | -                                                                   |
| cg22572779 | 6   | 10434761      | MGC40222 |              | -0.182            | 1.34x10 <sup>-5</sup> | -                                                                   |

| AL vs. NN  |     |               |          |              |                   |                       |         |
|------------|-----|---------------|----------|--------------|-------------------|-----------------------|---------|
| CpG ID     | Chr | Position hg19 | Gene     | CpG-location | Median difference | P-value               | GO-term |
| cg01980222 | 6   | 41130917      | TREM2    |              | -0.107            | 8.15x10 <sup>-5</sup> | -       |
| cg06196379 | 6   | 41254885      | TREM1    |              | -0.162            | 4.93x10 <sup>-8</sup> | -       |
| cg05345286 | 6   | 41606641      | MDFI     | CG Island    | -0.137            | 9.04x10 <sup>-4</sup> | -       |
| cg12368241 | 6   | 64355267      | PHF3     |              | -0.106            | 2.58x10 <sup>-4</sup> | -       |
| cg19339848 | 6   | 74170937      | MTO1     | CGI N Shore  | -0.150            | 7.74x10 <sup>-4</sup> | -       |
| cg14289461 | 6   | 112575929     | LAMA4    | CGI S Shore  | 0.102             | 6.25x10 <sup>-5</sup> | -       |
| cg05564266 | 6   | 118973597     | C6orf204 | CGI S Shore  | 0.265             | 3.50x10 <sup>-5</sup> | -       |
| cg15945754 | 6   | 118973695     | C6orf204 | CGI S Shore  | 0.198             | 5.34x10 <sup>-5</sup> | -       |
| cg10044101 | 6   | 133084289     | VNN2     |              | 0.180             | 1.19x10 <sup>-5</sup> | -       |
| cg21129531 | 7   | 127670703     | LRRC4    | CGI N Shore  | 0.245             | 8.03x10 <sup>-4</sup> | -       |
| cg19594666 | 7   | 127881280     | LEP      | CG Island    | 0.106             | 2.65x10 <sup>-4</sup> | -       |
| cg13120814 | 7   | 134832770     | FLJ11000 |              | -0.127            | 3.34x10 <sup>-4</sup> | -       |
| cg13434842 | 8   | 11567896      | GATA4    | CGI S Shore  | 0.101             | 4.60x10 <sup>-4</sup> | -       |
| cg14706739 | 8   | 21916355      | EPB49    | CGI S Shore  | 0.166             | 3.90x10 <sup>-7</sup> | -       |
| cg02067021 | 8   | 66934027      | DNAJC5B  |              | 0.113             | 4.71x10 <sup>-4</sup> | -       |
| cg22199118 | 8   | 69350927      | C8orf34  |              | -0.149            | 1.55x10 <sup>-4</sup> | -       |
| cg18939260 | 8   | 125741346     | MTSS1    | CGI S Shore  | 0.200             | 1.65x10 <sup>-4</sup> | -       |
| cg13784855 | 8   | 128806938     | PVT1     | CGI S Shore  | -0.231            | 5.20x10 <sup>-5</sup> | -       |
| cg15983520 | 8   | 145729106     | GPT      | CGI N Shore  | 0.126             | 3.10x10 <sup>-4</sup> | -       |
| cg04675937 | 9   | 22005419      | CDKN2B   |              | 0.109             |                       |         |

| AL vs. NN  |     |               |           |              |                   |                       |                                                                     |
|------------|-----|---------------|-----------|--------------|-------------------|-----------------------|---------------------------------------------------------------------|
| CpG ID     | Chr | Position hg19 | Gene      | CpG-location | Median difference | P-value               | GO-term                                                             |
| cg23587532 | 11  | 790669        | BM88      | CGI N Shore  | 0.112             | 2.04x10 <sup>-5</sup> | -                                                                   |
| cg11173246 | 11  | 841376        | TSPAN4    | CGI N Shore  | -0.159            | 4.02x10 <sup>-7</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg26808784 | 11  | 2017483       | H19       | CG Island    | 0.169             | 6.15x10 <sup>-4</sup> | -                                                                   |
| cg25336198 | 11  | 2182618       | INS       |              | -0.104            | 3.19x10 <sup>-5</sup> | -                                                                   |
| cg18788940 | 11  | 20385085      | HTATIP2   | CGI N Shore  | -0.128            | 5.10x10 <sup>-7</sup> | -                                                                   |
| cg03245641 | 11  | 64703415      | GPHA2     |              | 0.205             | 1.59x10 <sup>-4</sup> | -                                                                   |
| cg00350296 | 11  | 66084841      | CD248     | CGI S Shore  | 0.195             | 1.93x10 <sup>-4</sup> | -                                                                   |
| cg06539449 | 11  | 69461008      | CCND1     | CGI N Shore  | 0.106             | 3.26x10 <sup>-4</sup> | -                                                                   |
| cg03699566 | 11  | 71900652      | FOLR1     |              | 0.276             | 2.49x10 <sup>-5</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg02254407 | 11  | 73357159      | PLEKHB1   |              | 0.114             | 4.00x10 <sup>-4</sup> | -                                                                   |
| cg25511807 | 11  | 102401438     | MMP7      |              | -0.239            | 1.38x10 <sup>-6</sup> | -                                                                   |
| cg21633698 | 11  | 119294534     | THY1      |              | 0.124             | 2.17x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg24505122 | 12  | 1726292       | WNT5B     |              | 0.102             | 2.24x10 <sup>-4</sup> | -                                                                   |
| cg13435792 | 12  | 15092434      | C12orf46  |              | -0.263            | 6.30x10 <sup>-6</sup> | -                                                                   |
| cg19220825 | 12  | 50353951      | AQP5      | CGI N Shore  | -0.116            | 3.91x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg00213044 | 12  | 52886438      | KRT6C     |              | -0.119            | 2.97x10 <sup>-4</sup> | -                                                                   |
| cg23696712 | 12  | 53228141      | KRT6L     |              | 0.152             | 2.57x10 <sup>-5</sup> | -                                                                   |
| cg12962778 | 12  | 54778312      | ZNF385    |              | 0.101             | 3.50x10 <sup>-4</sup> | -                                                                   |
| cg02192520 | 12  | 56114155      | RDH5      | CGI S Shelf  | 0.235             | 6.37x10 <sup>-4</sup> | -                                                                   |
| cg00294382 | 12  | 56732721      | IL23A     |              | -0.129            | 0.0010                | -                                                                   |
| cg16521028 | 12  | 75874414      | GLIPR1    |              | -0.247            | 1.48x10 <sup>-4</sup> | -                                                                   |
| cg04123409 | 12  | 113841617     | SDS       |              | -0.107            | 5.97x10 <sup>-4</sup> | -                                                                   |
| cg22131172 | 13  | 111522865     | LOC283487 |              | -0.190            | 1.33x10 <sup>-6</sup> | -                                                                   |

| AL vs. NN  |     |               |           |              |                   |                       |                                                                     |
|------------|-----|---------------|-----------|--------------|-------------------|-----------------------|---------------------------------------------------------------------|
| CpG ID     | Chr | Position hg19 | Gene      | CpG-location | Median difference | P-value               | GO-term                                                             |
| cg03623878 | 13  | 113655560     | MCF2L     | CGI N Shore  | 0.171             | 3.29x10 <sup>-4</sup> | -                                                                   |
| cg11668844 | 13  | 113655622     | MCF2L     | CGI N Shore  | 0.211             | 1.86x10 <sup>-5</sup> | -                                                                   |
| cg18403361 | 14  | 38725750      | CLEC14A   | CGI S Shore  | -0.123            | 5.23x10 <sup>-4</sup> | -                                                                   |
| cg15787039 | 15  | 32934185      | SGNE1     |              | 0.135             | 3.79x10 <sup>-4</sup> | -                                                                   |
| cg22340747 | 15  | 45683210      | GATM      |              | 0.171             | 4.26x10 <sup>-5</sup> | -                                                                   |
| cg10805676 | 16  | 421990        | MRPL28    | CGI N Shore  | 0.110             | 3.01x10 <sup>-4</sup> | -                                                                   |
| cg03297731 | 16  | 30124293      | GDPD3     |              | -0.109            | 8.23x10 <sup>-6</sup> | -                                                                   |
| cg11403598 | 16  | 69374664      | COG8      | CGI S Shore  | -0.108            | 2.72x10 <sup>-4</sup> | -                                                                   |
| cg04958703 | 17  | 4844722       | SLC25A11  | CGI S Shore  | -0.103            | 1.13x10 <sup>-6</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg01472101 | 17  | 6983991       | CLEC10A   |              | -0.110            | 5.49x10 <sup>-4</sup> | -                                                                   |
| cg10801369 | 17  | 33417179      | RFFL      |              | -0.105            | 6.56x10 <sup>-4</sup> | -                                                                   |
| cg26499286 | 17  | 39472498      | KRTAP17-1 |              | -0.194            | 1.04x10 <sup>-5</sup> | -                                                                   |
| cg12866859 | 17  | 43224332      | HEXIM1    | CGI N Shore  | 0.109             | 0.0010                | -                                                                   |
| cg12910797 | 17  | 46651722      | HOXB3     | CGI N Shelf  | -0.299            | 7.71x10 <sup>-4</sup> | -                                                                   |
| cg01405107 | 17  | 46671635      | HOXB5     | CGI N Shore  | -0.176            | 2.64x10 <sup>-4</sup> | -                                                                   |
| cg04988978 | 17  | 56359578      | MPO       | CGI S Shelf  | -0.116            | 4.41x10 <sup>-4</sup> | -                                                                   |
| cg10275770 | 17  | 62084205      | ICAM2     |              | -0.186            | 3.60x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg06226384 | 17  | 64873351      | CACNG5    |              | -0.207            | 1.11x10 <sup>-5</sup> | -                                                                   |
| cg19147390 | 19  | 4911058       | UHRF1     | CGI S Shore  | -0.143            | 2.26x10 <sup>-6</sup> | -                                                                   |
| cg14156381 | 19  | 8212675       | FBN3      | CGI N Shore  | -0.100            | 8.59x10 <sup>-4</sup> | -                                                                   |
| cg24477567 | 19  | 11495295      | EPOR      | CGI S Shore  | 0.161             | 4.00x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg15746620 | 19  | 14785849      | EMR3      |              | -0.187            | 1.12x10 <sup>-4</sup> | -                                                                   |
| cg08379517 | 19  | 18509505      | LRRC25    |              | -0.248            | 9.42x10 <sup>-4</sup> | -                                                                   |

| AL vs. NN  |     |               |           |              |                   |                       |                                                                     |
|------------|-----|---------------|-----------|--------------|-------------------|-----------------------|---------------------------------------------------------------------|
| CpG ID     | Chr | Position hg19 | Gene      | CpG-location | Median difference | P-value               | GO-term                                                             |
| cg27461196 | 19  | 35630106      | FXYP1     | CGI N Shelf  | 0.136             | 1.16x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg21529807 | 19  | 42134478      | CEACAM4   |              | -0.132            | 5.13x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg15937958 | 19  | 42947133      | UNQ473    |              | -0.129            | 7.61x10 <sup>-5</sup> | -                                                                   |
| cg21491308 | 19  | 43892826      | TEX101    |              | -0.108            | 1.17x10 <sup>-4</sup> | -                                                                   |
| cg04833845 | 19  | 44286076      | KCNN4     |              | -0.159            | 1.19x10 <sup>-4</sup> | integral to plasma membrane (cc), intrinsic to plasma membrane (cc) |
| cg15361750 | 19  | 47839132      | GPR77     |              | -0.116            | 1.70x10 <sup>-4</sup> | -                                                                   |
| cg24012925 | 20  | 633418        | SRXN1     | CGI N Shore  | -0.123            | 6.61x10 <sup>-4</sup> | -                                                                   |
| cg01262913 | 21  | 38580486      | DSCR9     |              | -0.103            | 7.28x10 <sup>-4</sup> | -                                                                   |
| cg13265003 | 21  | 43919023      | SLC37A1   | CGI S Shore  | 0.135             | 8.46x10 <sup>-6</sup> | -                                                                   |
| cg05208878 | 22  | 22901596      | PRAME     | CG Island    | -0.123            | 6.16x10 <sup>-4</sup> | -                                                                   |
| cg10756887 | 22  | 24105692      | C22orf15  |              | 0.185             | 1.98x10 <sup>-4</sup> | -                                                                   |
| cg13351406 | 22  | 36031241      | LOC284912 |              | -0.109            | 2.09x10 <sup>-4</sup> | -                                                                   |
| cg09432376 | 22  | 36044226      | APOL6     |              | -0.158            | 5.84x10 <sup>-5</sup> | -                                                                   |
| cg06264060 | 22  | 41075007      | GPR24     |              | 0.163             | 4.33x10 <sup>-6</sup> | -                                                                   |
| cg26861460 | 22  | 44575455      | PARVG     |              | -0.153            | 1.49x10 <sup>-5</sup> | -                                                                   |
| AN vs. NN  |     |               |           |              |                   |                       |                                                                     |
| CpG ID     | Chr | Position hg19 | Gene      | CpG-location | Median difference | P-value               | GO-term                                                             |
| cg15703357 | 2   | 97171449      | NEURL3    | CGI N Shelf  | -0.107            | 1.26x10 <sup>-4</sup> | -                                                                   |
| cg19868730 | 3   | 119380012     | POPDC2    |              | -0.107            | 5.79x10 <sup>-4</sup> | -                                                                   |
| cg20950277 | 4   | 122085241     | TNIP3     |              | -0.166            | 6.83x10 <sup>-4</sup> | -                                                                   |
| cg01550148 | 5   | 134735544     | H2AFY     | CGI S Shore  | 0.107             | 8.81x10 <sup>-4</sup> | -                                                                   |
| cg13435792 | 12  | 15092434      | ERP27     |              | -0.200            | 8.02x10 <sup>-4</sup> | -                                                                   |
| cg14802310 | 12  | 49582599      | TUBA1A    | CG Island    | -0.105            | 7.07x10 <sup>-4</sup> | -                                                                   |

| AN vs. NN  |     |               |          |              |                   |                       |         |
|------------|-----|---------------|----------|--------------|-------------------|-----------------------|---------|
| CpG ID     | Chr | Position hg19 | Gene     | CpG-location | Median difference | P-value               | GO-term |
| cg13960126 | 19  | 6462999       | CRB3     | CGI N Shore  | -0.150            | 7.08x10 <sup>-4</sup> | -       |
| AL vs AN   |     |               |          |              |                   |                       |         |
| CpG ID     | Chr | Position hg19 | Gene     | CpG-location | Median difference | P-value               | GO-term |
| cg08840010 | 1   | 8000314       | TNFRSF9  | CGI N Shelf  | -0.104            | 3.95x10 <sup>-4</sup> | -       |
| cg15616400 | 1   | 16062894      | SLC25A34 |              | 0.103             | 7.91x10 <sup>-6</sup> | -       |
| cg06641366 | 1   | 90097604      | LRRC8C   | CGI N Shore  | 0.196             | 6.83x10 <sup>-5</sup> | -       |
| cg22718139 | 1   | 120311439     | HMGCS2   |              | 0.110             | 1.91x10 <sup>-5</sup> | -       |
| cg25082710 | 1   | 152880108     | IVL      |              | 0.117             | 2.56x10 <sup>-4</sup> | -       |
| cg16139316 | 1   | 153330758     | S100A9   |              | -0.187            | 4.61x10 <sup>-4</sup> | -       |
| cg08823182 | 1   | 153514482     | S100A5   |              | 0.107             | 2.96x10 <sup>-4</sup> | -       |
| cg10636246 | 1   | 159046973     | AIM2     |              | -0.154            | 1.70x10 <sup>-4</sup> | -       |
| cg23829949 | 1   | 244214679     | ZNF238   | CGI S Shore  | 0.109             | 1.72x10 <sup>-4</sup> | -       |
| cg27223827 | 2   | 106054920     | FHL2     |              | 0.123             | 8.80x10 <sup>-4</sup> | -       |
| cg10635061 | 2   | 106055006     | FHL2     |              | 0.154             | 1.04x10 <sup>-4</sup> | -       |
| cg09499849 | 2   | 158695158     | ACVR1    |              | -0.103            | 4.58x10 <sup>-5</sup> | -       |
| cg14399060 | 2   | 177015070     | HOXD4    | CG Island    | -0.264            | 3.85x10 <sup>-4</sup> | -       |
| cg26259363 | 2   | 220282281     | DES      | CGI N Shore  | 0.164             | 1.88x10 <sup>-4</sup> | -       |
| cg22917487 | 3   | 39322103      | CX3CR1   |              | 0.120             | 6.76x10 <sup>-5</sup> | -       |
| cg10523671 | 3   | 121612956     | SLC15A2  |              | 0.115             | 2.63x10 <sup>-4</sup> | -       |
| cg24315815 | 3   | 145969579     | PLSCR4   | CGI S Shore  | -0.100            | 1.96x10 <sup>-4</sup> | -       |
| cg15957394 | 4   | 7941823       | AFAP1    | CG Island    | -0.107            | 5.41x10 <sup>-4</sup> | -       |
| cg24999727 | 4   | 88243818      | HSD17B13 |              | 0.135             | 2.91x10 <sup>-4</sup> | -       |
| cg08241785 | 5   | 75919281      | F2RL2    |              | -0.113            | 1.39x10 <sup>-4</sup> | -       |
| cg13603171 | 6   | 132723164     | MOXD1    | CGI S Shore  | -0.109            | 6.32x10 <sup>-4</sup> | -       |
| cg15760840 | 7   | 27225222      | HOXA11   | CG Island    | -0.145            | 7.22x10 <sup>-4</sup> | -       |
| cg09914773 | 7   | 99383224      | CYP3A4   |              | 0.147             | 3.35x10 <sup>-4</sup> | -       |
| cg14646244 | 7   | 107300287     | SLC26A4  | CGI N Shore  | -0.145            | 3.27x10 <sup>-5</sup> | -       |

| AL vs AN   |     |               |           |              |                   |                       |         |
|------------|-----|---------------|-----------|--------------|-------------------|-----------------------|---------|
| CpG ID     | Chr | Position hg19 | Gene      | CpG-location | Median difference | P-value               | GO-term |
| cg14706739 | 8   | 21916355      | EPB49     | CGI S Shore  | 0.128             | $3.99 \times 10^{-6}$ | -       |
| cg00176210 | 8   | 41654967      | ANK1      | CG Island    | 0.123             | $3.63 \times 10^{-4}$ | -       |
| cg25538571 | 8   | 49502710      |           |              | -0.178            | $4.56 \times 10^{-4}$ | -       |
| cg18939260 | 8   | 125741346     | MTSS1     | CGI S Shore  | 0.118             | $1.95 \times 10^{-5}$ | -       |
| cg13784855 | 8   | 128806938     | PVT1      | CGI S Shore  | -0.111            | $7.05 \times 10^{-5}$ | -       |
| cg00620024 | 9   | 127952891     | PPP6C     | CGI S Shore  | 0.114             | $2.69 \times 10^{-4}$ | -       |
| cg13022129 | 9   | 131683862     | PHYHD1    |              | 0.202             | $1.37 \times 10^{-4}$ | -       |
| cg20162599 | 11  | 63990138      | FERMT3    | CGI N Shelf  | 0.102             | $6.30 \times 10^{-4}$ | -       |
| cg03699566 | 11  | 71900652      | FOLR1     |              | 0.136             | $3.28 \times 10^{-5}$ | -       |
| cg15227610 | 11  | 111782016     | CRYAB     |              | 0.136             | $1.93 \times 10^{-4}$ | -       |
| cg26066361 | 12  | 10282621      | CLEC7A    |              | -0.101            | $4.14 \times 10^{-4}$ | -       |
| cg04228042 | 12  | 14996527      | ART4      |              | 0.110             | $5.58 \times 10^{-4}$ | -       |
| cg05164634 | 12  | 49366538      | WNT10B    | CGI S Shelf  | -0.101            | $1.84 \times 10^{-5}$ | -       |
| cg18982568 | 12  | 53097169      | KRT77     |              | 0.116             | $3.22 \times 10^{-4}$ | -       |
| cg22131172 | 13  | 111522865     | C13orf29  |              | -0.100            | $7.68 \times 10^{-6}$ | -       |
| cg11668844 | 13  | 113655622     | MCF2L     | CGI N Shore  | 0.146             | $1.97 \times 10^{-4}$ | -       |
| cg00509616 | 15  | 57884415      | GCOM1     | CGI S Shore  | -0.113            | $2.69 \times 10^{-4}$ | -       |
| cg26499286 | 17  | 39472498      | KRTAP17-1 |              | -0.112            | $5.95 \times 10^{-5}$ | -       |
| cg00063144 | 17  | 39554055      | KRT31     |              | 0.141             | $2.77 \times 10^{-4}$ | -       |
| cg24477567 | 19  | 11495295      | EPOR      | CGI S Shore  | 0.102             | $6.79 \times 10^{-4}$ | -       |
| cg11398517 | 20  | 42355625      | GTSF1L    |              | -0.117            | $1.64 \times 10^{-4}$ | -       |
| cg02643667 | 21  | 43786699      | TFF1      |              | 0.108             | $1.92 \times 10^{-4}$ | -       |
| cg23185262 | 21  | 45137544      | PDXK      | CGI N Shore  | 0.105             | $8.58 \times 10^{-4}$ | -       |

**Supplementary Table S2:** EpiTYPER MassArray validation of differentially methylated sites in lesional (AL) and control (NN), lesional (AL) and non lesional (AN) as well as non-lesional (AN) and control (NN) epidermal samples were validated and fine mapped using the EpiTYPER MassARRAY technology.

| AL vs. NN |     |         |                                                            |                       |                   |                      |                   |
|-----------|-----|---------|------------------------------------------------------------|-----------------------|-------------------|----------------------|-------------------|
| Gene      | Chr | CpG     | Results of 27k: median difference $\Delta$ , correlation r | P-value               | median cases (AL) | median controls (NN) | median difference |
| LRRC8C    | 1   | CpG 1   | cg06641366: $\Delta=0.441$ , $r=0.986$                     | $1.43 \times 10^{-7}$ | 0.625             | 0.445                | 0.180             |
| LRRC8C    | 1   | CpG 2   |                                                            | $1.78 \times 10^{-7}$ | 0.655             | 0.365                | 0.290             |
| LRRC8C    | 1   | CpG 3   |                                                            | 0.0016                | 0.845             | 0.715                | 0.130             |
| LRRC8C    | 1   | CpG 5.6 |                                                            | $5.11 \times 10^{-8}$ | 0.790             | 0.193                | 0.598             |
| LRRC8C    | 1   | CpG 7   |                                                            | 0.0010                | 0.485             | 0.088                | 0.398             |
| LRRC8C    | 1   | CpG 8   |                                                            | 0.0020                | 0.140             | 0.048                | 0.093             |
| S100A5    | 1   | CpG 1   | cg08823182: $\Delta=0.225$ , $r=0.752$                     | 0.7569                | 0.710             | 0.660                | 0.050             |
| S100A5    | 1   | CpG 2   |                                                            | 0.8616                | 0.660             | 0.675                | -0.015            |
| S100A5    | 1   | CpG 3   |                                                            | 0.8269                | 0.880             | 0.865                | 0.015             |
| S100A5    | 1   | CpG 5.6 |                                                            | $2.38 \times 10^{-5}$ | 0.740             | 0.560                | 0.180             |
| SH2D2A    | 1   | CpG 1   | cg20839149: $\Delta=-0.296$ , $r=0.868$                    | 0.0735                | 0.130             | 0.315                | -0.185            |
| SH2D2A    | 1   | CpG 2   |                                                            | $2.86 \times 10^{-4}$ | 0.070             | 0.270                | -0.200            |
| SH2D2A    | 1   | CpG 3   | cg12499211: $\Delta=-0.223$ , $r=0.891$                    | 0.0605                | 0.040             | 0.090                | -0.050            |
| SH2D2A    | 1   | CpG 4   |                                                            | 0.0181                | 0.060             | 0.190                | -0.130            |
| SH2D2A    | 1   | CpG 5   |                                                            | 0.0257                | 0.010             | 0.050                | -0.040            |
| SH2D2A    | 1   | CpG 7   |                                                            | $1.26 \times 10^{-7}$ | 0.160             | 0.430                | -0.270            |
| SH2D2A    | 1   | CpG 9   |                                                            | $2.40 \times 10^{-7}$ | 0.330             | 0.655                | -0.325            |
| SH2D2A    | 1   | CpG 10  |                                                            | 0.0089                | 0.700             | 0.830                | -0.130            |
| CFLAR     | 2   | CpG 1   |                                                            | 1.0000                | 0.000             | 0.000                | 0.000             |
| CFLAR     | 2   | CpG 2   |                                                            | 0.4315                | 0.060             | 0.060                | 0.000             |
| CFLAR     | 2   | CpG 4   |                                                            | 0.4750                | 0.040             | 0.050                | -0.010            |
| CFLAR     | 2   | CpG 5.6 |                                                            | 1.0000                | 0.020             | 0.030                | -0.010            |
| CFLAR     | 2   | CpG 7.8 |                                                            | 0.8307                | 0.100             | 0.105                | -0.005            |
| CFLAR     | 2   | CpG 9   |                                                            | 0.0579                | 0.010             | 0.005                | 0.005             |

| AL vs. NN |     |                 |                                                            |                       |                   |                      |                   |
|-----------|-----|-----------------|------------------------------------------------------------|-----------------------|-------------------|----------------------|-------------------|
| Gene      | Chr | CpG             | Results of 27k: median difference $\Delta$ , correlation r | P-value               | median cases (AL) | median controls (NN) | median difference |
| CFLAR     | 2   | CpG 10          | cg18119407: $\Delta=-0.212, r=0.921$                       | 0.6542                | 0.010             | 0.020                | -0.010            |
| CFLAR     | 2   | CpG 11          |                                                            | 0.9039                | 0.030             | 0.035                | -0.005            |
| CFLAR     | 2   | CpG 12.13.14    |                                                            | 0.9606                | 0.060             | 0.060                | 0.000             |
| CFLAR     | 2   | CpG 15          |                                                            | 0.4656                | 0.020             | 0.030                | -0.010            |
| CFLAR     | 2   | CpG 16.17.18.19 |                                                            | $6.36 \times 10^{-4}$ | 0.130             | 0.295                | -0.165            |
| GPR55     | 2   | CpG 1.2         | cg20287234: $\Delta=-0.305, r=0.913$                       | 0.0033                | 0.080             | 0.245                | -0.165            |
| GPR55     | 2   | CpG 3           |                                                            | $8.43 \times 10^{-5}$ | 0.100             | 0.330                | -0.230            |
| GPR55     | 2   | CpG 4           |                                                            | $5.60 \times 10^{-5}$ | 0.110             | 0.310                | -0.200            |
| GPR55     | 2   | CpG 5           |                                                            | $1.13 \times 10^{-8}$ | 0.360             | 0.745                | -0.385            |
| GPR55     | 2   | CpG 6.7         |                                                            | $1.26 \times 10^{-4}$ | 0.190             | 0.580                | -0.390            |
| GPR55     | 2   | CpG 8.9         |                                                            | $7.07 \times 10^{-4}$ | 0.300             | 0.555                | -0.255            |
| GPR55     | 2   | CpG 10          |                                                            | 0.0017                | 0.260             | 0.520                | -0.260            |
| GPR55     | 2   | CpG 11          |                                                            | $3.23 \times 10^{-5}$ | 0.250             | 0.705                | -0.455            |
| GPR55     | 2   | CpG 12          |                                                            | $1.01 \times 10^{-5}$ | 0.180             | 0.440                | -0.260            |
| GPR55     | 2   | CpG 13.14       |                                                            | 0.0111                | 0.390             | 0.600                | -0.210            |
| ZNF662    | 3   | CpG 1           | cg26523005: $\Delta=0.105, r=0.869$                        | 0.1568                | 0.100             | 0.060                | 0.040             |
| ZNF662    | 3   | CpG 2           |                                                            | $1.18 \times 10^{-4}$ | 0.160             | 0.055                | 0.105             |
| ZNF662    | 3   | CpG 3           |                                                            | $3.64 \times 10^{-5}$ | 0.450             | 0.220                | 0.230             |
| ZNF662    | 3   | CpG 4.5         |                                                            | 0.0131                | 0.630             | 0.455                | 0.175             |
| TREM1     | 6   | CpG 1           | cg06196379: $\Delta=-0.162, r=0.293$                       | 0.0069                | 0.680             | 0.775                | -0.095            |
| TREM1     | 6   | CpG 2           |                                                            | 0.0680                | 0.150             | 0.225                | -0.075            |
| TREM1     | 6   | CpG 4           |                                                            | $8.27 \times 10^{-4}$ | 0.790             | 0.890                | -0.100            |
| EPB49     | 8   | CpG 1.2         |                                                            | 0.0147                | 0.250             | 0.120                | 0.130             |
| EPB49     | 8   | CpG 3           |                                                            | 0.0015                | 0.270             | 0.085                | 0.185             |
| EPB49     | 8   | CpG 4           |                                                            | 0.0316                | 0.190             | 0.070                | 0.120             |
| EPB49     | 8   | CpG 5           |                                                            | 0.0173                | 0.260             | 0.140                | 0.120             |
| EPB49     | 8   | CpG 6           |                                                            | 0.0070                | 0.400             | 0.190                | 0.210             |

| AL vs. NN |     |                 |                                                            |                       |                   |                      |                   |
|-----------|-----|-----------------|------------------------------------------------------------|-----------------------|-------------------|----------------------|-------------------|
| Gene      | Chr | CpG             | Results of 27k: median difference $\Delta$ , correlation r | P-value               | median cases (AL) | median controls (NN) | median difference |
| EPB49     | 8   | CpG 7           | cg14706739: $\Delta=0.166, r=0.85$                         | $2.99 \times 10^{-4}$ | 0.710             | 0.460                | 0.250             |
| EPB49     | 8   | CpG 8           |                                                            | $6.96 \times 10^{-5}$ | 0.370             | 0.165                | 0.205             |
| TSPAN4    | 11  | CpG 1           | cg11173246: $\Delta=-0.159, r=0.88$                        | 0.6830                | 0.170             | 0.190                | -0.020            |
| TSPAN4    | 11  | CpG 2           |                                                            | 0.6386                | 0.170             | 0.175                | -0.005            |
| TSPAN4    | 11  | CpG 3           |                                                            | 0.0342                | 0.530             | 0.640                | -0.110            |
| TSPAN4    | 11  | CpG 4.5         |                                                            | 0.3342                | 0.290             | 0.330                | -0.040            |
| TSPAN4    | 11  | CpG 6           |                                                            | 0.0146                | 0.340             | 0.460                | -0.120            |
| TSPAN4    | 11  | CpG 7           |                                                            | 0.0023                | 0.600             | 0.760                | -0.160            |
| TSPAN4    | 11  | CpG 9           |                                                            | 0.0279                | 0.520             | 0.675                | -0.155            |
| TSPAN4    | 11  | CpG 10          |                                                            | 0.0078                | 0.580             | 0.755                | -0.175            |
| TSPAN4    | 11  | CpG 11          |                                                            | 0.0050                | 0.370             | 0.530                | -0.160            |
| TSPAN4    | 11  | CpG 12          |                                                            | 0.0375                | 0.510             | 0.630                | -0.120            |
| HTATIP2   | 11  | CpG 1           | cg18788940: $\Delta=-0.128, r=0.642$                       | 0.0156                | 0.290             | 0.360                | -0.070            |
| HTATIP2   | 11  | CpG 2.3         |                                                            | 0.0180                | 0.010             | 0.020                | -0.010            |
| HTATIP2   | 11  | CpG 4.5.6.7     |                                                            | 1.0000                | 0.040             | 0.040                | 0.000             |
| HTATIP2   | 11  | CpG 8.9         |                                                            | 1.0000                | 0.030             | 0.030                | 0.000             |
| HTATIP2   | 11  | CpG 10.11       |                                                            | 0.8541                | 0.060             | 0.060                | 0.000             |
| HTATIP2   | 11  | CpG 12          |                                                            | 1.0000                | 0.020             | 0.020                | 0.000             |
| HTATIP2   | 11  | CpG 16.17.18.19 |                                                            | 1.0000                | 0.020             | 0.020                | 0.000             |
| HTATIP2   | 11  | CpG 20          |                                                            | 1.0000                | 0.010             | 0.010                | 0.000             |
| HTATIP2   | 11  | CpG 21          |                                                            | 1.0000                | 0.030             | 0.030                | 0.000             |
| HTATIP2   | 11  | CpG 22.23.24    |                                                            | 0.7582                | 0.060             | 0.060                | 0.000             |
| HTATIP2   | 11  | CpG 25.26       |                                                            | 0.0559                | 0.020             | 0.015                | 0.005             |
| MMP7      | 11  | CpG 1           |                                                            | $1.12 \times 10^{-6}$ | 0.510             | 0.715                | -0.205            |
| MMP7      | 11  | CpG 2           |                                                            | $2.24 \times 10^{-7}$ | 0.310             | 0.575                | -0.265            |
| MMP7      | 11  | CpG 3           |                                                            | $6.56 \times 10^{-8}$ | 0.310             | 0.575                | -0.265            |
| MMP7      | 11  | CpG 4           |                                                            | $6.87 \times 10^{-7}$ | 0.130             | 0.525                | -0.395            |

| AL vs. NN |     |           |                                                            |                       |                   |                      |                   |
|-----------|-----|-----------|------------------------------------------------------------|-----------------------|-------------------|----------------------|-------------------|
| Gene      | Chr | CpG       | Results of 27k: median difference $\Delta$ , correlation r | P-value               | median cases (AL) | median controls (NN) | median difference |
| MMP7      | 11  | CpG 5     | cg25511807: $\Delta=-0.239, r=0.841$                       | $1.08 \times 10^{-5}$ | 0.180             | 0.380                | -0.200            |
| MMP7      | 11  | CpG 6     |                                                            | $1.01 \times 10^{-4}$ | 0.050             | 0.185                | -0.135            |
| MMP7      | 11  | CpG 8     |                                                            | $7.83 \times 10^{-8}$ | 0.080             | 0.340                | -0.260            |
| ERP27     | 12  | CpG 1     | cg13435792: $\Delta=-0.263, r=0.961$                       | 0.4582                | 0.880             | 0.920                | -0.040            |
| ERP27     | 12  | CpG 3     |                                                            | $5.60 \times 10^{-6}$ | 0.580             | 0.940                | -0.360            |
| ERP27     | 12  | CpG 5     |                                                            | $2.65 \times 10^{-6}$ | 0.440             | 0.845                | -0.405            |
| ERP27     | 12  | CpG 6.7   |                                                            | $9.69 \times 10^{-6}$ | 0.430             | 0.800                | -0.370            |
| LOC283487 | 13  | CpG 2     | cg22131172: $\Delta=-0.190, r=0.922$                       | 0.0112                | 0.210             | 0.295                | -0.085            |
| LOC283487 | 13  | CpG 3     |                                                            | 0.0896                | 0.060             | 0.090                | -0.030            |
| LOC283487 | 13  | CpG 4     |                                                            | $3.13 \times 10^{-4}$ | 0.440             | 0.650                | -0.210            |
| LOC283487 | 13  | CpG 5     |                                                            | 0.2939                | 0.000             | 0.025                | -0.025            |
| LOC283487 | 13  | CpG 6     |                                                            | $3.16 \times 10^{-5}$ | 0.190             | 0.430                | -0.240            |
| SLC25A11  | 17  | CpG 37653 | cg04958703: $\Delta=-0.103, r=0.656$                       | 0.3850                | 0.930             | 0.940                | -0.010            |
| SLC25A11  | 17  | CpG 4     |                                                            | 0.1414                | 0.530             | 0.590                | -0.060            |
| SLC25A11  | 17  | CpG 5     |                                                            | 0.0114                | 0.430             | 0.520                | -0.090            |
| SLC25A11  | 17  | CpG 6     |                                                            | 0.0139                | 0.430             | 0.520                | -0.090            |
| SLC25A11  | 17  | CpG 8     |                                                            | 0.0108                | 0.430             | 0.520                | -0.090            |
| UHRF1     | 19  | CpG 1     | cg19147390: $\Delta=-0.143, r=0.895$                       | $1.21 \times 10^{-4}$ | 0.330             | 0.550                | -0.220            |
| UHRF1     | 19  | CpG 2     |                                                            | $7.42 \times 10^{-4}$ | 0.075             | 0.270                | -0.195            |
| UHRF1     | 19  | CpG 4     |                                                            | 0.0088                | 0.130             | 0.270                | -0.140            |
| UHRF1     | 19  | CpG 5.6   |                                                            | $1.72 \times 10^{-4}$ | 0.230             | 0.525                | -0.295            |
| UHRF1     | 19  | CpG 7.8   |                                                            | 0.0045                | 0.470             | 0.690                | -0.220            |
| UHRF1     | 19  | CpG 9     |                                                            | $1.14 \times 10^{-7}$ | 0.080             | 0.295                | -0.215            |
| UHRF1     | 19  | CpG 10    |                                                            | $8.32 \times 10^{-5}$ | 0.620             | 0.820                | -0.200            |
| UHRF1     | 19  | CpG 14    |                                                            | 0.0032                | 0.440             | 0.655                | -0.215            |
| UHRF1     | 19  | CpG 15.16 |                                                            | 0.0084                | 0.560             | 0.700                | -0.140            |

| AL vs. AN |     |         |                                                            |                       |                      |                          |                   |
|-----------|-----|---------|------------------------------------------------------------|-----------------------|----------------------|--------------------------|-------------------|
| Gene      | Chr | CpG     | Results of 27k: median difference $\Delta$ , correlation r | P-value               | median lesional (AL) | median non-lesional (AN) | median difference |
| LRRC8C    | 1   | CpG 1   | cg06641366: $\Delta=0.196, r=0.986$                        | 0.0813                | 0.635                | 0.575                    | 0.060             |
| LRRC8C    | 1   | CpG 2   |                                                            | 0.0112                | 0.680                | 0.555                    | 0.125             |
| LRRC8C    | 1   | CpG 3   |                                                            | 0.6973                | 0.830                | 0.860                    | -0.030            |
| LRRC8C    | 1   | CpG 5.6 |                                                            | $8.31 \times 10^{-4}$ | 0.870                | 0.540                    | 0.330             |
| LRRC8C    | 1   | CpG 7   |                                                            | $1.85 \times 10^{-4}$ | 0.585                | 0.235                    | 0.350             |
| LRRC8C    | 1   | CpG 8   |                                                            | 0.0026                | 0.213                | 0.070                    | 0.143             |
| EPB49     | 8   | CpG 1.2 | cg14706739: $\Delta=0.128, r=0.85$                         | 0.0386                | 0.250                | 0.110                    | 0.140             |
| EPB49     | 8   | CpG 3   |                                                            | 0.0912                | 0.270                | 0.120                    | 0.150             |
| EPB49     | 8   | CpG 4   |                                                            | 0.1725                | 0.120                | 0.100                    | 0.020             |
| EPB49     | 8   | CpG 5   |                                                            | 0.0732                | 0.260                | 0.130                    | 0.130             |
| EPB49     | 8   | CpG 6   |                                                            | 0.0194                | 0.400                | 0.200                    | 0.200             |
| EPB49     | 8   | CpG 7   |                                                            | 0.0011                | 0.810                | 0.550                    | 0.260             |
| EPB49     | 8   | CpG 8   |                                                            | 0.0323                | 0.350                | 0.200                    | 0.150             |
| AN vs. NN |     |         |                                                            |                       |                      |                          |                   |
| Gene      | Chr | CpG     | Results of 27k: median difference $\Delta$ , correlation r | P-value               | median cases (AN)    | median controls (NN)     | median difference |
| LRRC8C    | 1   | CpG 1   | cg06641366: $\Delta=0.210, r=0.986$                        | 0.0537                | 0.590                | 0.445                    | 0.145             |
| LRRC8C    | 1   | CpG 2   |                                                            | 0.0243                | 0.600                | 0.365                    | 0.235             |
| LRRC8C    | 1   | CpG 3   |                                                            | 0.1139                | 0.853                | 0.715                    | 0.138             |
| LRRC8C    | 1   | CpG 5.6 |                                                            | 0.0653                | 0.505                | 0.193                    | 0.313             |
| LRRC8C    | 1   | CpG 7   |                                                            | 0.1366                | 0.250                | 0.088                    | 0.163             |
| LRRC8C    | 1   | CpG 8   |                                                            | 0.4222                | 0.085                | 0.048                    | 0.038             |
| SLC25A34  | 1   | CpG 1   |                                                            | 0.2524                | 0.395                | 0.340                    | 0.055             |
| SLC25A34  | 1   | CpG 2   |                                                            | 0.8697                | 0.150                | 0.155                    | -0.005            |
| SLC25A34  | 1   | CpG 3.4 |                                                            | 0.6285                | 0.190                | 0.175                    | 0.015             |
| SLC25A34  | 1   | CpG 5   |                                                            | 0.6596                | 0.475                | 0.465                    | 0.010             |

| AN vs. NN |     |         |                                                            |         |                   |                      |                   |
|-----------|-----|---------|------------------------------------------------------------|---------|-------------------|----------------------|-------------------|
| Gene      | Chr | CpG     | Results of 27k: median difference $\Delta$ , correlation r | P-value | median cases (AN) | median controls (NN) | median difference |
| SLC25A34  | 1   | CpG 6   | cg15616400: $\Delta=0.025, r=0.852$                        | 0.8475  | 0.435             | 0.430                | 0.005             |
| SLC25A34  | 1   | CpG 7   |                                                            | 0.1521  | 0.540             | 0.515                | 0.025             |
| SLC25A34  | 1   | CpG 8   |                                                            | 0.3701  | 0.445             | 0.360                | 0.085             |
| SLC25A34  | 1   | CpG 9   |                                                            | 0.1573  | 0.395             | 0.340                | 0.055             |
| SLC25A34  | 1   | CpG 10  |                                                            | 0.2631  | 0.560             | 0.470                | 0.090             |
| SLC25A34  | 1   | CpG 11  |                                                            | 0.0305  | 0.785             | 0.705                | 0.080             |
| SLC25A34  | 1   | CpG 12  |                                                            | 0.8568  | 0.435             | 0.430                | 0.005             |
| SLC25A34  | 1   | CpG 13  |                                                            | 0.6616  | 0.475             | 0.465                | 0.010             |
| SLC25A34  | 1   | CpG 14  |                                                            | 0.0663  | 0.780             | 0.660                | 0.120             |
| EPB49     | 8   | CpG 1.2 | cg14706739: $\Delta=0.042, r=0.85$                         | 0.7667  | 0.105             | 0.120                | -0.015            |
| EPB49     | 8   | CpG 3   |                                                            | 0.3333  | 0.110             | 0.085                | 0.025             |
| EPB49     | 8   | CpG 4   |                                                            | 0.9895  | 0.080             | 0.070                | 0.010             |
| EPB49     | 8   | CpG 5   |                                                            | 0.6128  | 0.135             | 0.140                | -0.005            |
| EPB49     | 8   | CpG 6   |                                                            | 0.5815  | 0.190             | 0.190                | 0.000             |
| EPB49     | 8   | CpG 7   |                                                            | 0.1807  | 0.555             | 0.460                | 0.095             |
| EPB49     | 8   | CpG 8   |                                                            | 0.8120  | 0.190             | 0.165                | 0.025             |

**Supplementary Table S3:** Analysis of CpG sites located in established risk genes for atopic dermatitis, asthma and psoriasis for differential methylation associated with AD. 64 of 87 risk genes are represented by at least one site on the 27k Methylation chip. n.s.=not significant (P>0.05); \*= not significant if adjusted for multiple testing.

| Atopic Dermatitis |          |                       |            |            |      |            |      |            |      |            |      |            |      |
|-------------------|----------|-----------------------|------------|------------|------|------------|------|------------|------|------------|------|------------|------|
|                   |          |                       |            | AL vs. NN  |      | AN vs. NN  |      | Blood      |      | T-cells    |      | B-cells    |      |
| Gene              | Locus    | Author                | CpG        | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    |
| FLG               | 1q21.3   | Esparza-Gordillo 2009 | cg13447818 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| FLG               | 1q21.3   | Esparza-Gordillo 2009 | cg26390526 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SLC9A4            | 2q12.1   | Ellinghaus 2013       |            |            |      |            |      |            |      |            |      | -          | n.s. |
| IL2               | 4q27     | Ellinghaus 2013       | cg09526693 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| IL21              | 4q27     | Ellinghaus 2013       | cg00136405 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| IL13              | 5q31.1   | Paternoster 2011      | cg07810967 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| IL13              | 5q31.1   | Paternoster 2011      | cg14523284 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| KIF3A             | 5q31.1   | Paternoster 2011      |            |            |      |            |      |            |      |            |      |            |      |
| RAD50             | 5q31.1   | Paternoster 2011      | cg24974130 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| RAD50             | 5q31.1   | Paternoster 2011      | cg21935083 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| TNXB              | 6p21.33  | Weidinger 2013        | cg03543593 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| PRR5L             | 11p13    | Ellinghaus 2013       |            |            |      |            |      |            |      |            |      |            |      |
| AP5B1             | 11q13.1  | Paternoster 2011      |            |            |      |            |      |            |      |            |      |            |      |
| OVOL1             | 11q13.1  | Paternoster 2011      | cg03681481 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| OVOL1             | 11q13.1  | Paternoster 2011      | cg20909686 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| OVOL1             | 11q13.1  | Paternoster 2011      | cg20315951 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| C11orf30          | 11q13.5  | Esparza-Gordillo 2009 | cg20641660 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| C11orf30          | 11q13.5  | Esparza-Gordillo 2009 | cg15765532 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| LRRC32            | 11q13.5  | Esparza-Gordillo 2009 | cg13633560 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| LRRC32            | 11q13.5  | Esparza-Gordillo 2009 | cg20899321 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| CLEC16A           | 16p13.13 | Ellinghaus 2013       |            |            |      |            |      |            |      |            |      |            |      |
| ZNF652            | 17q21.32 | Ellinghaus 2013       | cg13382694 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| ZNF652            | 17q21.32 | Ellinghaus 2013       | cg22370370 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| ACTL9             | 19p13.2  | Paternoster 2011      | cg20587168 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |

| Asthma   |          |                      |            |            |      |            |      |            |      |            |      |            |      |
|----------|----------|----------------------|------------|------------|------|------------|------|------------|------|------------|------|------------|------|
|          |          |                      |            | AL vs. NN  |      | AN vs. NN  |      | Blood      |      | T-cells    |      | B-cells    |      |
| Gene     | Locus    | Author               | CpG        | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    |
| ACTL9    | 19p13.2  | Paternoster 2011     | cg18931750 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| ADAMTS10 | 19p13.2  | Paternoster 2011     | cg06994747 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| TNFRSF6B | 20q13.33 | Ellinghaus 2013      |            |            |      |            |      |            |      |            |      |            |      |
| IL6R     | 1q21.3   | Ferreira et al. 2011 | cg04185861 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL6R     | 1q21.3   | Ferreira et al. 2011 | cg25853020 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| PYHIN1   | 1q23.1   | Togerson et al. 2011 | cg19884600 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| DENND1B  | 1q31.3   | Sleiman et al. 2010  | cg13463167 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL18R1   | 2q12.1   | Moffat et a. 2010    | cg17869167 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL1RL1   | 2q12.1   | Moffat et a. 2010    | cg11916609 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL1RL1   | 2q12.1   | Moffat et a. 2010    | cg16386158 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL1RL1   | 2q12.1   | Togerson et al. 2011 | cg11916609 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL1RL1   | 2q12.1   | Togerson et al. 2011 | cg16386158 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| FLJ44477 | 4q31.21  | Hirota et al. 2011   |            | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| USP38    | 4q31.21  | Hirota et al. 2011   | cg01171588 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| USP38    | 4q31.21  | Hirota et al. 2011   | cg20716945 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| PDE4D    | 5q12.1   | Hirmes et al. 2009   | cg13112511 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| PDE4D    | 5q12.1   | Hirmes et al. 2009   | cg05992340 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| TSLP     | 5q22.1   | Togerson et al. 2011 | cg15089387 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL4      | 5q31.1   | Miller & Ho 2008     | cg26787239 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| HLA-DP   | 6p21.32  | Noguchi et al. 2011  |            |            |      |            |      |            |      |            |      |            |      |
| MHC      | 6p21.32  | Moffat et a. 2010    |            | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL33     | 9p24.1   | Moffat et a. 2010    | cg18236721 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| KRT8P16  | 10p14    | Hirota et al. 2011   |            |            |      |            |      |            |      |            |      |            |      |
| TCEB1P3  | 10p14    | Hirota et al. 2011   |            |            |      |            |      |            |      |            |      |            |      |
| c11orf30 | 11q13.5  | Ferreira et al. 2011 |            |            |      |            |      |            |      |            |      |            |      |
| LRRC2    | 11q13.5  | Ferreira et al. 2011 | cg10242476 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| LRRC2    | 11q13.5  | Ferreira et al. 2011 | cg27371741 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| LRRC2    | 11q13.5  | Ferreira et al. 2011 | cg10031651 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |

| Asthma    |          |                      |            |            |      |            |      |            |      |            |      |            |      |
|-----------|----------|----------------------|------------|------------|------|------------|------|------------|------|------------|------|------------|------|
|           |          |                      |            | AL vs. NN  |      | AN vs. NN  |      | Blood      |      | T-cells    |      | B-cells    |      |
| Gene      | Locus    | Author               | CpG        | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    |
| IKZF4     | 12q13.2  | Hirota et al. 2011   |            |            |      |            |      |            |      |            |      |            |      |
| SUOX      | 12q13.2  | Hirota et al. 2011   | cg06495347 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SUOX      | 12q13.2  | Hirota et al. 2011   | cg21554249 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| IFNG      | 12q15    | Miller & Ho 2008     | cg26227465 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SMAD3     | 15q22.33 | Moffat et a. 2010    | cg14556189 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| GSDMB     | 17q12    | Moffat et a. 2010    | cg10057218 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| GSDMB     | 17q12    | Moffat et a. 2010    | cg12360886 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| GSDMB     | 17q12    | Togerson et al. 2011 | cg10057218 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| GSDMB     | 17q12    | Togerson et al. 2011 | cg12360886 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| ORMDL3    | 17q12    | Moffat et al. 2007   | cg01482279 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| ORMDL3    | 17q12    | Moffat et al. 2007   | cg19511844 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| GSDMA     | 17q21.1  | Moffat et a. 2010    |            |            |      |            |      |            |      |            |      |            |      |
| SLC30A8   | 18q24.11 | Noguchi et al. 2011  | cg07459489 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SLC30A8   | 18q24.11 | Noguchi et al. 2011  | cg23338195 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| IL2RB     | 22q12.3  | Moffat et a. 2010    | cg26757673 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| Psoriasis |          |                      |            |            |      |            |      |            |      |            |      |            |      |
|           |          |                      |            | AL vs. NN  |      | AN vs. NN  |      | Blood      |      | T-cells    |      | B-cells    |      |
| Gene      | Locus    | Author               | CpG        | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    |
| IL23R     | 1p31.3   | Nair 2009            |            |            |      |            |      |            |      |            |      |            |      |
| IL28RA    | 1p36.11  | Tsoi 2012            | cg07509155 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| IL28RA    | 1p36.11  | Tsoi 2012            | cg08700651 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| RUNX3     | 1p36.11  | Tsoi 2012            | cg22737001 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| RUNX3     | 1p36.11  | Tsoi 2012            | cg18813928 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| RUNX3     | 1p36.11  | Tsoi 2012            | cg24019564 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| RUNX3     | 1p36.11  | Tsoi 2012            | cg25178645 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| RUNX3     | 1p36.11  | Tsoi 2012            | cg16529592 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| RUNX3     | 1p36.11  | Tsoi 2012            | cg14182690 | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |

| Psoriasis |         |              |            |            |        |            |      |            |      |            |      |            |      |
|-----------|---------|--------------|------------|------------|--------|------------|------|------------|------|------------|------|------------|------|
|           |         |              |            | AL vs. NN  |        | AN vs. NN  |      | Blood      |      | T-cells    |      | B-cells    |      |
| Gene      | Locus   | Author       | CpG        | Med. diff. | P      | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg02723372 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg13461622 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg00117172 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg27360282 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg06377278 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg14645650 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg03171924 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg04757093 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg18231267 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| RUNX3     | 1p36.11 | Tsoi 2012    | cg06037693 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| SLC45A1   | 1p36.23 | Tsoi 2012    |            |            |        |            |      |            |      |            |      |            |      |
| TNFRSF9*  | 1p36.23 | Tsoi 2012    | cg08840010 | -0.252     | 0.0010 | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| TNFRSF9   | 1p36.23 | Tsoi 2012    | cg23959705 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| LCE3B     | 1q21.3  | De Cid 2009  |            |            |        |            |      |            |      |            |      |            |      |
| LCE3C     | 1q21.3  | De Cid 2009  |            |            |        |            |      |            |      |            |      |            |      |
| B3GNT2    | 2p15    | Tsoi 2012    |            |            |        |            |      |            |      |            |      |            |      |
| REL       | 2p16.1  | Strange 2010 | cg09600437 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| GCA       | 2q24.2  | Strange 2010 | cg03549127 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| GCA       | 2q24.2  | Strange 2010 | cg01743370 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IFIH1     | 2q24.2  | Strange 2010 | cg06347928 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IFIH1     | 2q24.2  | Strange 2010 | cg07348311 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| KCNH7     | 2q24.2  | Strange 2010 | cg19965810 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| KCNH7     | 2q24.2  | Strange 2010 | cg25668368 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| ERAP1     | 5q15    | Strange 2010 | cg17522249 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| ERAP1     | 5q15    | Strange 2010 | cg14161426 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL13      | 5q31.1  | Nair 2009    | cg07810967 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| IL13      | 5q31.1  | Nair 2009    | cg14523284 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |
| ANXA6     | 5q33.1  | Nair 2009    | cg21623671 | -          | n.S.   | -          | n.S. | -          | n.S. | -          | n.S. | -          | n.S. |

[illegible]

| Psoriasis |          |             |            |            |                       |            |      |            |      |            |      |            |      |
|-----------|----------|-------------|------------|------------|-----------------------|------------|------|------------|------|------------|------|------------|------|
|           |          |             |            | AL vs. NN  |                       | AN vs. NN  |      | Blood      |      | T-cells    |      | B-cells    |      |
| Gene      | Locus    | Author      | CpG        | Med. diff. | P                     | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    | Med. diff. | P    |
| ETS1      | 11q24.3  | Tsoi 2012   | cg11861730 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| ETS1      | 11q24.3  | Tsoi 2012   | cg14998713 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| IL23A     | 12q13.2  | Nair 2009   | cg00294382 | -0.129     | 9.66x10 <sup>-4</sup> | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| STAT2     | 12q13.2  | Nair 2009   | cg05388361 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| STAT2     | 12q13.2  | Nair 2009   | cg21800439 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| KIAA0391  | 14q13.2  | Stuart 2010 |            |            |                       |            |      |            |      |            |      | -          | n.s. |
| NFKBIA    | 14q13.2  | Stuart 2010 | cg02318426 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| NFKBIA    | 14q13.2  | Stuart 2010 | cg05852416 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| PSMA6     | 14q13.2  | Stuart 2010 | cg08039281 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| PSMA6     | 14q13.2  | Stuart 2010 | cg22624926 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| FBXL19    | 16p11.2  | Stuart 2010 | cg04368877 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| FBXL19    | 16p11.2  | Stuart 2010 | cg22305782 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| PRM3      | 16p13.13 | Tsoi 2012   |            |            |                       |            |      |            |      |            |      |            |      |
| PRM3      | 16p13.13 | Tsoi 2012   |            |            |                       |            |      |            |      |            |      |            |      |
| SOCS1     | 16p13.13 | Tsoi 2012   | cg00487159 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SOCS1     | 16p13.13 | Tsoi 2012   | cg06220235 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SOCS1     | 16p13.13 | Tsoi 2012   | cg26012103 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SOCS1     | 16p13.13 | Tsoi 2012   | cg06295404 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SOCS1     | 16p13.13 | Tsoi 2012   | cg11973052 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SOCS1     | 16p13.13 | Tsoi 2012   | cg10784813 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| SOCS1     | 16p13.13 | Tsoi 2012   | cg01717706 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| NOS2      | 17q11.2  | Stuart 2010 | cg04483754 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| NOS2      | 17q11.2  | Stuart 2010 | cg07150830 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| PTRF      | 17q21.2  | Tsoi 2012   | cg13353683 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| PTRF      | 17q21.2  | Tsoi 2012   | cg14070162 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| STAT3     | 17q21.2  | Tsoi 2012   | cg18112163 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| STAT3     | 17q21.2  | Tsoi 2012   | cg20716209 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |
| STAT5A    | 17q21.2  | Tsoi 2012   | cg16777510 | -          | n.s.                  | -          | n.s. | -          | n.s. | -          | n.s. | -          | n.s. |

| Psoriasis |         |           |            |               |      |               |      |               |      |               |      |               |      |
|-----------|---------|-----------|------------|---------------|------|---------------|------|---------------|------|---------------|------|---------------|------|
|           |         |           | AL vs. NN  |               |      | AN vs. NN     |      | Blood         |      | T-cells       |      | B-cells       |      |
| Gene      | Locus   | Author    | CpG        | Med.<br>diff. | P    | Med.<br>diff. | P    | Med.<br>diff. | P    | Med.<br>diff. | P    | Med.<br>diff. | P    |
| STAT5A    | 17q21.2 | Tsoi 2012 | cg03001305 | -             | n.S. | -             | n.S. | -             | n.S. | -             | n.S. | -             | n.S. |
| STAT5B    | 17q21.2 | Tsoi 2012 | cg05780311 | -             | n.S. | -             | n.S. | -             | n.S. | -             | n.S. | -             | n.S. |
| STAT5B    | 17q21.2 | Tsoi 2012 | cg04745805 | -             | n.S. | -             | n.S. | -             | n.S. | -             | n.S. | -             | n.S. |

**Supplementary Table S4:** Differentially expressed transcripts (DET) with foldchange >1.3 and P<0.001 in AL/NN, AN/NN and AL/AN analysis. Significantly enriched (P Benjamini & Hochberg<0.05) GO-terms are indicated. Enrichment analysis was performed with DAVID (Huang da et al., 2009a, b)

| AL vs. NN |        |               |               |        |             |          |                                                                                                                                                                                                                                                |
|-----------|--------|---------------|---------------|--------|-------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene   | fold change | P-value  | GO-term                                                                                                                                                                                                                                        |
| 1         | p36.33 | 948803        | ILMN_2054019  | ISG15  | 2.207       | 9.39E-06 | -                                                                                                                                                                                                                                              |
| 1         | p36.11 | 24645812      | ILMN_2388874  | GRHL3  | 1.297       | 7.88E-04 | ectoderm development (bp), epidermis development (bp)                                                                                                                                                                                          |
| 1         | p36.11 | 27992572      | ILMN_2347798  | IFI6   | 2.566       | 1.62E-04 | -                                                                                                                                                                                                                                              |
| 1         | p31.1  | 79085607      | ILMN_1723912  | IFI44L | 1.609       | 4.08E-04 | -                                                                                                                                                                                                                                              |
| 1         | p13.3  | 110276554     | ILMN_1736184  | GSTM3  | 0.515       | 1.46E-04 | epithelium development (bp), epithelial cell differentiation (bp)                                                                                                                                                                              |
| 1         | q21.3  | 152538130     | ILMN_1808220  | LCE3E  | 8.568       | 2.12E-06 | ectoderm development (bp), epidermis development (bp), keratinization (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), epithelium development (bp), epithelial cell differentiation (bp)                          |
| 1         | q21.3  | 152551857     | ILMN_1718395  | LCE3D  | 8.793       | 3.47E-06 | ectoderm development (bp), epidermis development (bp), keratinization (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), epithelium development (bp), epithelial cell differentiation (bp)                          |
| 1         | q21.3  | 152956557     | ILMN_1716591  | SPRR1A | 6.349       | 1.95E-05 | ectoderm development (bp), epidermis development (bp), keratinization (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), cornified envelope (cc), epithelium development (bp), epithelial cell differentiation (bp) |

| AL vs. NN |       |               |               |        |             |          |                                                                                                                                                                                                                                                |
|-----------|-------|---------------|---------------|--------|-------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chr       | Band  | Position hg19 | Transcript ID | Gene   | fold change | P-value  | GO-term                                                                                                                                                                                                                                        |
| 1         | q21.3 | 153003678     | ILMN_1711174  | SPRR1B | 5.136       | 3.52E-04 | ectoderm development (bp), epidermis development (bp), keratinization (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), cornified envelope (cc), epithelium development (bp), epithelial cell differentiation (bp) |
| 1         | q21.3 | 153042704     | ILMN_1806059  | SPRR2B | 8.130       | 1.07E-04 | ectoderm development (bp), epidermis development (bp), keratinization (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), cornified envelope (cc), epithelium development (bp), epithelial cell differentiation (bp) |
| 1         | q21.3 | 153084590     | ILMN_1674367  | SPRR2F | 5.856       | 7.01E-04 | ectoderm development (bp), epidermis development (bp), keratinization (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), cornified envelope (cc), epithelium development (bp), epithelial cell differentiation (bp) |
| 1         | q21.3 | 153112967     | ILMN_2197577  | SPRR2C | 5.859       | 9.35E-04 | ectoderm development (bp), epidermis development (bp), keratinization (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), cornified envelope (cc), epithelium development (bp), epithelial cell differentiation (bp) |
| 1         | q21.3 | 153330330     | ILMN_1750974  | S100A9 | 14.031      | 2.29E-04 | -                                                                                                                                                                                                                                              |
| 1         | q21.3 | 153362508     | ILMN_1729801  | S100A8 | 8.367       | 3.73E-04 | -                                                                                                                                                                                                                                              |

| AL vs. NN |        |               |               |         |             |          |                                                                                                                                                                                                  |
|-----------|--------|---------------|---------------|---------|-------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene    | fold change | P-value  | GO-term                                                                                                                                                                                          |
| 1         | q21.3  | 153430220     | ILMN_1757351  | S100A7  | 9.802       | 2.98E-04 | ectoderm development (bp), epidermis development (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), epithelium development (bp), epithelial cell differentiation (bp) |
| 1         | q32.2  | 209859510     | ILMN_2389501  | HSD11B1 | 0.362       | 8.24E-04 | -                                                                                                                                                                                                |
| 1         | q32.3  | 211744910     | ILMN_2067852  | SLC30A1 | 1.347       | 7.73E-05 | -                                                                                                                                                                                                |
| 1         | q32.3  | 211744910     | ILMN_1745021  | SLC30A1 | 1.388       | 1.02E-04 | -                                                                                                                                                                                                |
| 1         | q42.2  | 233749750     | ILMN_1718863  | KCNK1   | 1.444       | 7.90E-04 | -                                                                                                                                                                                                |
| 2         | p25.1  | 8992820       | ILMN_1777853  | MBOAT2  | 1.370       | 1.24E-04 | -                                                                                                                                                                                                |
| 2         | q13    | 113730780     | ILMN_2158713  | IL1F9   | 2.734       | 8.87E-05 | -                                                                                                                                                                                                |
| 2         | q31.1  | 169921299     | ILMN_2281502  | DHRS9   | 2.091       | 5.05E-04 | epithelium development (bp), epithelial cell differentiation (bp)                                                                                                                                |
| 2         | q33.3  | 207040040     | ILMN_1655348  | GPR1    | 1.948       | 1.21E-04 | -                                                                                                                                                                                                |
| 3         | p22.1  | 42055294      | ILMN_1782069  | TRAK1   | 0.631       | 6.82E-04 | -                                                                                                                                                                                                |
| 3         | p14.3  | 55499743      | ILMN_1800317  | WNT5A   | 1.855       | 6.46E-04 | -                                                                                                                                                                                                |
| 3         | q21.1  | 122246806     | ILMN_1731224  | PARP9   | 1.909       | 4.32E-04 | -                                                                                                                                                                                                |
| 3         | q22.1  | 132036211     | ILMN_1758323  | ACPP    | 1.697       | 1.76E-05 | -                                                                                                                                                                                                |
| 3         | q22.2  | 134316643     | ILMN_1692261  | EPHB1   | 0.514       | 8.19E-04 | -                                                                                                                                                                                                |
| 3         | q29    | 192514604     | ILMN_1700967  | C3orf59 | 0.767       | 1.77E-06 | -                                                                                                                                                                                                |
| 4         | p16.1  | 6271576       | ILMN_1759023  | WFS1    | 0.482       | 3.94E-04 | -                                                                                                                                                                                                |
| 4         | p15.32 | 15961866      | ILMN_1761945  | FGFBP2  | 0.664       | 2.22E-04 | -                                                                                                                                                                                                |
| 4         | p14    | 36067620      | ILMN_1767541  | ARAP2   | 1.350       | 2.33E-04 | -                                                                                                                                                                                                |
| 4         | p14    | 40337346      | ILMN_2069286  | CHRNA9  | 1.482       | 6.82E-04 | -                                                                                                                                                                                                |
| 4         | q21.23 | 84213614      | ILMN_2092850  | HPSE    | 2.056       | 6.37E-04 | -                                                                                                                                                                                                |
| 4         | q22.1  | 89299891      | ILMN_1654639  | HERC6   | 2.130       | 7.41E-05 | -                                                                                                                                                                                                |
| 4         | q24    | 103172198     | ILMN_2233539  | SLC39A8 | 1.345       | 6.37E-04 | -                                                                                                                                                                                                |

| AL vs. NN |        |               |               |          |             |          |                                                       |
|-----------|--------|---------------|---------------|----------|-------------|----------|-------------------------------------------------------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term                                               |
| 4         | q26    | 118495667     | ILMN_1769734  | NT5C3    | 1.829       | 1.69E-04 | -                                                     |
| 5         | p13.2  | 36035119      | ILMN_1655565  | UGT3A2   | 0.375       | 2.08E-04 | -                                                     |
| 5         | q31.1  | 134362615     | ILMN_1674386  | PITX1    | 3.798       | 5.81E-04 | -                                                     |
| 5         | q31.1  | 135364584     | ILMN_1663866  | TGFBI    | 0.643       | 8.78E-04 | -                                                     |
| 5         | q32    | 148871760     | ILMN_2364174  | CSNK1A1  | 1.302       | 4.95E-04 | -                                                     |
| 5         | q33.1  | 150591711     | ILMN_2221046  | GM2A     | 1.740       | 8.70E-04 | -                                                     |
| 6         | p25.3  | 1312675       | ILMN_1669046  | FOXQ1    | 0.509       | 7.99E-04 | ectoderm development (bp), epidermis development (bp) |
| 6         | q27    | 170591294     | ILMN_1743373  | DLL1     | 0.639       | 7.09E-05 | -                                                     |
| 7         | p22.3  | 937540        | ILMN_2047511  | ADAP1    | 0.641       | 8.03E-04 | -                                                     |
| 7         | p22.3  | 2552163       | ILMN_1663080  | LFNG     | 0.484       | 9.03E-04 | -                                                     |
| 7         | p15.2  | 26191860      | ILMN_2049766  | NFE2L3   | 1.621       | 3.69E-04 | -                                                     |
| 7         | p14.3  | 30536237      | ILMN_2101526  | GGCT.1   | 1.770       | 1.89E-04 | -                                                     |
| 7         | q11.22 | 69063905      | ILMN_1749081  | AUTS2    | 0.733       | 8.00E-04 | -                                                     |
| 7         | q21.11 | 79998891      | ILMN_1796094  | CD36.1   | 5.543       | 1.27E-06 | -                                                     |
| 7         | q21.11 | 79998891      | ILMN_1784863  | CD36     | 3.987       | 3.00E-04 | -                                                     |
| 8         | p23.1  | 7286410       | ILMN_1714587  | DEFB103B | 4.708       | 3.15E-04 | -                                                     |
| 8         | p23.1  | 7286410       | ILMN_2132515  | DEFB103A | 3.284       | 7.79E-04 | -                                                     |
| 8         | q11.23 | 54764368      | ILMN_1738558  | RGS20.1  | 2.303       | 9.26E-05 | -                                                     |
| 8         | q24.3  | 144519825     | ILMN_1702389  | ZC3H3    | 0.761       | 4.50E-04 | -                                                     |
| 9         | p22.3  | 14081842      | ILMN_1848552  | NFIB     | 0.677       | 3.75E-04 | -                                                     |
| 9         | p22.3  | 15170843      | ILMN_1769290  | TTC39B.1 | 1.750       | 3.39E-04 | -                                                     |
| 9         | p13.2  | 36572859      | ILMN_2212909  | MELK     | 1.572       | 5.00E-04 | -                                                     |
| 9         | q21.11 | 71939488      | ILMN_2179717  | FAM189A2 | 0.566       | 2.16E-04 | -                                                     |
| 9         | q21.13 | 74729511      | ILMN_1812494  | GDA      | 1.336       | 9.28E-04 | -                                                     |
| 9         | q31.3  | 114122972     | ILMN_2261882  | KIAA0368 | 0.757       | 4.11E-04 | -                                                     |

| AL vs. NN |        |               |               |          |             |          |                                                       |
|-----------|--------|---------------|---------------|----------|-------------|----------|-------------------------------------------------------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term                                               |
| 10        | p12.31 | 20105168      | ILMN_1753312  | PLXDC2   | 1.469       | 7.54E-04 | -                                                     |
| 10        | q22.1  | 72058729      | ILMN_1690523  | LRRC20   | 2.243       | 4.46E-04 | -                                                     |
| 10        | q23.1  | 85933494      | ILMN_1802192  | C10orf99 | 5.658       | 3.00E-04 | -                                                     |
| 10        | q23.31 | 91152303      | ILMN_1707695  | IFIT1    | 2.111       | 6.77E-05 | -                                                     |
| 10        | q23.33 | 94211441      | ILMN_1769883  | IDE      | 1.552       | 1.98E-04 | -                                                     |
| 10        | q25.1  | 106028631     | ILMN_1740234  | GSTO2    | 0.764       | 4.07E-04 | -                                                     |
| 11        | q12.1  | 59548550      | ILMN_2146761  | FABP5    | 2.596       | 2.94E-04 | ectoderm development (bp), epidermis development (bp) |
| 11        | q13.2  | 67351066      | ILMN_1679809  | GSTP1    | 1.357       | 5.54E-04 | -                                                     |
| 11        | q13.3  | 69455855      | ILMN_1688480  | CCND1    | 0.417       | 5.72E-04 | -                                                     |
| 11        | q13.5  | 76493295      | ILMN_1801443  | TSKU     | 0.709       | 7.26E-04 | -                                                     |
| 12        | p13.1  | 12878851      | ILMN_1814859  | DDX47.1  | 0.770       | 5.89E-06 | -                                                     |
| 12        | q13.13 | 52840435      | ILMN_1721354  | KRT6B    | 14.217      | 1.25E-04 | ectoderm development (bp)                             |
| 12        | q13.13 | 52862300      | ILMN_1754576  | KRT6C    | 33.533      | 4.64E-04 | -                                                     |
| 12        | q13.13 | 52880958      | ILMN_2219002  | KRT6A    | 22.890      | 7.54E-06 | ectoderm development (bp)                             |
| 12        | q13.13 | 53083410      | ILMN_1801428  | KRT77    | 0.152       | 6.83E-04 | -                                                     |
| 12        | q14.2  | 64660763      | ILMN_1770616  | C12orf56 | 1.866       | 1.06E-05 | -                                                     |
| 12        | q23.1  | 96366440      | ILMN_2074748  | HAL      | 2.146       | 7.20E-05 | -                                                     |
| 12        | q23.1  | 96366440      | ILMN_1719988  | HAL      | 2.095       | 2.40E-04 | -                                                     |
| 12        | q24.13 | 113344582     | ILMN_2410826  | OAS1.1   | 1.483       | 2.05E-06 | -                                                     |
| 12        | q24.13 | 113376157     | ILMN_1745397  | OAS3     | 1.770       | 9.35E-05 | -                                                     |
| 12        | q24.13 | 113416200     | ILMN_1674063  | OAS2.3   | 3.705       | 3.29E-06 | -                                                     |
| 12        | q24.31 | 121458121     | ILMN_1674811  | OASL     | 3.222       | 2.44E-04 | -                                                     |
| 12        | q24.31 | 122355768     | ILMN_1800341  | WDR66    | 5.029       | 3.76E-06 | -                                                     |
| 13        | q12.11 | 20761609      | ILMN_1769388  | GJB2     | 4.115       | 7.71E-04 | -                                                     |
| 13        | q12.11 | 20796110      | ILMN_2226223  | GJB6     | 2.396       | 9.38E-05 | -                                                     |

| AL vs. NN |        |               |               |          |             |          |                                                       |
|-----------|--------|---------------|---------------|----------|-------------|----------|-------------------------------------------------------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term                                               |
| 13        | q12.11 | 20796110      | ILMN_1718671  | GJB6     | 3.582       | 5.40E-04 | -                                                     |
| 13        | q14.11 | 43460524      | ILMN_2388547  | EPSTI1   | 2.139       | 5.70E-05 | -                                                     |
| 13        | q22.1  | 73674713      | ILMN_1696302  | FABP5    | 2.926       | 8.84E-04 | ectoderm development (bp), epidermis development (bp) |
| 13        | q34    | 111766906     | ILMN_1796912  | ARHGEF7  | 0.709       | 8.49E-04 | -                                                     |
| 13        | q34    | 114523524     | ILMN_1784749  | GAS6.2   | 0.698       | 9.38E-04 | -                                                     |
| 14        | q11.2  | 21152746      | ILMN_1696974  | RNASE4   | 0.592       | 7.22E-04 | -                                                     |
| 14        | q11.2  | 21510385      | ILMN_1712849  | RNASE7   | 1.784       | 0.0010   | -                                                     |
| 14        | q11.2  | 23815515      | ILMN_1653200  | SLC22A17 | 0.666       | 6.98E-04 | -                                                     |
| 14        | q12    | 24620427      | ILMN_1745471  | IRF9     | 1.594       | 6.20E-04 | -                                                     |
| 14        | q32.12 | 94571182      | ILMN_2058782  | IFI27    | 9.888       | 6.16E-06 | -                                                     |
| 15        | q14    | 35270542      | ILMN_1734254  | ZNF770   | 1.450       | 0.0010   | -                                                     |
| 15        | q15.1  | 42359207      | ILMN_2217270  | PLA2G4D  | 2.419       | 3.74E-04 | -                                                     |
| 15        | q21.3  | 57668165      | ILMN_1730229  | CGNL1    | 0.407       | 1.19E-04 | -                                                     |
| 15        | q22.31 | 66585555      | ILMN_1795822  | DIS3L    | 0.648       | 7.35E-04 | -                                                     |
| 15        | q24.1  | 74032141      | ILMN_2141118  | C15orf59 | 0.559       | 9.76E-05 | -                                                     |
| 15        | q25.1  | 78632666      | ILMN_1658040  | CRABP1   | 0.447       | 7.65E-04 | -                                                     |
| 16        | p13.3  | 1203241       | ILMN_1671263  | CACNA1H  | 0.437       | 7.39E-04 | -                                                     |
| 16        | p12.2  | 22357257      | ILMN_1720270  | CDR2     | 0.731       | 1.91E-04 | -                                                     |
| 16        | p11.2  | 31500792      | ILMN_1685289  | C16orf58 | 0.743       | 3.81E-04 | -                                                     |
| 16        | q21    | 58496750      | ILMN_2305225  | NDRG4    | 2.965       | 2.42E-04 | -                                                     |
| 17        | q11.2  | 29233362      | ILMN_1763000  | ADAP2    | 1.913       | 3.18E-05 | -                                                     |
| 17        | q12    | 37415384      | ILMN_1754489  | FBXL20   | 1.569       | 3.75E-04 | -                                                     |
| 17        | q12    | 37782993      | ILMN_2304495  | PPP1R1B  | 0.442       | 2.02E-04 | -                                                     |
| 17        | q21.2  | 39766030      | ILMN_1736760  | KRT16    | 22.810      | 5.65E-05 | ectoderm development (bp), epidermis development (bp) |

| AL vs. NN |        |               |               |          |             |          |                                                                                                                                                                                                                                                |
|-----------|--------|---------------|---------------|----------|-------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term                                                                                                                                                                                                                                        |
| 18        | q11.2  | 21178890      | ILMN_2075643  | ANKRD29  | 1.921       | 3.92E-04 | -                                                                                                                                                                                                                                              |
| 18        | q12.2  | 33877680      | ILMN_1761322  | FHOD3    | 0.689       | 4.75E-04 | -                                                                                                                                                                                                                                              |
| 18        | q22.1  | 61637159      | ILMN_2397028  | SERPINB8 | 1.424       | 3.85E-04 | -                                                                                                                                                                                                                                              |
| 19        | p13.3  | 1285890       | ILMN_1764764  | MUM1     | 0.672       | 5.35E-04 | -                                                                                                                                                                                                                                              |
| 19        | p13.3  | 5842899       | ILMN_1653358  | FUT3     | 1.761       | 1.18E-04 | -                                                                                                                                                                                                                                              |
| 19        | p13.2  | 11685475      | ILMN_2078599  | ACP5     | 1.915       | 4.95E-04 | -                                                                                                                                                                                                                                              |
| 19        | q13.12 | 37025676      | ILMN_1660193  | ZNF529   | 0.733       | 8.91E-04 | -                                                                                                                                                                                                                                              |
| 19        | q13.2  | 40353964      | ILMN_2302757  | FCGBP    | 0.435       | 8.64E-04 | -                                                                                                                                                                                                                                              |
| 19        | q13.2  | 42891173      | ILMN_1803838  | CNFN     | 2.108       | 1.04E-04 | ectoderm development (bp), epidermis development (bp), keratinization (bp), keratinocyte differentiation (bp), epidermal cell differentiation (bp), cornified envelope (cc), epithelium development (bp), epithelial cell differentiation (bp) |
| 19        | q13.32 | 46733009      | ILMN_1743950  | IGFL1    | 2.628       | 1.83E-04 | -                                                                                                                                                                                                                                              |
| 19        | q13.43 | 58595212      | ILMN_1654946  | ZSCAN18  | 0.346       | 3.76E-04 | -                                                                                                                                                                                                                                              |
| 20        | p13    | 627259        | ILMN_1804822  | SRXN1    | 1.848       | 7.66E-04 | -                                                                                                                                                                                                                                              |
| 20        | p13    | 3229951       | ILMN_2164242  | UBE2F    | 1.511       | 2.97E-05 | -                                                                                                                                                                                                                                              |
| 20        | q13.12 | 43752066      | ILMN_1659085  | WFDC12   | 2.348       | 3.45E-04 | -                                                                                                                                                                                                                                              |
| 20        | q13.13 | 46285092      | ILMN_1667460  | SULF2    | 1.729       | 1.31E-04 | -                                                                                                                                                                                                                                              |
| 20        | q13.33 | 60883011      | ILMN_1773567  | LAMA5    | 0.647       | 7.47E-04 | ectoderm development (bp), epidermis development (bp), epithelium development (bp), epithelial cell differentiation (bp)                                                                                                                       |
| 21        | q22.3  | 42792231      | ILMN_1662358  | MX1      | 4.043       | 1.34E-05 | -                                                                                                                                                                                                                                              |
| 22        | q11.23 | 25202236      | ILMN_1762207  | SGSM1    | 0.538       | 1.73E-05 | -                                                                                                                                                                                                                                              |
| 22        | q12.3  | 32439019      | ILMN_1681526  | SLC5A1   | 1.565       | 1.80E-04 | -                                                                                                                                                                                                                                              |
| 22        | q12.3  | 35776354      | ILMN_1800512  | HMOX1    | 1.746       | 8.57E-05 | -                                                                                                                                                                                                                                              |

| AL vs. NN |        |               |               |          |             |          |         |
|-----------|--------|---------------|---------------|----------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
| 22        | q13.2  | 42069934      | ILMN_1763460  | NHP2L1   | 0.746       | 8.54E-04 | -       |
| 22        | q13.33 | 50961997      | ILMN_1701621  | SCO2     | 1.635       | 4.13E-05 | -       |
| AN vs. NN |        |               |               |          |             |          |         |
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
| 1         | p36.33 | 1550795       | ILMN_2282077  | MIB2     | 0.52        | 8.83E-04 | -       |
| 1         | p36.33 | 2115917       | ILMN_2097790  | C1orf86  | 0.56        | 8.12E-04 | -       |
| 1         | p36.22 | 12040369      | ILMN_1651385  | MFN2     | 0.70        | 4.61E-04 | -       |
| 1         | p36.12 | 22446461      | ILMN_1666392  | WNT4     | 0.70        | 7.42E-04 | -       |
| 1         | p36.12 | 23345941      | ILMN_1813840  | KDM1A    | 0.74        | 5.69E-05 | -       |
| 1         | p36.11 | 24128375      | ILMN_2122420  | HMGCL    | 0.61        | 2.19E-05 | -       |
| 1         | p35.1  | 32830704      | ILMN_1734483  | BSDC1    | 0.66        | 2.08E-04 | -       |
| 1         | p34.3  | 36921319      | ILMN_1680703  | MRPS15   | 0.67        | 2.40E-04 | -       |
| 1         | p34.1  | 46016215      | ILMN_1728047  | AKR1A1   | 0.63        | 7.28E-04 | -       |
| 1         | p33    | 47799469      | ILMN_2104877  | CMPK1    | 1.49        | 8.05E-04 | -       |
| 1         | p32.3  | 52521797      | ILMN_1759359  | BTF3L4   | 1.61        | 9.37E-04 | -       |
| 1         | p32.3  | 53679771      | ILMN_2082130  | C1orf123 | 0.72        | 2.52E-04 | -       |
| 1         | p32.3  | 54317392      | ILMN_2052163  | YIPF1    | 1.34        | 4.11E-04 | -       |
| 1         | p32.3  | 54497347      | ILMN_1792508  | TMEM59   | 1.83        | 4.98E-04 | -       |
| 1         | p32.3  | 54665840      | ILMN_2041327  | MRPL37   | 0.64        | 6.33E-06 | -       |
| 1         | p31.3  | 68150744      | ILMN_2052208  | GADD45A  | 1.81        | 9.69E-04 | -       |
| 1         | p31.3  | 68564156      | ILMN_1660549  | WLS      | 1.37        | 2.74E-04 | -       |
| 1         | p31.1  | 70671365      | ILMN_1657790  | SRSF11   | 1.48        | 4.49E-04 | -       |
| 1         | p22.1  | 92764522      | ILMN_1657754  | RPAP2    | 1.31        | 7.26E-04 | -       |
| 1         | p22.1  | 93615299      | ILMN_1803279  | TMED5    | 1.57        | 9.35E-04 | -       |
| 1         | p21.3  | 97144430      | ILMN_1658531  | RPL7P9   | 1.68        | 2.23E-06 | -       |
| 1         | p13.2  | 111991558     | ILMN_1721989  | ATP5F1   | 1.32        | 8.55E-04 | -       |
| 1         | q21.2  | 147400506     | ILMN_1804539  | GPR89B   | 1.48        | 8.69E-04 | -       |

## AN vs. NN

| Chr | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
|-----|--------|---------------|---------------|----------|-------------|----------|---------|
| 1   | q21.3  | 151138498     | ILMN_1746598  | SCNM1    | 0.67        | 3.97E-04 | -       |
| 1   | q21.3  | 151264273     | ILMN_1666597  | PI4KB    | 0.68        | 1.45E-05 | -       |
| 1   | q22    | 155200766     | ILMN_1667222  | MTX1P1   | 0.71        | 1.78E-04 | -       |
| 1   | q22    | 156024543     | ILMN_1756352  | LAMTOR2  | 0.60        | 4.49E-04 | -       |
| 1   | q23.3  | 161719548     | ILMN_1767892  | DUSP12   | 1.32        | 3.14E-04 | -       |
| 1   | q24.3  | 171669300     | ILMN_1664175  | VAMP4    | 1.34        | 3.96E-04 | -       |
| 1   | q25.3  | 184759858     | ILMN_1667966  | FAM129A  | 1.49        | 4.77E-04 | -       |
| 1   | q31.2  | 193028552     | ILMN_2272074  | TROVE2   | 1.36        | 2.39E-04 | -       |
| 1   | q32.2  | 211346830     | ILMN_1655710  |          | 1.64        | 9.74E-04 | -       |
| 1   | q41    | 220267444     | ILMN_1671207  | IARS2    | 1.45        | 5.94E-04 | -       |
| 1   | q42.11 | 224415036     | ILMN_1712636  | NVL      | 0.70        | 3.50E-04 | -       |
| 1   | q42.13 | 228294380     | ILMN_1813817  | MRPL55   | 0.52        | 6.45E-04 | -       |
| 1   | q42.13 | 228294380     | ILMN_2348090  | MRPL55   | 0.66        | 8.94E-04 | -       |
| 1   | q42.2  | 231472850     | ILMN_1655485  | SPRTN    | 1.31        | 8.56E-04 | -       |
| 1   | q42.2  | 231664287     | ILMN_2211672  | TSNAX    | 1.43        | 1.03E-04 | -       |
| 1   | q43    | 237144639     | ILMN_1683447  | RPL35P1  | 0.56        | 3.35E-04 | -       |
| 1   | q44    | 246729748     | ILMN_1670263  | CNST     | 1.60        | 8.67E-04 | -       |
| 1   | q44    | 249144205     | ILMN_1800750  | ZNF692   | 0.64        | 1.59E-04 | -       |
| 2   | p25.3  | 3383446       | ILMN_1693317  | TRAPPC12 | 0.67        | 7.55E-04 | -       |
| 2   | p25.1  | 9563697       | ILMN_2087528  | CPSF3    | 1.59        | 1.38E-04 | -       |
| 2   | p25.1  | 9628615       | ILMN_2121068  | ADAM17   | 0.71        | 1.53E-04 | -       |
| 2   | p25.1  | 9724101       | ILMN_1674385  | YWHAQ    | 1.39        | 1.10E-04 | -       |
| 2   | p24.1  | 20096514      | ILMN_2083588  | TTC32    | 1.38        | 3.59E-04 | -       |
| 2   | p23.3  | 26256979      | ILMN_1793433  | RAB10    | 1.72        | 2.28E-05 | -       |
| 2   | p21    | 46769867      | ILMN_1810559  | RHOQ     | 1.99        | 1.44E-07 | -       |
| 2   | p15    | 62115859      | ILMN_1761242  | COMMD1   | 0.65        | 2.59E-05 | -       |
| 2   | p13.3  | 69947923      | ILMN_1711408  | ANXA4    | 1.62        | 4.03E-04 | -       |
| 2   | p13.3  | 70436576      | ILMN_1778691  | TIA1     | 1.41        | 3.17E-04 | -       |

## AN vs. NN

| Chr | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
|-----|--------|---------------|---------------|----------|-------------|----------|---------|
| 2   | p13.3  | 70485269      | ILMN_1679725  | PCYOX1   | 1.51        | 1.15E-05 | -       |
| 2   | p11.2  | 85822857      | ILMN_1655340  | RNF181   | 0.75        | 7.08E-04 | -       |
| 2   | q11.1  | 95752952      | ILMN_1760441  | MRPS5    | 0.62        | 6.60E-04 | -       |
| 2   | q11.2  | 101892553     | ILMN_1665877  | RNF149   | 1.85        | 4.00E-04 | -       |
| 2   | q12.2  | 105974169     | ILMN_2355831  | FHL2     | 1.78        | 4.88E-04 | -       |
| 2   | q12.3  | 109204922     | ILMN_1733176  | LIMS1    | 1.65        | 3.36E-05 | -       |
| 2   | q13    | 110371911     | ILMN_1724040  | SOWAHC   | 1.50        | 1.00E-04 | -       |
| 2   | q13    | 113341817     | ILMN_1797530  | CHCHD5   | 0.63        | 5.73E-04 | -       |
| 2   | q13    | 113931548     | ILMN_2154115  | PSD4     | 0.67        | 9.38E-05 | -       |
| 2   | q23.1  | 149894981     | ILMN_1693119  | LYPD6B   | 0.54        | 4.28E-05 | -       |
| 2   | q24.2  | 160569010     | ILMN_1717337  | MARCH7   | 1.79        | 9.97E-05 | -       |
| 2   | q31.1  | 170666591     | ILMN_1691570  | METTL5   | 1.46        | 8.99E-04 | -       |
| 2   | q31.1  | 173600569     | ILMN_1661802  | RAPGEF4  | 1.34        | 7.49E-04 | -       |
| 2   | q31.1  | 175584636     | ILMN_2402936  | H3F3AP4  | 1.73        | 3.07E-04 | -       |
| 2   | q31.2  | 179296141     | ILMN_1758474  | PRKRA    | 1.40        | 2.01E-04 | -       |
| 2   | q32.2  | 191273081     | ILMN_1710209  | MFSD6    | 1.46        | 3.99E-04 | -       |
| 2   | q33.1  | 201843216     | ILMN_1779486  | FAM126B  | 1.37        | 6.95E-05 | -       |
| 2   | q33.1  | 203241659     | ILMN_2070896  | BMPR2    | 1.64        | 1.00E-04 | -       |
| 2   | q33.1  | 203241659     | ILMN_1789095  | BMPR2    | 1.44        | 2.91E-04 | -       |
| 2   | q33.2  | 204298405     | ILMN_2275502  | RAPH1    | 1.36        | 9.77E-04 | -       |
| 2   | q35    | 220462582     | ILMN_1690085  | STK11IP  | 0.72        | 4.07E-04 | -       |
| 2   | q36.3  | 228189885     | ILMN_1680171  | MFF      | 1.37        | 4.43E-04 | -       |
| 2   | q37.3  | 241375088     | ILMN_1801516  | GPC1     | 0.47        | 1.23E-04 | -       |
| 2   | q37.3  | 242254515     | ILMN_1748546  | SEPT2    | 1.56        | 2.12E-04 | -       |
| 3   | p25.3  | 9958758       | ILMN_1798790  | IL17RC   | 0.69        | 3.96E-04 | -       |
| 3   | p24.3  | 19988571      | ILMN_1805800  | RAB5A    | 1.82        | 7.28E-04 | -       |
| 3   | p22.1  | 42825790      | ILMN_1674522  | HIGD1A   | 1.68        | 9.79E-04 | -       |
| 3   | p21.31 | 48894369      | ILMN_1741392  | SLC25A20 | 0.69        | 4.49E-04 | -       |

| AN vs. NN |        |               |               |           |             |          |         |
|-----------|--------|---------------|---------------|-----------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene      | fold change | P-value  | GO-term |
| 3         | p21.31 | 49067140      | ILMN_1676002  | QRICH1    | 0.76        | 4.37E-04 | -       |
| 3         | p21.31 | 49754277      | ILMN_2392286  | AMIGO3    | 0.66        | 5.55E-04 | -       |
| 3         | p21.31 | 50392180      | ILMN_1712035  | TMEM115   | 0.69        | 1.54E-04 | -       |
| 3         | p14.1  | 69103881      | ILMN_1689142  | UBA3      | 1.34        | 7.66E-04 | -       |
| 3         | p11.2  | 87276435      | ILMN_1741176  | CHMP2B    | 1.51        | 9.75E-04 | -       |
| 3         | q12.1  | 99979844      | ILMN_2228044  | TBC1D23   | 1.37        | 4.81E-04 | -       |
| 3         | q12.3  | 101280706     | ILMN_1672565  | TRMT10C   | 1.36        | 8.90E-04 | -       |
| 3         | q12.3  | 101292939     | ILMN_1807994  | PCNP      | 1.48        | 1.86E-04 | -       |
| 3         | q12.3  | 101399935     | ILMN_1656662  | RPL24     | 0.68        | 2.49E-05 | -       |
| 3         | q13.2  | 113437841     | ILMN_2180606  | NAA50     | 1.45        | 1.44E-05 | -       |
| 3         | q21.1  | 122513642     | ILMN_1793743  | DIRC2     | 1.36        | 6.20E-04 | -       |
| 3         | q21.3  | 129033615     | ILMN_1773964  | H1FX      | 0.52        | 9.78E-04 | -       |
| 3         | q25.1  | 150259785     | ILMN_1706817  | SERP1     | 1.56        | 3.05E-05 | -       |
| 3         | q27.1  | 182655862     | ILMN_1810719  | DCUN1D1   | 1.69        | 5.64E-04 | -       |
| 3         | q27.1  | 183547173     | ILMN_2257665  | PARL      | 1.65        | 5.34E-04 | -       |
| 3         | q27.1  | 183892477     | ILMN_2402798  | AP2M1     | 0.53        | 4.69E-05 | -       |
| 3         | q29    | 194995465     | ILMN_2088825  | ACAP2     | 1.47        | 6.11E-06 | -       |
| 4         | p16.3  | 667369        | ILMN_2203588  | MYL5      | 0.74        | 6.94E-05 | -       |
| 4         | p16.1  | 6271576       | ILMN_1759023  | WFS1      | 0.60        | 6.74E-05 | -       |
| 4         | p15.2  | 24529098      | ILMN_2168449  | DHX15     | 1.46        | 4.65E-04 | -       |
| 4         | p15.2  | 26165077      | ILMN_1708537  | RBPJ      | 1.60        | 2.54E-04 | -       |
| 4         | p14    | 39552541      | ILMN_1713892  | C4orf34   | 1.96        | 4.52E-05 | -       |
| 4         | p12    | 48018791      | ILMN_1811593  | NIPAL1    | 1.55        | 1.12E-04 | -       |
| 4         | q13.3  | 71554196      | ILMN_1745423  | UTP3      | 1.44        | 4.19E-04 | -       |
| 4         | q21.1  | 77035812      | ILMN_1771835  | NUP54     | 1.55        | 8.27E-04 | -       |
| 4         | q23    | 100737990     | ILMN_1664691  | DAPP1     | 1.34        | 7.73E-05 | -       |
| 4         | q25    | 110354971     | ILMN_2334303  | SEC24B    | 1.39        | 1.95E-04 | -       |
| 4         | q26    | 120379123     | ILMN_1691402  | RP11-33B1 | 1.53        | 2.37E-04 | -       |

| AN vs. NN |        |               |               |                 |             |          |         |
|-----------|--------|---------------|---------------|-----------------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene            | fold change | P-value  | GO-term |
| 4         | q31.3  | 152041431     | ILMN_1653133  | SH3D19          | 1.53        | 3.63E-04 | -       |
| 4         | q31.3  | 153539784     | ILMN_2088124  | TMEM154         | 1.75        | 3.34E-04 | -       |
| 4         | q32.3  | 169418217     | ILMN_1698732  | PALLD           | 1.94        | 9.88E-05 | -       |
| 4         | q35.1  | 184560788     | ILMN_1708660  | RWDD4           | 1.40        | 6.33E-04 | -       |
| 5         | p15.31 | 7859272       | ILMN_1750160  | FASTKD3         | 1.35        | 8.28E-04 | -       |
| 5         | p12    | 43602825      | ILMN_2336647  | NNT             | 1.53        | 7.17E-05 | -       |
| 5         | q13.3  | 76326210      | ILMN_2064917  | AGGF1           | 1.62        | 2.58E-04 | -       |
| 5         | q14.1  | 79275584      | ILMN_1679071  | MTX3            | 1.49        | 1.32E-05 | -       |
| 5         | q23.2  | 126853301     | ILMN_1685140  | PRRC1           | 1.72        | 2.91E-04 | -       |
| 5         | q31.1  | 134669590     | ILMN_2373495  | H2AFY           | 1.32        | 7.51E-04 | -       |
| 5         | q31.2  | 137841784     | ILMN_2222991  | ETF1            | 1.55        | 2.72E-04 | -       |
| 5         | q32    | 147443535     | ILMN_1690017  | SPINK5          | 0.62        | 3.99E-04 | -       |
| 5         | q32    | 149473865     | ILMN_1815292  | CTB-13H5        | 1.87        | 6.30E-04 | -       |
| 5         | q33.1  | 151121877     | ILMN_1670609  | ATOX1           | 0.54        | 2.20E-04 | -       |
| 5         | q33.3  | 158690089     | ILMN_2202481  | UBLCP1          | 1.56        | 6.27E-04 | -       |
| 5         | q35.1  | 172483355     | ILMN_1776788  | CREBRF          | 1.65        | 3.25E-05 | -       |
| 6         | p24.3  | 8013800       | ILMN_1776352  | BLOC1S5         | 1.30        | 6.60E-04 | -       |
| 6         | p24.2  | 10747973      | ILMN_1685258  | TMEM14B         | 1.43        | 2.93E-04 | -       |
| 6         | p24.1  | 12514342      | ILMN_1716014  | RPL15P3         | 1.40        | 4.55E-04 | -       |
| 6         | p22.3  | 16299343      | ILMN_2153332  | ATXN1           | 1.64        | 4.50E-04 | -       |
| 6         | p22.1  | 30034486      | ILMN_1747598  | PPP1R11         | 1.42        | 3.53E-04 | -       |
| 6         | p22.1  | 30152232      | ILMN_1738704  | TRIM26          | 0.73        | 6.02E-04 | -       |
| 6         | p22.1  | 30297359      | ILMN_2186597  | TRIM39R         | 0.71        | 7.86E-05 | -       |
| 6         | p21.33 | 31497996      | ILMN_1686626  | ATP6V1G2-DDX39B | 0.39        | 9.72E-04 | -       |
| 6         | p21.33 | 31654739      | ILMN_2152402  | LY6G6E          | 0.70        | 2.73E-04 | -       |
| 6         | p21.33 | 31937587      | ILMN_1726990  | DOM3Z           | 0.72        | 2.86E-04 | -       |
| 6         | p21.32 | 33246885      | ILMN_2212354  | WDR46           | 0.65        | 7.36E-04 | -       |

| AN vs. NN |        |               |               |            |             |          |         |
|-----------|--------|---------------|---------------|------------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene       | fold change | P-value  | GO-term |
| 6         | p21.31 | 34231088      | ILMN_1775243  | RPL35P2    | 0.64        | 3.36E-05 | -       |
| 6         | p21.2  | 37225548      | ILMN_2123730  | TBC1D22B   | 0.64        | 9.11E-05 | -       |
| 6         | p21.1  | 43193367      | ILMN_2380588  | C6orf108   | 0.52        | 6.30E-05 | -       |
| 6         | p21.1  | 44187393      | ILMN_2338963  | SLC29A1    | 0.70        | 8.59E-04 | -       |
| 6         | p12.3  | 51274879      | ILMN_1748904  | RP3-437C15 | 1.48        | 5.09E-04 | -       |
| 6         | p12.1  | 54711569      | ILMN_1782863  | FAM83B     | 1.45        | 8.17E-04 | -       |
| 6         | p12.1  | 56322785      | ILMN_1675992  | DST        | 1.57        | 1.66E-04 | -       |
| 6         | q13    | 70385694      | ILMN_1652128  | LMBRD1     | 1.80        | 2.40E-04 | -       |
| 6         | q13    | 71123011      | ILMN_2225608  | FAM135A    | 1.41        | 9.51E-05 | -       |
| 6         | q14.1  | 75962640      | ILMN_1735680  | TMEM30A    | 1.48        | 8.66E-04 | -       |
| 6         | q15    | 89319985      | ILMN_1734198  | RNGTT      | 0.72        | 6.94E-04 | -       |
| 6         | q21    | 109687717     | ILMN_1783852  | CD164      | 1.49        | 1.18E-04 | -       |
| 6         | q22.1  | 116422012     | ILMN_1680673  | NT5DC1     | 1.74        | 1.79E-05 | -       |
| 6         | q22.33 | 127609855     | ILMN_2167011  | ECHDC1     | 1.35        | 6.24E-04 | -       |
| 6         | q23.3  | 136663875     | ILMN_2216815  | MAP7       | 1.67        | 1.56E-04 | -       |
| 6         | q23.3  | 136878185     | ILMN_1726547  | MAP3K5     | 1.50        | 1.66E-04 | -       |
| 6         | q27    | 167622119     | ILMN_1746652  | RP11-568A7 | 1.62        | 5.55E-04 | -       |
| 7         | p22.1  | 6061881       | ILMN_2156267  | EIF2AK1    | 0.65        | 8.91E-05 | -       |
| 7         | p21.3  | 12250926      | ILMN_2067607  | TMEM106B   | 1.78        | 7.50E-05 | -       |
| 7         | p15.3  | 22550235      | ILMN_2038774  | EEF1A1P6   | 1.31        | 3.86E-04 | -       |
| 7         | p14.3  | 30050203      | ILMN_1665243  | FKBP14     | 1.32        | 8.88E-05 | -       |
| 7         | p14.3  | 30536237      | ILMN_2101526  | GGCT       | 1.62        | 5.42E-04 | -       |
| 7         | p14.2  | 35840542      | ILMN_1729019  | SEPT7      | 1.71        | 3.52E-04 | -       |
| 7         | p13    | 44646238      | ILMN_1733869  | OGDH       | 0.55        | 5.71E-04 | -       |
| 7         | q11.23 | 72300235      | ILMN_1679045  | SBDSP1     | 1.63        | 2.71E-04 | -       |
| 7         | q22.1  | 98923533      | ILMN_1759915  | ARPC1A     | 0.48        | 7.33E-04 | -       |
| 7         | q22.1  | 99046579      | ILMN_2310621  | ATP5J2     | 0.69        | 7.42E-04 | -       |
| 7         | q22.1  | 99746530      | ILMN_1779735  | C7orf59    | 0.41        | 1.22E-05 | -       |

| AN vs. NN |        |               |               |           |             |          |         |
|-----------|--------|---------------|---------------|-----------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene      | fold change | P-value  | GO-term |
| 7         | q22.1  | 100303676     | ILMN_1680091  | POP7      | 0.53        | 2.11E-04 | -       |
| 7         | q22.1  | 100875373     | ILMN_1658351  | CLDN15    | 0.50        | 3.85E-04 | -       |
| 7         | q22.1  | 102937869     | ILMN_1728660  | PMPCB     | 1.43        | 3.17E-04 | -       |
| 7         | q22.3  | 105730949     | ILMN_2377174  | SYPL1     | 1.99        | 2.79E-04 | -       |
| 7         | q22.3  | 107204403     | ILMN_1776858  | DUS4L     | 1.38        | 5.62E-06 | -       |
| 7         | q33    | 134464401     | ILMN_1730487  | CALD1     | 1.77        | 6.03E-04 | -       |
| 7         | q33    | 135611509     | ILMN_1791478  | MTPN      | 1.73        | 5.86E-04 | -       |
| 7         | q36.1  | 150754297     | ILMN_2078389  | SLC4A2    | 0.67        | 9.10E-04 | -       |
| 7         | q36.1  | 150782954     | ILMN_1795918  | AGAP3     | 0.77        | 2.02E-04 | -       |
| 8         | p21.2  | 26240414      | ILMN_1718961  | BNIP3L    | 1.85        | 8.70E-04 | -       |
| 8         | p21.1  | 27590835      | ILMN_1793146  | CCDC25    | 1.37        | 3.05E-04 | -       |
| 8         | p21.1  | 28558844      | ILMN_1778226  | EXTL3     | 0.70        | 7.50E-04 | -       |
| 8         | p12    | 29952914      | ILMN_1752591  | LEPROTL1  | 1.70        | 4.42E-05 | -       |
| 8         | p12    | 30643126      | ILMN_1768582  | PPP2CB    | 2.53        | 9.21E-06 | -       |
| 8         | p12    | 34180510      | ILMN_1671372  | RP1-84O15 | 1.39        | 5.51E-04 | -       |
| 8         | p11.21 | 41348001      | ILMN_1778673  | GOLGA7    | 1.93        | 1.33E-04 | -       |
| 8         | p11.21 | 42708444      | ILMN_1709265  | RNF170    | 1.65        | 3.54E-06 | -       |
| 8         | q13.1  | 66514694      | ILMN_1722066  | ARMC1     | 1.40        | 5.41E-04 | -       |
| 8         | q13.3  | 71485677      | ILMN_1737146  | TRAM1     | 1.91        | 1.13E-04 | -       |
| 8         | q22.3  | 104310661     | ILMN_1659297  | FZD6      | 1.87        | 5.72E-04 | -       |
| 8         | q24.12 | 120220610     | ILMN_1770653  | MAL2      | 1.54        | 7.68E-05 | -       |
| 8         | q24.13 | 124260849     | ILMN_2402558  | ZHX1      | 1.53        | 9.24E-05 | -       |
| 8         | q24.13 | 125500726     | ILMN_1701058  | TATDN1    | 1.51        | 2.62E-04 | -       |
| 8         | q24.13 | 126010739     | ILMN_2041293  | SQLE      | 1.46        | 1.86E-04 | -       |
| 8         | q24.21 | 130853716     | ILMN_2122374  | FAM49B    | 1.38        | 4.19E-04 | -       |
| 8         | q24.3  | 145728356     | ILMN_1795257  | GPT       | 0.70        | 3.68E-04 | -       |
| 9         | p24.1  | 6011043       | ILMN_1780842  | RANBP6    | 1.37        | 9.24E-04 | -       |
| 9         | p23    | 12693435      | ILMN_2054652  | TYRP1     | 1.68        | 4.97E-04 | -       |

| AN vs. NN |        |               |               |          |             |          |         |
|-----------|--------|---------------|---------------|----------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
| 9         | p22.1  | 19049372      | ILMN_1783709  | RRAGA    | 1.41        | 3.63E-04 | -       |
| 9         | p21.3  | 22002902      | ILMN_2376723  | CDKN2B   | 1.67        | 5.30E-04 | -       |
| 9         | p21.3  | 22002902      | ILMN_1723198  | CDKN2B   | 1.91        | 1.55E-04 | -       |
| 9         | p13.3  | 35099888      | ILMN_1663002  | STOML2   | 0.52        | 2.31E-04 | -       |
| 9         | p13.3  | 35812957      | ILMN_1697820  | HINT2    | 0.73        | 3.34E-04 | -       |
| 9         | q21.2  | 80912059      | ILMN_1692938  | PSAT1    | 1.31        | 4.77E-04 | -       |
| 9         | q21.31 | 82006219      | ILMN_1677237  | CHCHD2P9 | 0.69        | 3.98E-04 | -       |
| 9         | q22.31 | 95473645      | ILMN_2380418  | BICD2    | 1.45        | 9.00E-05 | -       |
| 9         | q22.33 | 101984346     | ILMN_1801852  | SEC61B   | 1.33        | 9.12E-04 | -       |
| 9         | q31.1  | 108006903     | ILMN_1700695  | SLC44A1  | 1.37        | 6.91E-04 | -       |
| 9         | q31.1  | 108006903     | ILMN_1758673  | SLC44A1  | 1.52        | 6.47E-04 | -       |
| 9         | q31.3  | 111696461     | ILMN_2191929  | FAM206A  | 1.44        | 5.15E-04 | -       |
| 9         | q31.3  | 111777432     | ILMN_1788384  | TMEM245  | 1.86        | 2.15E-04 | -       |
| 9         | q32    | 114980715     | ILMN_1768197  | PTBP3    | 1.48        | 6.20E-04 | -       |
| 9         | q34.13 | 134000948     | ILMN_1666049  | NUP214   | 0.68        | 7.41E-05 | -       |
| 9         | q34.13 | 134735494     | ILMN_1716876  | MED27    | 5.45        | 6.46E-04 | -       |
| 9         | q34.2  | 135906076     | ILMN_1723895  | GTF3C5   | 0.60        | 2.83E-04 | -       |
| 9         | q34.3  | 139567595     | ILMN_1732176  | AGPAT2   | 0.56        | 7.47E-04 | -       |
| 9         | q34.3  | 139702413     | ILMN_1760628  | RABL6    | 0.61        | 4.33E-04 | -       |
| 10        | p13    | 16632610      | ILMN_1721657  | RSU1     | 1.58        | 1.12E-04 | -       |
| 10        | p11.22 | 33466420      | ILMN_1699574  | NRP1     | 1.63        | 5.87E-04 | -       |
| 10        | q11.21 | 43077042      | ILMN_1901934  | ZNF33B   | 0.76        | 1.88E-04 | -       |
| 10        | q21.2  | 61788159      | ILMN_2390609  | ANK3     | 1.84        | 1.19E-05 | -       |
| 10        | q22.1  | 70883268      | ILMN_1781039  | VPS26A   | 1.80        | 8.46E-06 | -       |
| 10        | q23.1  | 86088342      | ILMN_1742124  | FAM190B  | 1.40        | 9.69E-04 | -       |
| 10        | q23.31 | 89622870      | ILMN_1701134  | PTEN     | 1.54        | 4.24E-05 | -       |
| 10        | q23.31 | 90694831      | ILMN_1671703  | ACTA2    | 2.82        | 1.42E-04 | -       |
| 10        | q24.32 | 103348045     | ILMN_2047112  | DPCD     | 0.71        | 7.67E-05 | -       |

AN vs. NN

| Chr | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
|-----|--------|---------------|---------------|----------|-------------|----------|---------|
| 10  | q24.32 | 104183002     | ILMN_1773018  | CUEDC2   | 0.74        | 1.82E-04 | -       |
| 10  | q25.1  | 111767720     | ILMN_1787378  | ADD3     | 1.35        | 5.77E-04 | -       |
| 10  | q26.3  | 131265448     | ILMN_1795639  | MGMT     | 0.70        | 2.76E-04 | -       |
| 11  | p15.5  | 417933        | ILMN_1798679  | ANO9     | 0.56        | 8.03E-04 | -       |
| 11  | p15.5  | 494512        | ILMN_1660880  | RNH1     | 0.53        | 5.09E-04 | -       |
| 11  | p15.5  | 1968508       | ILMN_1806123  | MRPL23   | 0.59        | 8.28E-04 | -       |
| 11  | p15.4  | 2920951       | ILMN_2382505  | SLC22A18 | 0.59        | 6.69E-04 | -       |
| 11  | p15.4  | 7686331       | ILMN_1739576  | CYB5R2   | 0.65        | 8.40E-04 | -       |
| 11  | p15.3  | 10818597      | ILMN_1761519  | EIF4G2   | 1.55        | 3.33E-04 | -       |
| 11  | p15.1  | 17809595      | ILMN_1760049  | SERGEF   | 0.73        | 1.64E-05 | -       |
| 11  | p15.1  | 20385269      | ILMN_1664303  | HTATIP2  | 1.45        | 6.37E-04 | -       |
| 11  | p15.1  | 20409076      | ILMN_1662964  | PRMT3    | 1.38        | 8.83E-04 | -       |
| 11  | p14.1  | 30344598      | ILMN_1767642  | ARL14EP  | 1.47        | 3.31E-04 | -       |
| 11  | p13    | 34937677      | ILMN_1652357  | PDHX     | 1.38        | 6.90E-04 | -       |
| 11  | p11.2  | 47586888      | ILMN_1756355  | NDUFS3   | 0.63        | 2.36E-04 | -       |
| 11  | q12.1  | 57067112      | ILMN_1690826  | TNKS1BP1 | 0.51        | 4.67E-04 | -       |
| 11  | q13.1  | 63742079      | ILMN_1809495  | COX8A    | 0.47        | 2.23E-04 | -       |
| 11  | q13.1  | 63766030      | ILMN_1740960  | MACROD1  | 0.65        | 2.78E-04 | -       |
| 11  | q13.1  | 64008475      | ILMN_1674337  | FKBP2    | 0.60        | 3.13E-05 | -       |
| 11  | q13.1  | 64052729      | ILMN_1804332  | GPR137   | 0.54        | 5.58E-04 | -       |
| 11  | q13.1  | 64619114      | ILMN_1651832  | EHD1     | 0.57        | 8.68E-05 | -       |
| 11  | q13.1  | 64692143      | ILMN_2124082  | PPP2R5B  | 0.76        | 9.72E-04 | -       |
| 11  | q13.1  | 64888100      | ILMN_1664614  | FAU      | 0.69        | 4.18E-05 | -       |
| 11  | q13.1  | 64948665      | ILMN_1705261  | CAPN1    | 1.50        | 3.61E-05 | -       |
| 11  | q13.1  | 65383244      | ILMN_1783350  | PCNXL3   | 0.73        | 6.94E-04 | -       |
| 11  | q13.1  | 65622272      | ILMN_1705617  | CFL1     | 1.54        | 9.07E-04 | -       |
| 11  | q13.2  | 66104804      | ILMN_2398432  | BRMS1    | 0.66        | 1.52E-04 | -       |
| 11  | q13.2  | 66512242      | ILMN_1790637  | C11orf80 | 0.56        | 4.13E-04 | -       |

| AN vs. NN |        |               |               |          |             |          |         |
|-----------|--------|---------------|---------------|----------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
| 11        | q13.4  | 71639747      | ILMN_2356031  | RNF121   | 0.63        | 1.22E-04 | -       |
| 11        | q21    | 93268634      | ILMN_1809347  |          | 1.47        | 5.99E-04 | -       |
| 11        | q21    | 95523625      | ILMN_1791568  | CEP57    | 1.30        | 1.39E-04 | -       |
| 11        | q22.1  | 101981192     | ILMN_1709479  | YAP1     | 1.46        | 4.94E-04 | -       |
| 11        | q22.3  | 105948216     | ILMN_2096191  | AASDHPPT | 1.53        | 8.53E-04 | -       |
| 11        | q23.2  | 114270752     | ILMN_2183331  | RBM7     | 1.46        | 4.25E-04 | -       |
| 11        | q23.3  | 118889142     | ILMN_1814650  | TRAPPC4  | 0.54        | 1.50E-04 | -       |
| 12        | p13.31 | 6874682       | ILMN_1721046  | PTMS     | 0.57        | 1.73E-04 | -       |
| 12        | p12.3  | 16035325      | ILMN_1731194  | STRAP    | 1.64        | 4.47E-04 | -       |
| 12        | p12.3  | 16064106      | ILMN_1811551  | DERA     | 1.41        | 5.40E-05 | -       |
| 12        | p12.3  | 19592633      | ILMN_1803376  | AEBP2    | 1.41        | 1.15E-04 | -       |
| 12        | p11.23 | 27126128      | ILMN_1803995  | TM7SF3   | 1.47        | 5.94E-04 | -       |
| 12        | p11.22 | 28332210      | ILMN_1676523  | CCDC91   | 1.33        | 9.63E-04 | -       |
| 12        | p11.22 | 29490285      | ILMN_1712766  | ERGIC2   | 1.34        | 9.60E-04 | -       |
| 12        | q13.12 | 49208676      | ILMN_2195482  | CACNB3   | 0.72        | 9.80E-05 | -       |
| 12        | q13.12 | 50569571      | ILMN_1704369  | LIMA1    | 1.45        | 9.39E-04 | -       |
| 12        | q13.3  | 57057127      | ILMN_1719749  | PTGES3   | 1.43        | 2.28E-04 | -       |
| 12        | q14.2  | 64173583      | ILMN_1689704  | TMEM5    | 1.37        | 2.93E-04 | -       |
| 12        | q14.3  | 65563351      | ILMN_1727361  | LEMD3    | 1.53        | 7.11E-04 | -       |
| 12        | q14.3  | 66516842      | ILMN_2122176  | LLPH     | 1.57        | 7.26E-04 | -       |
| 12        | q21.2  | 76745577      | ILMN_2405078  | OSBPL8   | 1.73        | 2.68E-06 | -       |
| 12        | q21.2  | 76745577      | ILMN_1782459  | OSBPL8   | 1.78        | 5.36E-04 | -       |
| 12        | q21.31 | 82746085      | ILMN_1662318  | CCDC59   | 1.58        | 7.69E-04 | -       |
| 12        | q24.11 | 110288959     | ILMN_1764380  | GLTP     | 1.40        | 2.15E-05 | -       |
| 12        | q24.11 | 111157485     | ILMN_1701855  | PPP1CC   | 1.51        | 4.65E-05 | -       |
| 12        | q24.31 | 122755979     | ILMN_2404085  | CLIP1    | 1.80        | 2.30E-04 | -       |
| 12        | q24.31 | 123955925     | ILMN_1805643  | RILPL1   | 1.47        | 9.18E-04 | -       |
| 12        | q24.31 | 124118376     | ILMN_1725666  | GTF2H3   | 1.45        | 7.52E-04 | -       |

## AN vs. NN

| Chr | Band   | Position hg19 | Transcript ID | Gene      | fold change | P-value  | GO-term |
|-----|--------|---------------|---------------|-----------|-------------|----------|---------|
| 13  | q12.11 | 20532848      | ILMN_1661636  | ZMYM2     | 1.46        | 4.11E-04 | -       |
| 13  | q14.13 | 47065065      | ILMN_2187718  | COX17P1   | 0.59        | 6.72E-04 | -       |
| 13  | q14.2  | 48510622      | ILMN_2150019  | SUCLA2    | 1.50        | 3.78E-04 | -       |
| 13  | q14.2  | 48807294      | ILMN_1751708  | ITM2B     | 1.61        | 5.11E-04 | -       |
| 14  | q11.2  | 23527773      | ILMN_1699636  | ACIN1     | 0.68        | 9.17E-04 | -       |
| 14  | q11.2  | 23790498      | ILMN_1759154  | PABPN1    | 0.64        | 1.71E-04 | -       |
| 14  | q11.2  | 24583836      | ILMN_1765825  | DCAF11    | 1.31        | 1.67E-04 | -       |
| 14  | q12    | 31091318      | ILMN_1800543  | SCFD1     | 1.64        | 1.48E-04 | -       |
| 14  | q12    | 31363005      | ILMN_1772946  | STRN3     | 1.42        | 2.32E-04 | -       |
| 14  | q13.2  | 35554673      | ILMN_1662617  | PPP2R3C   | 1.39        | 1.15E-04 | -       |
| 14  | q21.2  | 45584803      | ILMN_2104784  | FKBP3     | 1.31        | 2.15E-04 | -       |
| 14  | q22.1  | 52456193      | ILMN_1696708  | C14orf166 | 1.33        | 5.43E-04 | -       |
| 14  | q23.1  | 58666798      | ILMN_1798254  | ACTR10    | 1.35        | 9.65E-04 | -       |
| 14  | q23.1  | 58711549      | ILMN_2387553  | PSMA3     | 1.76        | 4.47E-04 | -       |
| 14  | q23.2  | 63838075      | ILMN_1666761  | PPP2R5E   | 1.52        | 1.74E-04 | -       |
| 14  | q31.3  | 89029253      | ILMN_2335669  | ZC3H14    | 1.48        | 8.18E-05 | -       |
| 14  | q32.2  | 96829814      | ILMN_2181883  | C14orf129 | 1.48        | 1.46E-04 | -       |
| 14  | q32.2  | 100705322     | ILMN_1770892  | YY1       | 1.51        | 3.26E-04 | -       |
| 14  | q32.2  | 100705322     | ILMN_2181540  | YY1       | 1.48        | 1.25E-04 | -       |
| 14  | q32.31 | 102783714     | ILMN_2186858  | ZNF839    | 0.75        | 3.96E-04 | -       |
| 14  | q32.33 | 105219437     | ILMN_1787248  | SIVA1     | 0.54        | 6.28E-04 | -       |
| 15  | q14    | 38780304      | ILMN_1768958  | RASGRP1   | 1.48        | 3.99E-04 | -       |
| 15  | q22.2  | 60780483      | ILMN_2322499  | RORA      | 2.23        | 4.85E-04 | -       |
| 15  | q22.31 | 65409717      | ILMN_1772959  | PDCD7     | 1.60        | 1.23E-05 | -       |
| 15  | q25.1  | 78832747      | ILMN_2198376  | PSMA4     | 1.90        | 5.07E-04 | -       |
| 15  | q25.1  | 80351910      | ILMN_2156953  | ZFAND6    | 1.54        | 5.07E-05 | -       |
| 15  | q25.3  | 89010684      | ILMN_1722905  | MRPS11    | 0.74        | 1.80E-04 | -       |
| 15  | q26.3  | 99192200      | ILMN_1744023  | IGF1R     | 1.40        | 4.39E-04 | -       |

| AN vs. NN |        |               |               |          |             |          |         |
|-----------|--------|---------------|---------------|----------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
| 15        | q26.3  | 102506255     | ILMN_1739199  | WASH3P   | 0.49        | 6.07E-04 | -       |
| 16        | p11.2  | 29454226      | ILMN_1782633  |          | 0.43        | 1.68E-04 | -       |
| 16        | p11.2  | 29454551      | ILMN_1810680  |          | 0.58        | 2.26E-04 | -       |
| 16        | p11.2  | 29454570      | ILMN_1659343  |          | 0.60        | 9.41E-04 | -       |
| 16        | p11.2  | 29802040      | ILMN_1814589  | KIF22    | 0.69        | 2.70E-04 | -       |
| 16        | p11.2  | 29973998      | ILMN_1737644  | TMEM219  | 0.64        | 5.29E-04 | -       |
| 16        | q12.2  | 56642111      | ILMN_1686664  | MT2A     | 0.43        | 8.31E-06 | -       |
| 16        | q13    | 56764017      | ILMN_2196569  | NUP93    | 0.62        | 6.79E-05 | -       |
| 16        | q23.3  | 84087368      | ILMN_1651719  | MBTPS1   | 0.61        | 2.56E-04 | -       |
| 16        | q24.3  | 88875747      | ILMN_1722491  | APRT     | 0.47        | 9.53E-04 | -       |
| 16        | q24.3  | 88875747      | ILMN_1726410  | APRT     | 0.42        | 5.06E-04 | -       |
| 17        | p13.3  | 685513        | ILMN_1689652  | RNMTL1   | 0.76        | 4.51E-04 | -       |
| 17        | p13.1  | 7999218       | ILMN_1678255  | ALOXE3   | 0.53        | 2.71E-04 | -       |
| 17        | p13.1  | 8091652       | ILMN_2225746  | C17orf59 | 0.76        | 1.95E-04 | -       |
| 17        | p11.2  | 17584787      | ILMN_2060770  | RAI1     | 1.53        | 3.51E-04 | -       |
| 17        | p11.2  | 19140654      | ILMN_1815519  | EPN2     | 0.62        | 9.44E-04 | -       |
| 17        | q11.2  | 29109702      | ILMN_1660579  | CRLF3    | 1.40        | 6.50E-04 | -       |
| 17        | q21.31 | 40925454      | ILMN_2149566  | VPS25    | 0.59        | 9.64E-04 | -       |
| 17        | q21.32 | 46184911      | ILMN_1683950  | SNX11    | 1.42        | 3.30E-04 | -       |
| 17        | q21.32 | 46970127      | ILMN_1676393  | ATP5G1   | 0.68        | 2.28E-05 | -       |
| 17        | q21.33 | 47481414      | ILMN_1692651  | PHB      | 0.69        | 4.44E-04 | -       |
| 17        | q21.33 | 48445218      | ILMN_1811327  | MRPL27   | 0.67        | 9.86E-04 | -       |
| 17        | q21.33 | 49039535      | ILMN_2263718  | SPAG9    | 1.72        | 3.29E-04 | -       |
| 17        | q22    | 56566898      | ILMN_1771019  | MTMR4    | 1.68        | 4.05E-04 | -       |
| 17        | q25.1  | 73126320      | ILMN_1806432  | NT5C     | 0.72        | 7.90E-05 | -       |
| 17        | q25.1  | 74722921      | ILMN_1764323  | METTTL23 | 1.37        | 9.67E-04 | -       |
| 17        | q25.3  | 79008948      | ILMN_1699727  | BAIAP2   | 0.51        | 4.10E-04 | -       |
| 17        | q25.3  | 79981178      | ILMN_2275803  | LRRC45   | 0.66        | 2.36E-04 | -       |

## AN vs. NN

| Chr | Band   | Position hg19 | Transcript ID | Gene    | fold change | P-value  | GO-term |
|-----|--------|---------------|---------------|---------|-------------|----------|---------|
| 18  | p11.22 | 9334765       | ILMN_2214144  | TWSG1   | 1.85        | 7.88E-04 | -       |
| 18  | q11.2  | 21032787      | ILMN_2404135  | RIOK3   | 1.72        | 3.96E-06 | -       |
| 18  | q11.2  | 21032787      | ILMN_1724700  | RIOK3   | 1.90        | 2.60E-05 | -       |
| 18  | q11.2  | 23596578      | ILMN_1741782  | SS18    | 1.32        | 8.43E-04 | -       |
| 18  | q12.1  | 28709199      | ILMN_2402640  | DSC1    | 1.81        | 8.39E-05 | -       |
| 19  | p13.3  | 1941188       | ILMN_1706521  | CSNK1G2 | 3.85        | 5.91E-05 | -       |
| 19  | p13.3  | 4324041       | ILMN_1704500  | STAP2   | 0.46        | 9.76E-05 | -       |
| 19  | p13.3  | 4360370       | ILMN_1788062  | SH3GL1  | 0.71        | 3.69E-04 | -       |
| 19  | p13.3  | 5674958       | ILMN_1685088  | RPL36   | 0.61        | 4.71E-04 | -       |
| 19  | p13.3  | 5866182       | ILMN_2175712  | FUT5    | 0.50        | 9.72E-04 | -       |
| 19  | p13.2  | 7587496       | ILMN_1764383  | MCOLN1  | 0.58        | 8.64E-04 | -       |
| 19  | p13.2  | 7745761       | ILMN_2372639  | TRAPPC5 | 0.52        | 7.79E-04 | -       |
| 19  | p13.2  | 7991604       | ILMN_1784031  | TIMM44  | 0.68        | 2.10E-04 | -       |
| 19  | p13.2  | 12786534      | ILMN_1752967  | DHPS    | 0.64        | 1.46E-04 | -       |
| 19  | p13.2  | 12786534      | ILMN_2326997  | DHPS    | 0.69        | 2.35E-04 | -       |
| 19  | p13.11 | 17378232      | ILMN_1806937  | BABAM1  | 0.75        | 3.54E-04 | -       |
| 19  | p13.11 | 18043824      | ILMN_1811775  | CCDC124 | 0.61        | 4.70E-04 | -       |
| 19  | q13.11 | 33685490      | ILMN_2127605  | LRP3    | 0.61        | 6.13E-05 | -       |
| 19  | q13.2  | 38893775      | ILMN_1771870  | FAM98C  | 0.66        | 2.79E-04 | -       |
| 19  | q13.2  | 39261608      | ILMN_2064860  | LGALS7  | 0.73        | 1.41E-04 | -       |
| 19  | q13.2  | 39306068      | ILMN_1653115  | ECH1    | 0.57        | 6.86E-04 | -       |
| 19  | q13.2  | 39421348      | ILMN_1714515  | MRPS12  | 0.64        | 4.40E-04 | -       |
| 19  | q13.2  | 40325094      | ILMN_1719205  | FBL     | 0.77        | 6.83E-04 | -       |
| 19  | q13.2  | 41305048      | ILMN_1768773  | EGLN2   | 0.76        | 1.35E-04 | -       |
| 19  | q13.31 | 43979255      | ILMN_1805853  | PHLDB3  | 0.54        | 8.96E-04 | -       |
| 19  | q13.32 | 45409011      | ILMN_1740938  | APOE    | 0.49        | 2.47E-04 | -       |
| 19  | q13.33 | 48885827      | ILMN_2130411  | KDELR1  | 1.82        | 3.70E-04 | -       |
| 19  | q13.33 | 49458072      | ILMN_2321064  | BAX     | 0.55        | 3.70E-04 | -       |

| AN vs. NN |        |               |               |          |             |          |         |
|-----------|--------|---------------|---------------|----------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
| 19        | q13.33 | 49949550      | ILMN_1675131  | PIH1D1   | 0.68        | 2.98E-04 | -       |
| 19        | q13.33 | 49999634      | ILMN_1740587  | RPS11    | 1.30        | 3.16E-04 | -       |
| 19        | q13.33 | 50354138      | ILMN_1700109  | PTOV1    | 0.70        | 4.82E-04 | -       |
| 19        | q13.41 | 51848410      | ILMN_2300970  | ETFB     | 0.62        | 4.73E-04 | -       |
| 19        | q13.42 | 54606036      | ILMN_1784641  | NDUFA3   | 0.54        | 1.64E-05 | -       |
| 19        | q13.42 | 54694119      | ILMN_2368292  | TSEN34   | 1.32        | 1.30E-05 | -       |
| 20        | p13    | 4666882       | ILMN_1737988  | PRNP     | 1.44        | 6.55E-05 | -       |
| 20        | q11.22 | 33104214      | ILMN_2157435  | DYNLRB1  | 0.70        | 9.46E-04 | -       |
| 20        | q11.23 | 35280169      | ILMN_2385097  | NDRG3    | 1.34        | 1.22E-05 | -       |
| 20        | q11.23 | 36145819      | ILMN_1675612  | BLCAP    | 0.73        | 8.20E-05 | -       |
| 20        | q13.12 | 44563267      | ILMN_2232368  | PCIF1    | 0.67        | 6.75E-04 | -       |
| 20        | q13.12 | 44689624      | ILMN_1770035  | NCOA5    | 0.73        | 4.62E-04 | -       |
| 20        | q13.13 | 49505585      | ILMN_1657993  | ADNP     | 1.38        | 7.78E-04 | -       |
| 20        | q13.31 | 56063448      | ILMN_1809439  | HMGB1P1  | 1.51        | 4.16E-04 | -       |
| 20        | q13.33 | 58508819      | ILMN_1718712  | FAM217B  | 1.52        | 1.30E-05 | -       |
| 20        | q13.33 | 60878061      | ILMN_1760143  | ADRM1    | 0.71        | 8.27E-05 | -       |
| 21        | q21.3  | 27088815      | ILMN_1772929  | ATP5J    | 1.61        | 4.73E-04 | -       |
| 21        | q21.3  | 30428126      | ILMN_1717868  | CCT8     | 1.58        | 3.69E-04 | -       |
| 22        | q11.21 | 18900294      | ILMN_1671365  | PRODH    | 0.54        | 1.90E-04 | -       |
| 22        | q11.21 | 21353393      | ILMN_1652486  | THAP7    | 0.67        | 8.04E-04 | -       |
| 22        | q12.1  | 29190543      | ILMN_1809433  | XBP1     | 1.64        | 5.48E-04 | -       |
| 22        | q12.2  | 29950797      | ILMN_1805916  | NIPSNAP1 | 1.43        | 6.71E-04 | -       |
| 22        | q12.3  | 32435477      | ILMN_1664610  | RPS17P16 | 1.37        | 1.70E-04 | -       |
| 22        | q12.3  | 35796056      | ILMN_1815169  | MCM5     | 0.55        | 3.15E-04 | -       |
| 22        | q12.3  | 36883237      | ILMN_2130635  | FOXRED2  | 0.77        | 7.61E-04 | -       |
| 22        | q12.3  | 36906897      | ILMN_1739847  | EIF3D    | 0.69        | 2.57E-04 | -       |
| 22        | q12.3  | 37406900      | ILMN_1691572  | TST      | 0.72        | 3.60E-04 | -       |
| 22        | q13.2  | 41460056      | ILMN_2038772  |          | 0.48        | 3.25E-05 | -       |

| AN vs. NN |        |               |               |            |             |          |         |
|-----------|--------|---------------|---------------|------------|-------------|----------|---------|
| Chr       | Band   | Position hg19 | Transcript ID | Gene       | fold change | P-value  | GO-term |
| 22        | q13.2  | 41460056      | ILMN_1749447  |            | 0.53        | 4.91E-05 | -       |
| 22        | q13.2  | 42017123      | ILMN_2166506  | XRCC6      | 0.53        | 1.81E-04 | -       |
| 22        | q13.33 | 50639408      | ILMN_1769787  | RP3-402G11 | 0.62        | 4.15E-04 | -       |
| AL vs AN  |        |               |               |            |             |          |         |
| Chr       | Band   | Position hg19 | Transcript ID | Gene       | fold change | P-value  | GO-term |
| 1         | p36.32 | 2409915       | ILMN_2061565  | PLCH2      | 0.50        | 9.57E-04 | -       |
| 1         | p34.2  | 43996547      | ILMN_2380163  | PTPRF      | 0.72        | 8.69E-04 | -       |
| 1         | p33    | 47649265      | ILMN_1708580  | PDZK1IP1   | 1.75        | 1.52E-05 | -       |
| 1         | p31.3  | 68591041      | ILMN_2283325  | WLS        | 0.61        | 8.95E-04 | -       |
| 1         | p22.1  | 94027347      | ILMN_1763638  | BCAR3      | 0.42        | 6.50E-05 | -       |
| 1         | q21.3  | 152321213     | ILMN_1743715  | FLG2       | 0.47        | 6.49E-04 | -       |
| 1         | q21.3  | 152538130     | ILMN_1808220  | LCE3E      | 7.18        | 3.26E-04 | -       |
| 1         | q21.3  | 152551857     | ILMN_1718395  | LCE3D      | 4.37        | 2.48E-04 | -       |
| 1         | q23.1  | 157678876     | ILMN_2247664  | FCRL2      | 0.62        | 7.68E-04 | -       |
| 1         | q32.1  | 202930997     | ILMN_1729237  | CYB5R1     | 0.68        | 4.66E-04 | -       |
| 1         | q32.2  | 209859510     | ILMN_2389501  | HSD11B1    | 0.42        | 7.28E-04 | -       |
| 1         | q42.3  | 235330210     | ILMN_2269564  | ARID4B     | 0.68        | 6.78E-04 | -       |
| 2         | q11.2  | 99410309      | ILMN_1776121  | KIAA1211L  | 0.49        | 4.71E-04 | -       |
| 2         | q13    | 113735596     | ILMN_2158713  | IL36G      | 2.65        | 7.66E-04 | -       |
| 2         | q31.1  | 171785036     | ILMN_1748018  | GORASP2    | 1.32        | 7.29E-05 | -       |
| 3         | p25.1  | 14186647      | ILMN_1790807  | XPC        | 0.60        | 5.98E-04 | -       |
| 3         | p22.1  | 42201661      | ILMN_1782069  | TRAK1      | 0.60        | 2.67E-04 | -       |
| 3         | q21.1  | 122044091     | ILMN_1669888  | CSTA       | 2.12        | 5.19E-04 | -       |
| 3         | q23    | 139279022     | ILMN_2153485  | NMNAT3     | 0.54        | 5.45E-04 | -       |
| 3         | q23    | 142025449     | ILMN_1809086  | XRN1       | 0.66        | 6.18E-04 | -       |
| 3         | q27.1  | 183353356     | ILMN_1678671  | KLHL24     | 0.56        | 9.05E-04 | -       |
| 3         | q29    | 193853934     | ILMN_1710284  | HES1       | 0.76        | 2.88E-04 | -       |

| AL vs AN |        |               |               |          |             |          |         |
|----------|--------|---------------|---------------|----------|-------------|----------|---------|
| Chr      | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
| 4        | q12    | 55524085      | ILMN_2229379  | KIT      | 0.53        | 8.15E-04 | -       |
| 4        | q35.1  | 184580420     | ILMN_1752086  | TRAPPC11 | 0.72        | 8.93E-04 | -       |
| 5        | q15    | 98104999      | ILMN_1776213  | RGMB     | 0.36        | 3.08E-04 | -       |
| 5        | q31.1  | 132202252     | ILMN_1666471  | UQCRQ    | 1.56        | 1.19E-04 | -       |
| 5        | q31.1  | 135364584     | ILMN_1663866  | TGFBI    | 0.62        | 8.01E-05 | -       |
| 5        | q35.1  | 172385732     | ILMN_2110532  | RPL26L1  | 1.67        | 1.37E-04 | -       |
| 5        | q35.1  | 172483355     | ILMN_1776788  | CREBRF   | 0.54        | 2.60E-04 | -       |
| 6        | p25.3  | 1312675       | ILMN_1669046  | FOXQ1    | 0.51        | 2.86E-04 | -       |
| 6        | p22.3  | 24428405      | ILMN_1765419  | GPLD1    | 0.73        | 2.88E-05 | -       |
| 6        | q25.1  | 149068464     | ILMN_1700024  | UST      | 0.65        | 4.43E-05 | -       |
| 7        | p15.3  | 23286182      | ILMN_2407389  | GPNMB    | 0.55        | 9.75E-04 | -       |
| 7        | p11.2  | 55086794      | ILMN_1798975  | EGFR     | 0.59        | 2.44E-04 | -       |
| 7        | q21.11 | 79998891      | ILMN_1796094  | CD36     | 4.53        | 2.38E-04 | -       |
| 7        | q31.1  | 110303110     | ILMN_1809292  | IMMP2L   | 0.77        | 8.18E-04 | -       |
| 8        | p23.1  | 7272382       | ILMN_1680965  | DEFB4B   | 11.38       | 8.92E-04 | -       |
| 8        | q22.1  | 98881339      | ILMN_1698685  | MATN2    | 0.71        | 6.29E-04 | -       |
| 9        | p13.2  | 36572859      | ILMN_2212909  | MELK     | 1.76        | 9.97E-04 | -       |
| 9        | q21.11 | 71944241      | ILMN_2179717  | FAM189A2 | 0.61        | 1.51E-04 | -       |
| 9        | q21.33 | 89559279      | ILMN_2062701  | GAS1     | 0.48        | 9.27E-04 | -       |
| 9        | q21.33 | 90340434      | ILMN_1812995  | CTSL1    | 2.93        | 6.24E-04 | -       |
| 9        | q33.2  | 125133359     | ILMN_2339835  | PTGS1    | 0.53        | 6.63E-04 | -       |
| 10       | p12.33 | 17631958      | ILMN_1725791  | PTPLA    | 1.40        | 9.05E-04 | -       |
| 10       | q11.21 | 43084563      | ILMN_1742935  | ZNF33B   | 0.71        | 1.73E-04 | -       |
| 10       | q22.1  | 72058729      | ILMN_1690523  | LRRC20   | 2.80        | 1.57E-04 | -       |
| 10       | q22.3  | 81910645      | ILMN_1685170  | ANXA11   | 0.57        | 8.04E-04 | -       |
| 10       | q23.1  | 85933494      | ILMN_1802192  | C10orf99 | 5.86        | 3.13E-04 | -       |
| 10       | q25.1  | 105995114     | ILMN_1808196  | GSTO1    | 1.60        | 6.43E-04 | -       |
| 10       | q26.13 | 125505152     | ILMN_1741688  | CPXM2    | 0.69        | 7.82E-04 | -       |

| AL vs AN |        |               |               |          |             |          |         |
|----------|--------|---------------|---------------|----------|-------------|----------|---------|
| Chr      | Band   | Position hg19 | Transcript ID | Gene     | fold change | P-value  | GO-term |
| 11       | q12.2  | 60897728      | ILMN_1789233  | VPS37C   | 0.67        | 6.92E-04 | -       |
| 11       | q12.3  | 62283377      | ILMN_1714567  | AHNAK    | 0.47        | 1.62E-04 | -       |
| 11       | q13.3  | 69924408      | ILMN_1717909  | ANO1     | 0.69        | 3.45E-04 | -       |
| 11       | q13.5  | 76494283      | ILMN_1801443  | TSKU     | 0.53        | 1.33E-04 | -       |
| 11       | q14.1  | 77532155      | ILMN_1779163  | C11orf67 | 0.59        | 9.47E-04 | -       |
| 12       | q13.13 | 52840435      | ILMN_1721354  | KRT6B    | 12.42       | 4.25E-04 | -       |
| 12       | q14.1  | 58213710      | ILMN_1692962  | CTDSP2   | 0.75        | 4.84E-04 | -       |
| 12       | q23.3  | 106457118     | ILMN_1689318  | NUAK1    | 0.41        | 6.54E-05 | -       |
| 12       | q24.13 | 113376157     | ILMN_1745397  | OAS3     | 1.58        | 5.18E-04 | -       |
| 13       | q13.1  | 32975814      | ILMN_1799487  | N4BP2L1  | 0.66        | 1.62E-04 | -       |
| 14       | q11.2  | 20937538      | ILMN_2172174  | PNP      | 2.25        | 1.11E-04 | -       |
| 14       | q11.2  | 21152336      | ILMN_1760727  | ANG      | 0.49        | 8.64E-04 | -       |
| 14       | q11.2  | 23495060      | ILMN_1744649  | PSMB5    | 1.84        | 6.97E-04 | -       |
| 14       | q11.2  | 23815515      | ILMN_1653200  | SLC22A17 | 0.69        | 4.80E-04 | -       |
| 14       | q23.1  | 60715986      | ILMN_1903159  | PPM1A    | 0.55        | 6.19E-04 | -       |
| 14       | q32.2  | 99977603      | ILMN_1838863  | CCDC85C  | 1.40        | 2.66E-04 | -       |
| 15       | q21.1  | 45422131      | ILMN_2404182  | DUOX1    | 1.40        | 6.92E-04 | -       |
| 15       | q21.3  | 57668703      | ILMN_1730229  | CGNL1    | 0.32        | 2.26E-05 | -       |
| 15       | q22.31 | 64388190      | ILMN_2365479  | SNX1     | 0.74        | 5.87E-06 | -       |
| 16       | p13.13 | 11038345      | ILMN_1781752  | CLEC16A  | 0.67        | 1.13E-04 | -       |
| 16       | q13    | 56700643      | ILMN_1715401  | MT1G     | 1.66        | 4.65E-05 | -       |
| 16       | q23.1  | 74411156      | ILMN_2147105  | NPIPL2   | 0.56        | 8.28E-05 | -       |
| 16       | q24.2  | 87863629      | ILMN_1720373  | SLC7A5   | 2.16        | 9.29E-04 | -       |
| 17       | p11.2  | 16733157      | ILMN_1713813  | KRT16P2  | 11.23       | 2.02E-04 | -       |
| 17       | p11.2  | 18335365      | ILMN_1797704  | KRT16P1  | 11.76       | 9.02E-04 | -       |
| 17       | p11.2  | 20404826      | ILMN_1750748  | KRT16P3  | 12.12       | 3.14E-04 | -       |
| 17       | q11.2  | 29248698      | ILMN_1763000  | ADAP2    | 2.69        | 1.49E-04 | -       |
| 17       | q21.2  | 39766030      | ILMN_1736760  | KRT16    | 23.68       | 2.15E-05 | -       |

| AL vs AN |        |               |               |           |             |          |         |
|----------|--------|---------------|---------------|-----------|-------------|----------|---------|
| Chr      | Band   | Position hg19 | Transcript ID | Gene      | fold change | P-value  | GO-term |
| 17       | q23.1  | 57642886      | ILMN_2248589  | DHX40     | 0.69        | 6.90E-04 | -       |
| 18       | q21.33 | 61322431      | ILMN_1703855  | SERPINB3  | 7.32        | 8.85E-04 | -       |
| 19       | p13.3  | 708953        | ILMN_1812031  | PALM      | 0.61        | 9.76E-05 | -       |
| 19       | p13.3  | 2428164       | ILMN_1708101  | LMNB2     | 1.48        | 1.41E-04 | -       |
| 19       | q13.33 | 49199232      | ILMN_1794659  | FUT2      | 1.78        | 9.49E-04 | -       |
| 19       | q13.42 | 56159401      | ILMN_1682567  | CCDC106   | 0.72        | 3.60E-04 | -       |
| 20       | p13    | 3276140       | ILMN_2164242  | C20orf194 | 1.78        | 4.87E-04 | -       |
| 21       | q22.11 | 31586324      | ILMN_2072568  | CLDN8     | 0.31        | 2.29E-04 | -       |
| 21       | q22.11 | 31586324      | ILMN_1746676  | CLDN8     | 0.48        | 3.24E-05 | -       |
| 22       | q11.21 | 21271714      | ILMN_1690122  | CRKL      | 0.75        | 3.14E-04 | -       |
| 22       | q11.23 | 25202236      | ILMN_1762207  | SGSM1     | 0.45        | 9.57E-04 | -       |
| 22       | q13.33 | 50961997      | ILMN_1701621  | SCO2      | 1.85        | 7.11E-04 | -       |

**Supplementary Table S5:** Differentially expressed transcripts with genome wide significance ( $P < 4.8 \times 10^{-6}$ ) using median regression adjusted for age and sex for AL/NN and AN/NN. Sorted by chromosome; GO Term bp biological process, mf molecular function, cc cellular component

| AL vs. NN                                      |     |         |                       |             |                                                                                                                                                   |
|------------------------------------------------|-----|---------|-----------------------|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Transcript ID                                  | Chr | Gene    | P-value               | fold change | GO-term (bp, mf, cc)                                                                                                                              |
| ILMN_1808220                                   | 1   | LCE3E   | $2.12 \times 10^{-6}$ | 8.57        | keratinization (bp)                                                                                                                               |
| ILMN_1718395                                   | 1   | LCE3D   | $3.47 \times 10^{-6}$ | 8.79        | keratinization (bp)                                                                                                                               |
| ILMN_1700967                                   | 3   | C3orf59 | $1.77 \times 10^{-6}$ | 0.77        | -                                                                                                                                                 |
| ILMN_1796094                                   | 7   | CD36.1  | $1.27 \times 10^{-6}$ | 5.54        | surface receptor signaling pathway (bp) phagocytosis recognition (bp), cellular response to bacterial lipopeptide (bp), integral to membrane (cc) |
| ILMN_2410826                                   | 12  | OAS1.1  | $2.05 \times 10^{-6}$ | 1.48        | immune response (bp), cytokine mediated signaling pathway (bp), defense response to virus (bp)                                                    |
| ILMN_1674063                                   | 12  | OAS2.3  | $3.29 \times 10^{-6}$ | 3.70        | immune response (bp), cytokine mediated signaling pathway (bp), defense response to virus (bp)                                                    |
| ILMN_1800341                                   | 12  | WDR66   | $3.76 \times 10^{-6}$ | 5.03        | calcium ion binding (mf)                                                                                                                          |
| AN vs. NN                                      |     |         |                       |             |                                                                                                                                                   |
| Transcript ID                                  | Chr | Gene    | P-value               | fold change | GO-term (bp, mf, cc)                                                                                                                              |
| ILMN_1810559/<br>ILMN_3251455                  | 2   | RHOQ    | $1.44 \times 10^{-7}$ | 1.99        | small GTPase mediated signal transduction (bp), regulation of cell shape (bp), actin filament (cc)                                                |
| ILMN_1709265                                   | 8   | RNF170  | $3.54 \times 10^{-6}$ | 1.65        | protein ubiquitination (bp), ligase activity (mf), endoplasmic reticulum membrane (cc)                                                            |
| ILMN_1782459/<br>ILMN_2405078                  | 12  | OSBPL8  | $2.68 \times 10^{-6}$ | 1.73        | lipid transport (bp)                                                                                                                              |
| ILMN_1733747/<br>ILMN_2404135/<br>ILMN_1724700 | 18  | RIOK3   | $3.96 \times 10^{-6}$ | 1.72        | chromosome segregation (bp), protein serine/threonine kinase activity (mf)                                                                        |

**Supplementary Table S6:** EpiTYPER MassArray and real time qPCR validation and fine mapping of DMS (AL/NN) correlated with *in-cis* and *in-trans* mRNA-expression levels.

| Methylation               |        |           |                                                             |                       |                 | Expression |        |                                |                                   |                 | Correlation           |         |
|---------------------------|--------|-----------|-------------------------------------------------------------|-----------------------|-----------------|------------|--------|--------------------------------|-----------------------------------|-----------------|-----------------------|---------|
| Chr                       | Gene   | CpG       | Results of 27k:<br>median diff. $\Delta$ ,<br>correlation r | P-value               | median<br>diff. | Chr        | Gene   | Results of<br>HT12:<br>P-value | P-value                           | median<br>diff. | $r_{\text{spearman}}$ | P-value |
| <i>in-cis</i> correlation |        |           |                                                             |                       |                 |            |        |                                |                                   |                 |                       |         |
| 1                         | S100A5 | CpG 1     |                                                             | 0.7569                | 0.050           |            |        |                                |                                   |                 |                       |         |
| 1                         | S100A5 | CpG 2     |                                                             | 0.8616                | -0.015          |            |        |                                |                                   |                 |                       |         |
| 1                         | S100A5 | CpG 3     |                                                             | 0.8269                | 0.015           |            |        |                                |                                   |                 |                       |         |
| 1                         | S100A5 | CpG 5.6   | cg08823182:<br>$\Delta = 0.225, r = 0.752$                  | $2.38 \times 10^{-5}$ | 0.180           | 1          | S100A2 | ILMN_1725852:<br>0.0128        | $2.65 \times 10^{-5}$             | 2.214           | 0.549                 | 0.0225  |
| 3                         | VHL    | CpG_1.2.3 |                                                             | 0.0320                | -0.110          |            |        |                                |                                   |                 |                       |         |
| 3                         | VHL    | CpG_4     |                                                             | 0.9193                | -0.055          |            |        |                                |                                   |                 |                       |         |
| 3                         | VHL    | CpG_5     |                                                             | 0.9850                | -0.005          |            |        |                                |                                   |                 |                       |         |
| 3                         | VHL    | CpG_6     |                                                             | 0.0072                | -0.125          |            |        |                                |                                   |                 |                       |         |
| 3                         | VHL    | CpG_7     |                                                             | 0.2755                | -0.025          |            |        |                                |                                   |                 |                       |         |
| 3                         | VHL    | CpG_8.9   |                                                             | 0.0033                | -0.170          |            |        |                                |                                   |                 |                       |         |
| 3                         | VHL    | CpG_11.12 | cg20916523:<br>$\Delta = -0.217, r = 0.774$                 | 0.0081                | -0.135          | 3          | IRAK2  | ILMN_1745964:<br>0.0223        | not validated with real time qPCR |                 |                       |         |
| 11                        | CD248  | CpG 1     |                                                             | 0.0317                | 0.070           |            |        |                                |                                   |                 |                       |         |
| 11                        | CD248  | CpG 3     | cg00350296:<br>$\Delta = 0.195, r = 0.895$                  | $5.31 \times 10^{-4}$ | 0.190           | 11         | CD248  | ILMN_1726589:<br>0.0221        | not validated with real time qPCR |                 |                       |         |
| 11                        | CD248  | CpG 4     |                                                             | $1.94 \times 10^{-4}$ | 0.115           |            |        |                                |                                   |                 |                       |         |
| 11                        | CD248  | CpG 5     |                                                             | $9.34 \times 10^{-5}$ | 0.185           |            |        |                                |                                   |                 |                       |         |
| 11                        | CD248  | CpG 6     |                                                             | 0.0103                | 0.140           |            |        |                                |                                   |                 |                       |         |
| 11                        | CD248  | CpG 7.8.9 |                                                             | 0.0018                | 0.080           |            |        |                                |                                   |                 |                       |         |
| 11                        | CD248  | CpG 10    |                                                             | $5.75 \times 10^{-4}$ | 0.135           |            |        |                                |                                   |                 |                       |         |
| 11                        | CD248  | CpG 11    |                                                             | $3.43 \times 10^{-4}$ | 0.115           |            |        |                                |                                   |                 |                       |         |



| Methylation                 |        |         |                                                             |                       |                 | Expression |       |                                        |                       |                 | Correlation           |                       |
|-----------------------------|--------|---------|-------------------------------------------------------------|-----------------------|-----------------|------------|-------|----------------------------------------|-----------------------|-----------------|-----------------------|-----------------------|
| Chr                         | Gene   | CpG     | Results of 27k:<br>median diff. $\Delta$ ,<br>correlation r | P-value               | median<br>diff. | Chr        | Gene  | Results of<br>HT12:<br>P-value         | P-value               | median<br>diff. | $r_{\text{spearman}}$ | P-value               |
| 14                          | IFI27  | CpG 5   |                                                             | 0.1869                | -0.170          |            |       |                                        |                       |                 |                       |                       |
| 14                          | IFI27  | CpG 6   |                                                             | 0.0250                | -0.300          |            |       |                                        |                       |                 |                       |                       |
| 14                          | IFI27  | CpG 7   |                                                             | 0.4636                | -0.090          |            |       |                                        |                       |                 |                       |                       |
| 14                          | IFI27  | CpG 8   |                                                             | 0.0081                | -0.310          |            |       |                                        |                       |                 |                       |                       |
| 14                          | IFI27  | CpG 9   |                                                             | 0.0392                | -0.220          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 1   | cg03297731:<br>$\Delta=-0.109, r=0.805$                     | 0.0077                | -0.150          | 16         | GDPD3 | ILMN_1774901:<br>0.0110                | $3.18 \times 10^{-4}$ | 3.570           | -0.595                | 0.0117                |
| 16                          | GDPD3  | CpG 2   |                                                             | 0.0041                | -0.110          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 3   |                                                             | 0.8872                | -0.020          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 4   |                                                             | 0.1442                | -0.010          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 6   |                                                             | 0.0066                | -0.015          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 7   |                                                             | 0.0353                | -0.035          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 9.1 |                                                             | 0.3385                | -0.015          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 11  |                                                             | 0.1919                | -0.025          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 12  |                                                             | 1.0000                | 0.000           |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 13  |                                                             | 0.2113                | -0.010          |            |       |                                        |                       |                 |                       |                       |
| 16                          | GDPD3  | CpG 14  |                                                             | 0.0674                | -0.050          |            |       |                                        |                       |                 |                       |                       |
| <i>in-trans</i> correlation |        |         |                                                             |                       |                 |            |       |                                        |                       |                 |                       |                       |
| 1                           | LRRC8C | CpG 1   |                                                             | $1.43 \times 10^{-7}$ | 0.180           |            |       |                                        |                       |                 |                       |                       |
| 1                           | LRRC8C | CpG 2   |                                                             | $1.78 \times 10^{-7}$ | 0.290           |            |       |                                        |                       |                 |                       |                       |
| 1                           | LRRC8C | CpG 3   |                                                             | 0.0016                | 0.130           |            |       |                                        |                       |                 |                       |                       |
| 1                           | LRRC8C | CpG 5.6 | cg06641366:<br>$\Delta=0.441, r=0.986$                      | $5.11 \times 10^{-8}$ | 0.598           | 7          | CD36  | ILMN_1796094:<br>$1.27 \times 10^{-6}$ | $3.18 \times 10^{-4}$ | 1.944           | 0.806                 | $9.24 \times 10^{-5}$ |
| 1                           | LRRC8C | CpG 7   |                                                             | 0.0010                | 0.398           |            |       |                                        |                       |                 |                       |                       |
| 1                           | LRRC8C | CpG 8   |                                                             | 0.0020                | 0.093           |            |       |                                        |                       |                 |                       |                       |

| Methylation                                                 |       |         |                                       |                       |                 | Expression                     |       |                                        |                       |                 | Correlation           |         |
|-------------------------------------------------------------|-------|---------|---------------------------------------|-----------------------|-----------------|--------------------------------|-------|----------------------------------------|-----------------------|-----------------|-----------------------|---------|
| Results of 27k:<br>median diff. $\Delta$ ,<br>correlation r |       |         |                                       |                       |                 | Results of<br>HT12:<br>P-value |       |                                        |                       |                 |                       |         |
| Chr                                                         | Gene  | CpG     |                                       | P-value               | median<br>diff. | Chr                            | Gene  | P-value                                | P-value               | median<br>diff. | $r_{\text{spearman}}$ | P-value |
| 8                                                           | EPB49 | CpG 1.2 |                                       | 0.0147                | 0.130           |                                |       |                                        |                       |                 |                       |         |
| 8                                                           | EPB49 | CpG 3   |                                       | 0.0015                | 0.185           |                                |       |                                        |                       |                 |                       |         |
| 8                                                           | EPB49 | CpG 4   |                                       | 0.0316                | 0.120           |                                |       |                                        |                       |                 |                       |         |
| 8                                                           | EPB49 | CpG 5   |                                       | 0.0173                | 0.120           |                                |       |                                        |                       |                 |                       |         |
| 8                                                           | EPB49 | CpG 6   |                                       | 0.0070                | 0.210           |                                |       |                                        |                       |                 |                       |         |
|                                                             |       |         | cg14706739:<br>$\Delta=0.166, r=0.85$ |                       |                 |                                |       | ILMN_1718395:<br>$3.47 \times 10^{-6}$ | $2.65 \times 10^{-5}$ | 0.247           | 0.349                 | 0.1691  |
| 8                                                           | EPB49 | CpG 7   |                                       | $2.99 \times 10^{-4}$ | 0.250           | 1                              | LCE3D |                                        |                       |                 |                       |         |
|                                                             |       |         |                                       |                       |                 |                                |       | ILMN_2058782:<br>$6.16 \times 10^{-6}$ | $2.65 \times 10^{-5}$ | 12.456          | 0.466                 | 0.0594  |
| 8                                                           | EPB49 | CpG 8   |                                       | $6.96 \times 10^{-5}$ | 0.205           | 14                             | IFI27 |                                        |                       |                 |                       |         |

**Supplementary Table S7:** Overlap of DMS with top 50 DMS described in Roberson et al. 2011. Additionally DETs are presented, if they map to the same genes.

|     |          |            | Psoriasis lesional skin vs. NN |         | AL vs. NN       |                       |                 |                       |
|-----|----------|------------|--------------------------------|---------|-----------------|-----------------------|-----------------|-----------------------|
|     |          |            | 27k Methylation                |         | 27k Methylation |                       | HT12 Expression |                       |
| Chr | Gene     | CpG        | median diff.                   | P-value | median diff.    | P-value               | foldchange      | P-value               |
| 1   | HDAC1    | cg24468890 | -0.07                          | 0.015   | -               | n.s.                  | -               | n.s.                  |
| 1   | CLDN19   | cg11075745 | 0.06                           | 0.025   | -               | n.s.                  | -               | n.s.                  |
| 1   | LRRC8C   | cg06641366 | 0.2                            | 0.008   | 0.441           | 3.49x10 <sup>-8</sup> | -               | n.s.                  |
| 1   | CHI3L2   | cg10045881 | -0.16                          | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 1   | SPRR2E   | cg00152644 | -0.08                          | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 1   | S100A9   | cg03165378 | -0.22                          | 0.004   | -               | n.s.                  | 14.03           | 2.29x10 <sup>-4</sup> |
| 1   | S100A9   | cg16139316 | -0.38                          | <0.001  | -               | n.s.                  | 14.03           | 2.29x10 <sup>-4</sup> |
| 1   | S100A12  | cg02813121 | -0.1                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 1   | EFNA3    | cg17582777 | 0.11                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 2   | CFLAR    | cg18119407 | -0.12                          | 0.004   | -0.212          | 1.86x10 <sup>-6</sup> | -               | n.s.                  |
| 2   | KYNU     | cg06131859 | -0.26                          | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 3   | PODXL2   | cg05781767 | 0.18                           | <0.001  | 0.133           | 6.22x10 <sup>-5</sup> | -               | n.s.                  |
| 4   | TNIP3    | cg20950277 | -0.19                          | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 6   | UNC5CL   | cg22346765 | -0.14                          | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 6   | TREM2    | cg01980222 | -0.09                          | 0.005   | -0.107          | 8.15x10 <sup>-5</sup> | -               | n.s.                  |
| 6   | LAMA4    | cg14289461 | 0.18                           | <0.001  | 0.102           | 6.25x10 <sup>-5</sup> | -               | n.s.                  |
| 7   | FLJ37538 | cg08626653 | 0.11                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 8   | SLC18A1  | cg22441882 | 0.13                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 8   | EPB49    | cg14706739 | 0.18                           | <0.001  | 0.166           | 3.90x10 <sup>-7</sup> | -               | n.s.                  |
| 8   | MTSS1    | cg18939260 | 0.13                           | 0.01    | 0.200           | 1.65x10 <sup>-4</sup> | -               | n.s.                  |
| 8   | PVT1     | cg13784855 | -0.1                           | 0.002   | -0.231          | 5.20x10 <sup>-5</sup> | -               | n.s.                  |
| 8   | PPP1R16A | cg12515371 | 0.13                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 8   | GPT      | cg15983520 | 0.09                           | <0.001  | 0.126           | 3.10x10 <sup>-4</sup> | -               | n.s.                  |
| 9   | SHC3     | cg13351583 | -0.09                          | <0.001  | -0.145          | 6.48x10 <sup>-4</sup> | -               | n.s.                  |
| 9   | GARNL3   | cg00342530 | 0.16                           | <0.001  | -               | n.s.                  | -               | n.s.                  |

|     |          |            | Psoriasis lesional skin vs. NN |         | AL vs. NN       |                       |                 |                       |
|-----|----------|------------|--------------------------------|---------|-----------------|-----------------------|-----------------|-----------------------|
|     |          |            | 27k Methylation                |         | 27k Methylation |                       | HT12 Expression |                       |
| Chr | Gene     | CpG        | median diff.                   | P-value | median diff.    | P-value               | foldchange      | P-value               |
| 10  | C10orf72 | cg08427977 | -0.11                          | <0.001  | -0.170          | 3.68x10 <sup>-5</sup> | -               | n.s.                  |
| 10  | C10orf99 | cg04126866 | -0.2                           | <0.001  | -               | n.s.                  | 4.44            | 3.00x10 <sup>-4</sup> |
| 11  | FOLR1    | cg03699566 | 0.23                           | <0.001  | 0.276           | 2.49x10 <sup>-5</sup> | -               | n.s.                  |
| 12  | NRIP2    | cg05194726 | 0.18                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 12  | ERP27    | cg13435792 | -0.21                          | <0.001  | -0.263          | 6.30x10 <sup>-6</sup> | -               | n.s.                  |
| 12  | KRT6B    | cg12795208 | -0.11                          | <0.001  | -               | n.s.                  | 14.22           | 1.25x10 <sup>-4</sup> |
| 12  | RDH5     | cg02192520 | 0.26                           | <0.001  | 0.235           | 6.37x10 <sup>-4</sup> | -               | n.s.                  |
| 12  | OAS2     | cg20870559 | -0.2                           | <0.001  | -0.241          | 0.001                 | 2.87            | 3.29x10 <sup>-6</sup> |
| 13  | MCF2L    | cg03623878 | 0.16                           | <0.001  | 0.171           | 3.29x10 <sup>-4</sup> | -               | n.s.                  |
| 13  | MCF2L    | cg11668844 | 0.19                           | <0.001  | 0.211           | 1.86x10 <sup>-5</sup> | -               | n.s.                  |
| 14  | IFI27    | cg20161089 | -0.23                          | <0.001  | -0.222          | 0.0196                | 9.89            | 6.16x10 <sup>-6</sup> |
| 16  | SLITL2   | cg09276451 | 0.1                            | 0.002   | -               | n.s.                  | -               | n.s.                  |
| 16  | CCL17    | cg07634706 | 0.07                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 16  | CDH1     | cg20716119 | 0.05                           | 0.005   | -               | n.s.                  | -               | n.s.                  |
| 16  | CHST6    | cg02298612 | 0.11                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 17  | RILP     | cg04049033 | 0.06                           | 0.035   | -               | n.s.                  | -               | n.s.                  |
| 17  | CSF3     | cg21432842 | -0.09                          | 0.002   | -               | n.s.                  | -               | n.s.                  |
| 17  | KRTHA2   | cg08611714 | -0.18                          | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 18  | ATP8B1   | cg25979644 | -0.24                          | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 18  | SERPINB3 | cg10533434 | -0.2                           | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 19  | EDG6     | cg20583073 | -0.07                          | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 19  | FCGBP    | cg19103704 | -0.15                          | <0.001  | -               | n.s.                  | 0.43            | 8.64x10 <sup>-4</sup> |
| 19  | KLK1     | cg26415633 | 0.12                           | 0.02    | -               | n.s.                  | -               | n.s.                  |
| 21  | BTG3     | cg14380517 | 0.1                            | <0.001  | -               | n.s.                  | -               | n.s.                  |
| 21  | SLC37A1  | cg13265003 | 0.12                           | <0.001  | 0.135           | 8.46x10 <sup>-6</sup> | -               | n.s.                  |
| 22  | APOL1    | cg07713361 | -0.06                          | 0.006   | -               | n.s.                  | -               | n.s.                  |

**Supplementary Table S8:** Correlation of *IFI27* CpG methylation from the EpiTyper analysis with *IFI27* mRNA expression from the RT qPCR approach.

| Gene  | Chr | pos      | CpG          | CpG.27k             | r      | P                    |
|-------|-----|----------|--------------|---------------------|--------|----------------------|
| IFI27 | 14  | 94577564 | A 21 CpG 1   |                     | -0.316 | 0.2333               |
| IFI27 | 14  | 94577537 | A 21 CpG 2   |                     | -0.680 | 0.0027               |
| IFI27 | 14  | 94577515 | A 21 CpG 3.4 | cg20161089: r=0.955 | -0.755 | 4.6x10 <sup>-4</sup> |
| IFI27 | 14  | 94577457 | A 21 CpG 5   |                     | -0.685 | 0.0024               |
| IFI27 | 14  | 94577430 | A 21 CpG 6   |                     | -0.620 | 0.0079               |
| IFI27 | 14  | 94577376 | A 21 CpG 7   |                     | -0.655 | 0.0043               |
| IFI27 | 14  | 94577295 | A 21 CpG 8   |                     | -0.639 | 0.0058               |
| IFI27 | 14  | 94577251 | A 21 CpG 9   |                     | -0.613 | 0.0089               |

**Supplementary Table S9:** Bisulfite specific primer sequences for different amplicons of the Sequenom EpiTYPER Assay

| <b>CpG ID</b>         | <b>F Primer 5'-3'</b>         | <b>R Primer 5'-3'</b>          |
|-----------------------|-------------------------------|--------------------------------|
| cg15616400            | TAGGTGTGGGTATAGAGGTAGTTGG     | CACCACCTCCAAAAAATTAATAAAA      |
| cg06641366            | AGGGGGAAAGTAATGTAAAGTTTAAGA   | CACCCAATTTCAAATAAAAAAACA       |
| cg08823182            | GAAGAAGGGAAATTAGGTTGTTTTG     | ATTCTCAATCCTCCATACCAAAAAT      |
| cg20839149/cg12499211 | TATATTTGGGTTAGGGGGAATTTTA     | AAACTTCCTAACACCTAAACACAAAA     |
| cg18119407            | TGTGGTTTAGGTTGGAGTGTAGTG      | ACTATAACTCCCAAACAACAATTATAAACA |
| cg20287234            | TTTTTTTTGATTTGATTTAGGGTTG     | AATAACAACCAAAACTTTCCTCTCC      |
| cg20916523            | TTAAAGTGTTGGGTTTATGGGTATG     | AACAAACAAATAAATCAATTTCCCA      |
| cg26523005            | GGTTGGGGAGGAATTTTTTTT         | TAAC TCCCCAAAAAATACTAAACATC    |
| cg06196379            | GTTTTTTTAAATTGTTTTTGGGGTT     | AAAAACAAAAAACCTTTACTCTCC       |
| cg14706739            | AATAGTATTTTGGGTGGGGAGG        | CTAAATTAAAAAAACCCTCATCCCA      |
| cg11173246            | GGAGGTTATATGGGAGGTTTTTGT      | TACTAACCACCCTCATCAAAC TTTA     |
| cg18788940            | GGGGATTATTGAAGATTAAGTTTGG     | AAAACATCCCACCTTCCCTAA          |
| cg00350296            | GTTTTAGGTTTTTATGGGGTTGAGAG    | CAAAAAAATCATCTACAAACCAACAT     |
| cg06539449            | GAAAGGTAGTTATTTTGAAGGGGAG     | ACTCCTAATCTAAACACAAACAACACC    |
| cg25511807            | GGAATTTTAAGTAAGTGGGTGTGA      | AAAAACAAATACATTATATACTTCCTACCA |
| cg13435792            | AGGTTGAGGTAGGAGGATGGTTT       | AACTTTTCAATAATTCCCATCACCT      |
| cg00213044            | TTTTTAGGTTTTTTTTGGTAGGAAGG    | AAACCCTAACTTCCCTATATACCCC      |
| cg20870559            | GTGGAATTTTTTGT TTTT TAGAGATT  | CCTCTAAACTTCAATTTCAATTTCTTA    |
| cg22131172            | GAGGTAGGTTGTAGGGAGTTAAGA      | ATTTTAAAAAATAACCTCATCCCCA      |
| cg20161089            | GAGGTGTTTGT TTTT ATGTAATTTTTT | AACCTTAAACATCCACTCTCTACCC      |
| cg03297731            | TGGAGAATATTATGGAGGTTATGGA     | TACCCACATCCCTATTTAAACCC        |
| cg04958703            | GTTGGTTTTGAATTGGGATTATAGA     | AAAAAAACAAAATATCCACCCCTAA      |
| cg19147390            | ATTTGAGGTTTTTGTGGATTTTTT      | AAATTTTACTATCCCTCCCTCA         |

**Supplementary Table S10:** Specific primer sequences for real time qPCR

| Transcript ID | F Primer 5'-3'         | R Primer 5'-3'         |
|---------------|------------------------|------------------------|
| IFI27         | ATCAGCAGTGACCAGTGTGG   | GCCACAACCTCCTCCAATCAC  |
| KRT6A         | CTGAGATCGACCACGTCAAG   | CAGCTTGTTCTTGGCATCCT   |
| KRT6B.1       | AGGTACATCACTTGCCATTCAG | TCTAGGTCCAGCTGCAGATG   |
| GDPD3         | GAAATGGCTGATCATGAGGAA  | GCTGCTTCAAAATCCGACTC   |
| S100A2        | TTCAAGCTGAGTAAGGGGGA   | ATCAGCTTCTTCAGCCCCTC   |
| OAS2.3        | CCATGGTGGGCCCTTAGTTT   | CCAAGCCTCACTGTCCAGAG   |
| CD36.1        | CAGAGGCTGACAACTTCACAG  | AGGGTACGGAACCAAACCTCAA |
| LCE3D         | CAGGAACAGCCTTCTCCTG    | CAGACACTGTACTGGGCTC    |

**Supplementary Table S11:** Real time qPCR validation. mRNA-expression levels of transcripts which were correlated with methylation levels of CpG-sites *in-cis* and *in-trans* (see table 4) were validated using real time qPCR. Expression differences were calculated by mean expression in cases – mean expression in controls. P-values were calculated based on real time qPCR measurements by Wilcoxon signed rank test (wc). For HT-12 we used linear models (lm) on log<sub>2</sub>-transformed expression levels adjusted for age and sex.

| RT-PCR        |            |               |        |                       | HT-12 Chip |               |       |                       |
|---------------|------------|---------------|--------|-----------------------|------------|---------------|-------|-----------------------|
| Gene          | mean cases | mean controls | diff   | P <sub>wc</sub>       | mean cases | mean controls | diff  | P <sub>lm</sub>       |
| <i>IFI27</i>  | 13.031     | 0.575         | 12.456 | 2.65x10 <sup>-5</sup> | 13.067     | 9.762         | 3.306 | 6.16x10 <sup>-6</sup> |
| <i>KRT6A</i>  | 6.278      | 0.046         | 6.232  | 2.65x10 <sup>-5</sup> | 13.326     | 8.810         | 4.517 | 7.54x10 <sup>-6</sup> |
| <i>KRT6B</i>  | 0.501      | 0.006         | 0.495  | 5.03x10 <sup>-4</sup> | 9.704      | 6.990         | 2.713 | 0.0083                |
| <i>GDPD3</i>  | 4.909      | 1.339         | 3.570  | 3.18x10 <sup>-4</sup> | 9.097      | 8.293         | 0.804 | 0.0110                |
| <i>S100A2</i> | 2.606      | 0.392         | 2.214  | 2.65x10 <sup>-5</sup> | 8.391      | 7.600         | 0.791 | 0.0128                |
| <i>OAS2</i>   | 0.022      | 0.001         | 0.021  | 2.65x10 <sup>-5</sup> | 9.056      | 7.167         | 1.889 | 3.29x10 <sup>-6</sup> |
| <i>CD36</i>   | 2.098      | 0.155         | 1.944  | 3.18x10 <sup>-4</sup> | 10.319     | 7.849         | 2.471 | 1.27x10 <sup>-6</sup> |
| <i>LCE3D</i>  | 0.252      | 0.005         | 0.247  | 2.65x10 <sup>-5</sup> | 11.940     | 8.804         | 3.136 | 3.47x10 <sup>-6</sup> |