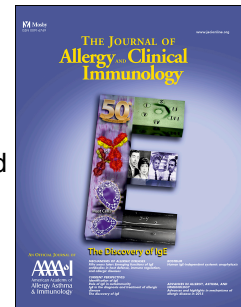


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Moving towards endotypes in atopic dermatitis: identification of patient clusters based on serum biomarker analysis

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Abstract

Background: Atopic dermatitis (AD) is a complex, chronic, inflammatory skin disease with a diverse clinical presentation. It is however unclear whether this diversity exists at a biological level.

Objective: To test the hypothesis that AD is heterogeneous at the biological level of individual inflammatory mediators.

Methods: Serum from 193 moderate to severe adult AD patients (geomean (95%CI) SASSAD of 22.3 (21.3, 23.3) and 39.1 (37.5, 40.9) respectively) and 30 non-AD healthy controls was analysed for 147 serum mediators, total IgE and 130 allergen specific IgEs. Population heterogeneity was assessed by principal component analysis (PCA) followed by unsupervised k-means cluster analysis of the principal components.

Results: AD patients showed pronounced evidence of inflammation compared to healthy controls. PCA of AD serum data revealed the presence of four potential AD patient clusters. Fifty-seven principal components (PCs) described approximately 90% of the variance. Unsupervised k-means cluster analysis of the 57 largest PCs delivered 4 distinct clusters of AD patients. Cluster 1 had high SASSAD and BSA with the highest levels of PARC, TIMP-1 and sCD14. Cluster 2 had low SASSAD with the lowest levels of IFN- α , TIMP-1 and VEGF. Cluster 3 had high SASSAD with the lowest levels of IFN- β , IL-1 and epithelial cytokines. Cluster 4 had low SASSAD but highest levels of inflammatory markers: IL-1, IL-4, IL-13 and TSLP.

Conclusion: AD is a heterogeneous disease both clinically and biologically. Four distinct AD patient clusters have been identified that could represent endotypes with unique biological mechanisms. Elucidation of these endotypes warrants further investigation and will require future intervention trials with specific agents such as biologics.

Key messages:

- In a population of moderate to severe atopic dermatitis patients, we have identified four distinct clusters based on serum biomarker profiles, illustrating the biological heterogeneity of atopic dermatitis.
- The patient clusters identified could represent underlying endotypes that have unique biology driving the disease pathogenesis and could therefore lead to a more personalised approach for biologic therapeutic use.
- The clear differences in biomarker expression profiles between atopic dermatitis patients and healthy controls indicates systemic inflammation in atopic dermatitis patients.

Capsule summary:

This is the first study that identifies distinct clusters of atopic dermatitis patients based on a serum biomarker profile. The identification of these clusters could enable more specific targeting of the underlying disease pathways and contribute to personalized medicine.

Key words: Atopic dermatitis, unsupervised cluster analysis, disease heterogeneity, clusters, phenotypes, endotypes, personalised medicine, principal component analysis

Abbreviations:

AD: atopic dermatitis

BSA: body surface area

PCA: principal component analysis

SASSAD: six area, six sign atopic dermatitis

ISAC: immuno-solid phase allergen chip

Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease worldwide. The underlying pathological mechanisms are incompletely described and AD presents clinically with a broad range of features. Different clinical AD phenotypes have been described that are based on characteristics such as age of onset, or the presence of other atopic diseases such as allergic rhinitis and asthma.^{1, 2} Despite efforts to better understand AD pathogenesis through defining phenotypical subsets, for example patients with intrinsic as compared to those with extrinsic AD,^{3, 4} AD pathogenesis remains poorly understood. Indeed it is hypothesised that AD cannot be explained by one mechanism alone; this hypothesis also suggests that it is unlikely that newly developed biological drugs that target highly specific biological axes of the immune or skin barrier development systems will be effective in all AD patients. Consistent with this thinking recent clinical trials with the anti-IL4R α monoclonal antibody dupilumab have been very encouraging, but it is clear that this treatment is not equally effective in all patients, and that an alternative therapeutic approach will be required in some patients. Indeed, in the recently published phase 3 dupilumab trials the primary outcome of reduction in IGA to 0 or 1 occurred in 38% of patients.⁵ In the exciting future of personalised healthcare it is critical to be able to provide the right drug to the right patient. Hence, it is essential to gain better insight into the heterogeneous nature of the disease at the biological level. We hypothesised that the heterogeneity in AD could be described via differential serum biomarker profiles and set out to test this using a broad Luminex panel assessed in a large 200-patient cohort of moderate and severe AD patients. When these data were subjected to principal component analysis (PCA) followed by unsupervised cluster analysis, we were able to identify four patient clusters with distinct serum biomarker profiles and overlapping clinical phenotypes that may represent distinct disease endotypes.

Methods

Study design

We hypothesised that AD is heterogeneous at the biological level of individual serum inflammatory mediators. To test this hypothesis we measured 147 analytes in the serum of 200 moderate to severe AD patients and 30 non-atopic dermatitis healthy controls via Luminex-based multiplex immunoassays, total IgE and allergen-specific IgEs (ISAC) were also assessed. Clinical characteristics were extracted from the patients' electronic files. Principal component analysis (PCA) of the serum biomarker data (including total IgE) followed by unsupervised k-means cluster analysis was used to identify heterogeneous patient clusters. ISAC data was not included in PCA analysis since it was comprised of semi-quantitative data only (detailed methods related to measurement of serum mediators and statistical analysis are available in the Methods section in this article's Online Repository).

Patients and controls

The rule of thumb adopted for sizing populations for multivariate principal components is five times the number of independent variables measured.⁶ The number of independent variables mentioned above is the number of unique variables that are not correlating to any other variable. Our experience from asthma research suggests⁷ that analytes are often highly correlated; extrapolating this suggested that within 150 analytes there are likely to be about 20 unique independent variables. Following the guidance above, the required sample size was 100 (5*20) moderate, and 100 severe patients. From a biobank of over 1000 AD patients, 200 patients who were all treated with only topical corticosteroids, were selected. To select patients they were first grouped based on the Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score⁸ into six groups; moderate patients with SASSAD scores ranging from (i) 15-20 (ii) 21-25 (iii) 26-30 and severe patients with SASSAD scores ranging from (i) 31-35 (ii) 36-40 (iii) >40. Then, as previous analysis revealed that gender and age were factors of interest in AD⁹, the six groups were normalised on sex and age prior to final selection. Final selection included equal numbers from each of the six SASSAD groups. Thirty healthy controls without a previous history of AD, allergic asthma or allergic rhinoconjunctivitis, and approximately age and sex matched to the AD patients, were recruited from UMC Utrecht and included in the study.

All AD patients were diagnosed with AD according to the criteria of Hanifin and Rajka.¹⁰ However, AD patients present with a wide spectrum of clinical features that can vary considerably between individuals. From our observations in the clinic we have the impression that there are two mutually exclusive subsets of patients; patients with a predominantly chronic lichenified eczema, and patients with a predominantly erythematous eczema. In order to correlate clusters with clinical features, we labelled patients as chronic lichenified eczema or erythematous eczema.

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148 The protocols of this study were approved by the Institutional Review Board of the University

149 Medical Center Utrecht (Utrecht, The Netherlands), adhering to the Declaration of Helsinki

150 Principles.

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Results

Patient demographics, clinical characteristics and serum biomarker profiles

From the 200 serum samples, seven were different time points from the same individuals and hence were not included in the final patient selection. Therefore a total of 193 moderate to severe AD patients were studied, made up of 95 moderate and 98 severe patients. Thirty adult controls with no history of AD, allergic asthma or allergic rhinitis were also recruited for the study, although they were older than the AD patients (geomean (95%CI) age of 39.1 (34.3, 44.6) years versus 30.6 (28.3, 33.2) years for moderate and 31.1 (28.5, 34.0) years for severe patients). Moderate AD patients had a lower SASSAD and lower median body surface area (BSA) involvement than severe AD patients (geomean (95%CI) SASSAD 22.3 (21.3, 23.3) versus 39.1 (37.5, 40.9), respectively and median (Q1, Q3) BSA of 33% (21, 48) versus 54% (39, 72), respectively). All AD patients had elevated levels of serum TARC compared to healthy controls (median (Q1, Q3) of 3950 (2104-8944) pg/mL in severe AD, 1505 (654, 3200) pg/mL in moderate AD and 97 (68, 137) pg/mL in controls). Patient characteristics are summarised in **Table 1**.

For all patients and healthy controls, serum concentrations of 147 analytes were determined via multiplex immunoassay. Serum total and specific IgEs, periostin, DPP4, anti-*Staphylococcus aureus* alpha toxin IgG levels were also measured. A bioassay was used to measure the neutralising ability of *Staphylococcus aureus* alpha toxin antibodies in AD and healthy control serum. For technical reasons, IL-19, GRO- α and SR-PSOX could not be measured in healthy controls. In AD patients, all analytes were detectable (see **Tables E2-E7 in the Online Repository**). In serum of healthy controls, IL-3, leukaemia inhibitory factor (LIF), eotaxin, I309, and macrophage colony-stimulating factor (M-CSF) were undetectable (see **Tables E2-E7 in the Online Repository**). In general AD patients had a clearly different serum biomarker profile from healthy controls with large upregulation of key inflammatory biomarker families in AD versus control including Th2, epithelial and IL-1 family cytokines as well as total IgE and specific IgEs (see **Tables E4-E8 in the Online Repository**).

Principal component analysis and unsupervised cluster analysis reveals four clusters of AD patients

To test the hypothesis that AD was biologically heterogeneous we performed PCA on the Box-Cox transformed serum biomarker dataset which revealed the likely presence of four clusters (**Fig 1A**). Summation of the variances showed that the first 57 principal components described 90% of the dataset variance (**Fig 1B**). Therefore the first 57 principal components were included in an unsupervised k-means cluster analysis which delivered four AD clusters (**Fig 1C** and see **movie E10 in the Online Repository**).

Characterisation of AD clusters

AD cluster membership, or control status, was added back to the complete dataset and all variables were compared by cluster versus the healthy controls. Clinical characteristics (not included in the clusters analysis) were analysed between the four clusters and are shown in **Table 2**. Averages of serum analytes per cluster were calculated and tabulated to characterise the clusters (**see Table E2 and E3 in the Online Repository**). As expected more frequent sensitization to allergen components measured by ISAC was seen in AD patients compared to healthy controls (**see Table E8 in the Online Repository**). However, no clear differences in sensitization patterns were observed between the patient clusters (**see Table E9 in the Online Repository**). Measurement of anti-*S. aureus* alpha toxin IgG was used as a systemic marker of AD patient *S. aureus* exposure, however this showed no difference between clusters. Total IgE levels did also not show any significant differences between the four clusters (**see Table E3 in the Online Repository**). Key characteristics, both clinical and serum profiles, for each AD cluster are described below.

Cluster 1 (high SASSAD/BSA, PARC/TIMP-1/sCD14 high) represented 23% of the AD population and was 59% female. Cluster 1 patients had a geomean (95%CI) age of 31.2 (27.7, 35.1) years and, alongside cluster 3, the highest severity score. Cluster 1 geomean (95%CI) SASSAD was 35.3 (31.9, 39.0), which was greater than clusters 2 and 4, and cluster 1 median (Q1,Q3) BSA score was 54 (40.4, 69), which was greater than clusters 2 and 3. Cluster 1 was uniquely defined by having the highest levels of PARC, TARC and TIMP-1 (both greater than clusters 2, 3, 4 and healthy controls) and was distinguished from clusters 2, 3 and 4 by having the highest level of sCD14 (**see Table E2 in the Online Repository**). Clinically cluster 1, alongside cluster 3, had the highest incidence of asthma (54% vs 53%, respectively) which was greater than that in clusters 2 and 4 (43% vs 36%, respectively) although cluster 1 was unique in having the highest incidence of asthma and rhinitis (47% vs 38%, 38%, 32%, respectively). Cluster 1 patients had a similar frequency of erythematous phenotype to cluster 4 (15% vs 19%, respectively) which was above that observed in clusters 2 and 3 (8 and 4%, respectively). Cluster 1 patients also shared with cluster 4 patients the highest frequency of infant onset AD (57% vs 56%, respectively) which surpassed those in clusters 2 and 3 (45% and 42%, respectively)(**Table 2**).

Cluster 2 (low SASSAD, IFN- α /TIMP-1/VEGF low) represented 29% of the AD population and was 56% female. Cluster 2 patients were younger than cluster 3 patients with a geomean age (95%CI) of 28.1 (25.3, 31.1) years and, alongside cluster 4, the lowest severity score. Cluster 2 geomean (95%CI) SASSAD was 25.5 (23.2, 28) which was lower than both clusters 1 and 3, and cluster 2 median BSA (Q1, Q3) was 36 (24, 54) which was less than cluster 1 (**Table 2**). Cluster 2 was uniquely defined by having the lowest levels of TIMP-1 (lower than clusters 1,3,4 and healthy controls), VEGF and IFN- α (lower than clusters 1, 3, 4, but higher than healthy controls). Clinically cluster 2 patients had a similar frequency of lichenified phenotype as cluster 3 (74% vs 76%,

respectively) which was above that observed in clusters 1 and 4 (60% and 43%, respectively). Cluster 2 patients also had the highest frequency of childhood onset AD (47%) which surpassed those in clusters 1, 3 and 4 (36%, 43% and 30%, respectively).

Cluster 3 (high SASSAD, IFN- β /IL-1/epithelial cytokine low) was the largest cluster, representing 33% of the AD population, and was 53% female. Cluster 3 patients were older than both cluster 2 and 4 patients with a geomean (95% CI) age of 35.0 (31.4, 39.0) years. Cluster 3, alongside cluster 1, had the highest severity score. Cluster 3 geomean (95% CI) SASSAD was 32.1 (29.7, 34.8), which was higher than both clusters 2 and 4. Cluster 3 median BSA (Q1, Q3) was 40.5 (27, 54) which was less than cluster 1. Cluster 3 was uniquely defined by having the lowest levels of IFN- β , IL-1Ra, IL-26, MIG (all less than control and clusters 1, 2, 4), eotaxin, IL-1 β , IL-1R1, IL-4, IL-9, IL-12, IL-15, IL-21, IL-25, IL-33, TREM1, TSLP (all more than controls but less than clusters 1,2,4), CTACK, IL-1 α , Gro- α , IL-19, IL-37 (all less than clusters 1, 2, 4). Clinically, cluster 3 patients had the lowest frequency of erythematous phenotype (4% vs 15%, 8%, 19%, respectively) as well as, together with cluster 4, the highest frequency of adult onset AD (12% vs 5%, 4%, 11%, respectively) (**Table 2**). Cluster 3 patients also had the highest frequency of comorbid asthma alone (15% vs 7%, 6%, 4% respectively) as well as, together with cluster 1, the highest frequency of comorbid asthma alone or with rhinitis (53% vs 54%, 43%, 36%, respectively) (**Table 2**).

Cluster 4 (female predominant, low SASSAD, IL-1/4/13 and TSLP high) represented 15% of the AD population and was the most female predominant group (68%). Cluster 4 patients were younger than cluster 3 patients with a geomean (95% CI) age of 27.4 (23.3, 32.1) years and, alongside cluster 2, the lowest severity score. Cluster 4 geomean (95% CI) SASSAD was 25.8 (22.4, 29.7) which was lower than both clusters 1 and 3 and cluster 4 median BSA (Q1, Q3) was 43.5 (33, 55). Cluster 4 was uniquely defined as profoundly inflamed by having the highest levels of BLC, elastase, eotaxin, EPOR, FGF-b, GCP-2, GM-CSF, IFN- γ , IL-1 α , IL-1 β , IL-1Ra, IL-1R1, IL-4, IL-8, IL-9, IL-11, IL-13, IL-15, IL-17, IL-19, IL-20, IL-21, IL-37, LAIR1, LIGHT, MCP-3, MIP-1 α , NGF, SOST, sVEGF-R1, TNF- α , TNF- β , TREM-1, TSLP, XCL-1 (all more than clusters 1,2,3 and healthy controls), GRO- α , IFN- β , IL-2, PLGF (all more than clusters 1,2,3)(see **Table E2 in the Online Repository**). Clinically, cluster 4 patients had the highest frequency of erythematous phenotype (19% vs 15%, 8%, 4%, respectively). Cluster 4 patients also had the lowest frequency of comorbid asthma (36% vs 54%, 43% and 53%, respectively) and the highest frequency of no comorbid asthma or rhinitis (36% vs 23%, 26% and 20%, respectively) (**Table 2**).

Discussion

Atopic dermatitis is recognized as a complex and highly heterogeneous disease, characterised by a diverse clinical manifestation, but little work has been performed to characterise the biological differences underlying this clinical heterogeneity. Classically, clinical characteristics such as disease severity, age of onset, and the presence of atopic comorbidities are used to divide AD into different disease phenotypes.² However, these phenotypical characteristics do not seem to relate to specific disease mechanisms and have not yet given us new insights in the underlying pathology of disease. It has become increasingly clear that AD is not only heterogeneous based on clinical characteristics, but that different underlying pathophysiological processes are found in different subgroups of patients.¹¹

¹² The primary goals of our study were firstly to test whether AD is heterogeneous at the level of the serum biomarker profile and then to describe this heterogeneity and its relationship to clinical presentation.

To the best of our knowledge, this is the first study that classifies AD patients on serum biomarker based clusters. We used a purely data-driven approach to cluster serum biomarker profiles in a population of moderate to severe AD patients. This approach revealed four distinct clusters of AD patients, showing that adult AD truly is a heterogeneous disorder. Each cluster has a distinct profile of soluble mediators that together may indicate these clusters are driven by distinct, as yet unidentified, underlying pathways.

Classification based on subgroups defined by distinct functional or pathophysiological mechanisms is termed endotyping.^{13, 14} The four distinct patient clusters that we identified in this study could represent endotypes that have unique biology driving the pathogenesis of disease. Further biological studies and interventional trials will be needed to confirm the endotype of each cluster. However, it is hoped that endotypes could be used to target specific therapies in future clinical trials and daily practice.

Each cluster in our analysis is characterised by certain serum biomarkers and clinical characteristics which are significantly differentially expressed. Two of the clusters, 1 and 3 (SASSADs of 35 and 32), were relatively more severe than clusters 2 and 4 (SASSADs of 25 and 26). Of the more severe clusters, cluster 1 was delineated from the others by having the highest levels of PARC, TARC, TIMP-1 and sCD14. In contrast, cluster 3 was defined by the lowest levels of host-defence associated molecules including IFN- β and MIG, IL-1 family members IL-1 α and IL-1 β , Th2 cytokines IL-4 and IL-9, as well as the key immune initiating epithelial cytokines, IL-25, IL-33 and TSLP. Of the less severe clusters, cluster 2 was defined by having the lowest levels of TIMP-1, VEGF and IFN- α whereas cluster 4 was defined by being female predominant (68%) and having the highest levels of multiple inflammatory cytokines including the IL-1 family, Th2 cytokines IL-4, IL-9, IL-13 and the epithelial cytokine TSLP.

Moving beyond individual cluster differentiating patterns of mediator expression there were also interesting commonalities across the clusters (**Figure 1C**). Patients in cluster 1 and 4, representing 48% of patients, showed particularly high Th2-cytokine levels and an erythematous skin phenotype, and would hypothetically represent ideal patients for Th2 targeting drugs that are currently being tested, including the anti-IL-4R α antibody dupilumab, and anti-IL-13 antibodies Lebrikizumab and Tralokinumab (NCT02755649, NCT02340234, NCT02347176).¹⁵⁻¹⁷ Moreover, given the recent success of dupilumab in AD trials, the biomarker expression of these two clusters could directly relate to the underlying pathophysiological processes in these patients.

Clusters 2 and 3, representing 52% of the patients, share a Th2-cytokine low and pauci-inflammatory mediator state (analogous to that seen in Th2-low asthma)¹⁸ as well as presenting with a greater frequency of lichenified skin phenotype. These clusters would hypothetically represent patient groups that are not ideal for Th2 targeting drugs and that a more comprehensive biological characterisation of disease mechanisms in these patients will be required to allow generation of more tailored therapeutics.

The statistically non-significant association of an erythematous skin with a strong epithelial cytokine and Th2 phenotype, and the association of a lichenified skin with a weak epithelial cytokine and Th2 phenotype, is intriguing and could imply a mechanistic link (**Figure 1C**). Whether this mechanistic link is real or simply represents biomarkers of an as yet unidentified biological mechanism remains to be elucidated. Similarly, understanding how the underlying biology of patients in clusters 2 and 3 could drive the lichenification process needs further investigation.

Taken together the clusters found in our study, approximately 48% “Th2 high” and 52% “Th2 low”, are consistent with recent phase 3 data from dupilumab in AD⁵ demonstrating that 62% patients did not achieve the primary endpoint of reduction in IGA and would support the use of biomarkers to identify optimal dupilumab responders in future trials. Whilst, both clusters 1 and 4 have high Th2 cytokines, they can be clearly differentiated from each other through high expression of PARC and TSLP respectively. This might indicate a pathophysiological process in cluster 4 in which the higher levels of TSLP could drive a more pruritic phenotype.¹⁹ Thus, patients in cluster 4 could represent those patients that would respond best to new anti-TSLP biologics currently being tested.

The identification of phenotypes, leading to hypothetical endotypes, based on cluster analyses of immune mediators has been demonstrated in other diseases including asthma,^{7, 20, 21} COPD⁷ and chronic rhinosinusitis.²² If such endotyping can be confirmed with interventional studies it will prove useful with the introduction of new targeted therapies, since patients with different endotypes may respond differently to the same treatment. Sub-grouping patients based on a serum biomarker and blood eosinophils has already been proven to be useful in asthma, where anti-IL-13 therapy appears to be most effective in the specific subgroup of patients with high serum levels of periostin.^{23, 24}

Similarly, quantifying blood eosinophils in asthmatics has facilitated the identification of those patients that best respond to IL-5 axis targeting drugs, such as Benralizumab.²⁵ The ability to

endotype AD patients may contribute to precision medicine by allowing treatment to be tailored for individual patients.¹⁴ This would not only be beneficial for patients, but would also reduce health-care costs.²⁶ We expect that biomarker analyses may become essential in all clinical trials, to enable a better selection of patient populations and optimize therapy.

Data presented in this study also confirms that there is systemic inflammation in AD patients, supporting the hypothesis that AD is a systemic disorder. The high expression of many inflammatory cytokines and chemokines in the serum of AD patients resulted in clear differences in biomarker expression profiles between AD patients and healthy controls, as shown in **Table E4 and E5 in the Online Repository**. The concept of AD as a systemic disorder was recently highlighted in a meta-analysis of data from the AD transcriptome.²⁷ Given that three population-based studies have shown an association between adult AD, cardiovascular disease, and increased heart attacks²⁸ systemic inflammation in AD may, as in psoriasis, contribute to cardiovascular disease.²⁹

The results of this study thus warrant further investigation. One limitation of this study is the inability to identify a clear association between the four clusters and clinical characteristics other than severity scores such as the presence of allergic asthma or rhinitis, and age of onset of the disease. The patients in this study were selected solely on disease severity (SASSAD), sex and age, no other clinical characteristics peculiar to AD were considered for selecting patients. Additionally detailed clinical characterisation was not available for every patient. Therefore, the absence of an association between the clusters and other clinical characteristics may be due to missing data or the consequence of the unbalanced presence of these clinical characteristics across the hypothetical endotypes. It also highlights the significant challenges in identifying endotypes with underlying pathophysiological mechanisms based on clinical features such as age of onset or the presence of other atopic diseases. The fact that we could not find any clear differences in sensitization patterns based on 150 specific IgE levels between the patient clusters strengthens this hypothesis. This would also be in accordance with the findings of dupilumab trials in which treatment effects were found to be similar in both intrinsic and extrinsic AD patient groups.^{3,4}

Additionally, the present study is retrospective, and its findings will need further validation of the utility of serum biomarkers for clustering AD. The clusters that were identified in this study should be confirmed in an independent patient population in a prospective study. Prospective studies including more biomarkers may, we anticipate, reveal more subgroups of patients and give more insight into the association with clinical characteristics. Also, a longitudinal study may provide us additional insights into the stability of biomarkers in a patient over time. The current study focused on serum biomarkers, which may just represent the down-stream effects of certain underlying pathways. Interventional clinical trials will help to confirm whether the serum biomarkers associated with each cluster directly relate to a pathological mechanism and thus confirm clusters as specific endotypes. In order to more precisely endotype patients and identify underlying pathways, future studies should follow a multi-

layer approach, integrating high-throughput data from genomics, transcriptomics, lipomics, and proteomics with extensive clinical data.

In summary, in a population of moderate to severe AD patients, we have identified four clearly differentiated clusters, illustrating the heterogeneity of AD, at the molecular and phenotypic level. Each cluster is characterised by a specific serum biomarker profile, implying that each of these clusters is driven by a distinct underlying pathway and may represent endotypes. The identification of these endotypes through future interventional studies with specific pathway neutralising agents could enable more specific targeting of the underlying disease pathways and contribute to more personalized treatment strategies for AD patients in the future.

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467 **Table 1.** Patients' baseline characteristics.

Clinical Characteristics	Healthy controls (n=30)	Moderate AD patients (n=95)	Severe AD patients (n=98)
Age (y) ^{GM}	39.1 (34.3-44.6) ^{>mod, >sev}	30.6 (28.3-33.2) ^{<HC}	31.1 (28.5-34.0) ^{<HC}
Female, n (%)	15 (50%)	57 (60%)	55 (66%)
SASSAD ^{GM}	NA	22.3 (21.3-23.3) ^{<sev}	39.1 (37.5-40.9) ^{>mod}
Body Surface Area (%) ^{Med}	NA	33.0 (21.0-48.0) ^{<sev}	54.0 (39.0-72.0) ^{>mod}
TARC (pg/ml) ^{Med}	96.5 (65.5 - 141.1) ^{<mod, <sev}	1499.0 (619.7-3245.0) ^{>HC, <sev}	3950.0 (2094.0-9460.0) ^{>HC, >mod}
Total IgE (kU/L) ^{Med}	37.2 (13.5 - 93.9) ^{<mod, <sev}	1041 (251.0-3210) ^{>HC, <sev}	4166.0 (1015.0-9385.0) ^{>HC, >mod}
Atopic diseases, n (%)			
- allergic rhinitis	NA	30 (32%)	22 (22%)
- allergic asthma	NA	8 (8%)	8 (8%)
- allergic asthma and rhinitis	NA	36 (38%)	36 (37%)
- no atopic disease reported	NA	21 (22%)	29 (30%)
- missing data	NA	0 (0%)	3 (3%)
Age of onset AD			
0-1 yrs	NA	42 (44%)	46 (47%)
1-12 yrs	NA	42 (44%)	32 (33%)
12-18 yrs	NA	3 (3%)	5 (5%)
>18 yrs	NA	5 (5%)	10 (10%)
missing data	NA	3 (3%)	5 (5%)
Clinical label			
- predominantly lichenification	NA	43 (45%)	54 (55%)
- predominantly erythema	NA	6 (6%)	11 (11%)
- no clinical label	NA	46 (48%)	43 (44%)

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469 Categorical variables are presented as counts and percentages; log-normally distributed variables are
 470 presented as geomean (95% CI); non-normally distributed data are presented as median (25th-75th
 471 percentile) of logged data. Variable types are shown in superscript next to variable name; Med
 472 (median), GM (geometric mean). Superscript letters after measure of central tendency are groups that
 473 are significantly different at a level of $p < 0.05$; <mod, sev, HC = statistically less than moderate (mod)
 474 AD, severe (sev) AD, healthy controls (HC); >mod, sev, HC = statistically greater than moderate AD,
 475 severe AD, healthy controls. No superscript letters denotes no statistical difference between groups.

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Table 2. Key demographic data for the four AD clusters and healthy controls.

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Healthy Controls
N (% AD patients)	44 (23)	54 (29)	62 (33)	28 (15)	30 (NA)
Age ^{GM} (y)	31.2 (27.7, 35.1)	^{<HC,3} 28.1 (25.3, 31.1)	^{>2,4} 35.0 (31.4, 39.0)	^{<HC,3} 27.4 (23.3, 32.1)	^{>2,4} 39.1 (34.3, 44.6)
Sex (% female)	59.1	55.6	53.2	67.9	50
SASSAD score ^{GM}	^{>2,4} 35.3 (31.9, 39.0)	^{<1,3} 25.5 (23.2, 28.0)	^{>2,4} 32.1 (29.7, 34.8)	^{<1,3} 25.8 (22.4, 29.7)	NA
BSA score ^{Med}	^{>2,3} 54.0 (40.4, 69.0)	^{<1} 36.0 (24.0, 54.0)	^{<1} 40.5 (27.0, 53.5)	43.5 (33, 54.7)	NA
Comorbidities (%)					
- none	23.3	26.4	19.7	35.7	NA
- asthma (A)	7.0	5.7	14.8	3.6	NA
- rhinitis (R)	23.3	30.2	27.9	28.6	NA
- A & R	46.5	37.7	37.7	32.1	NA
- all asthma	53.5	43.4	52.5	35.7	NA
Age of onset (%)					
- infancy	57.1	45.1	41.7	55.6	NA
- childhood	35.7	47.1	43.3	29.6	NA
- puberty	2.4	3.9	3.3	3.7	NA
- adult	4.8	3.9	11.7	11.1	NA
Clinical labels (%)					
- predominantly lichenification	60.0	73.7	76.1	42.9	NA
- predominantly erythema	15.0	7.9	4.3	19.0	NA
- no clinical label	25.0	18.4	19.6	38.1	NA

Variable types are shown in superscript next to variable name; M (mean), Med (median), GM (geometric mean). Healthy controls (HC). Categorical variables are presented as counts and percentages. Numbers shown in brackets after measure of central tendency are 95% confidence intervals (for mean and geomean) or interquartile range (median). Superscript numbers after measure of central tendency are groups that are significantly different at a level of $p < 0.05$.

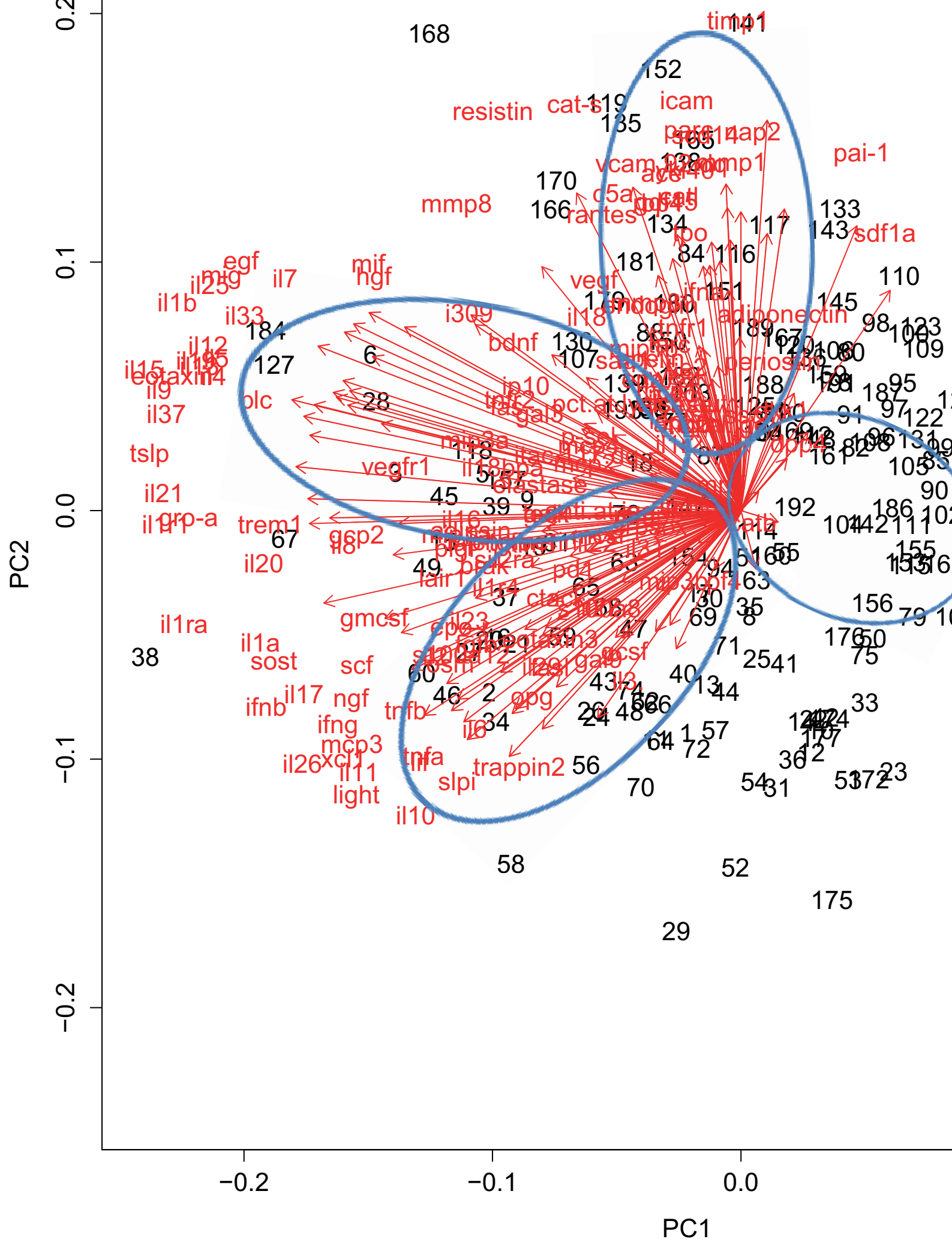
Figure Legends

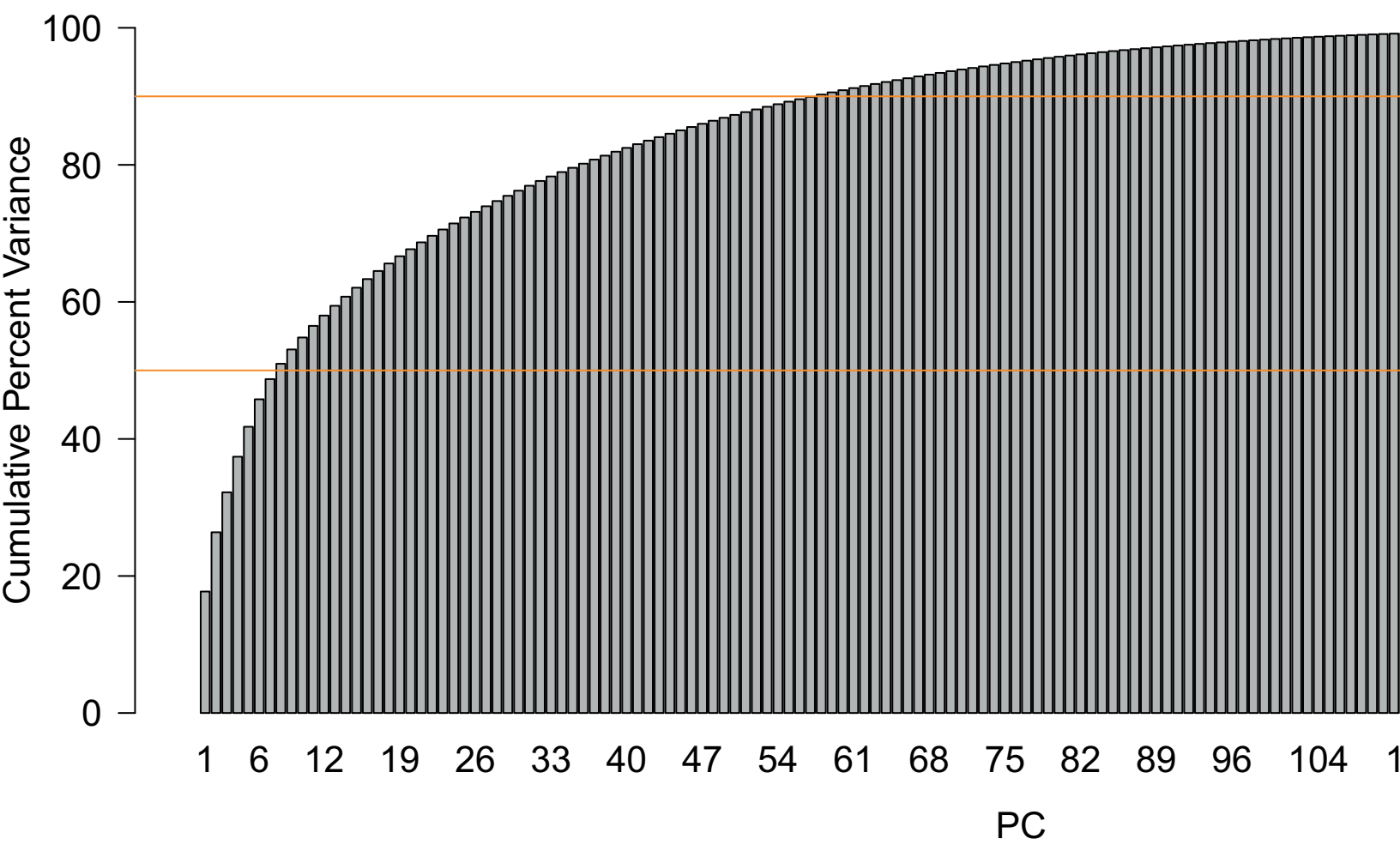
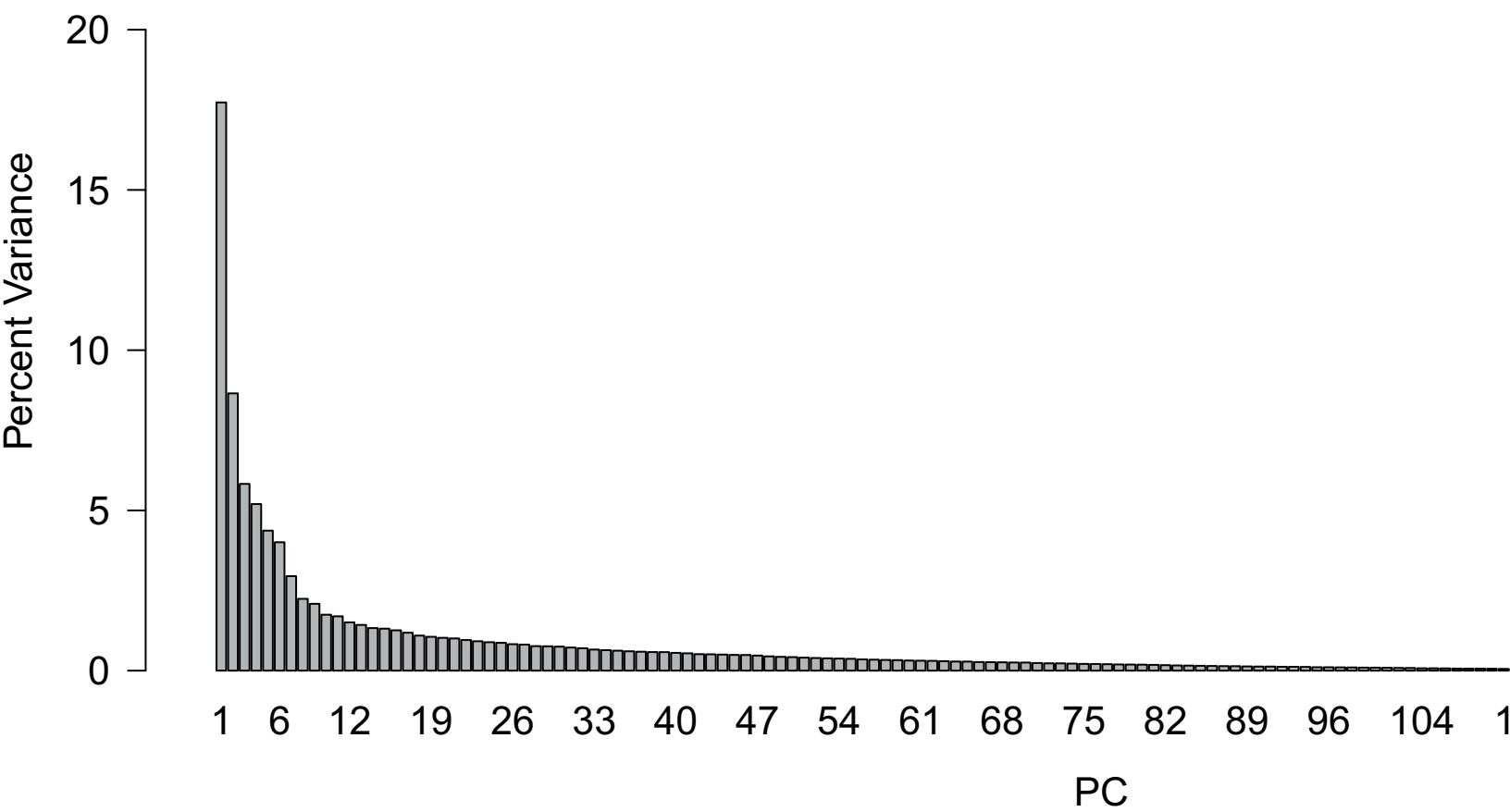
Figure 1. PCA and cluster analysis of AD patients.

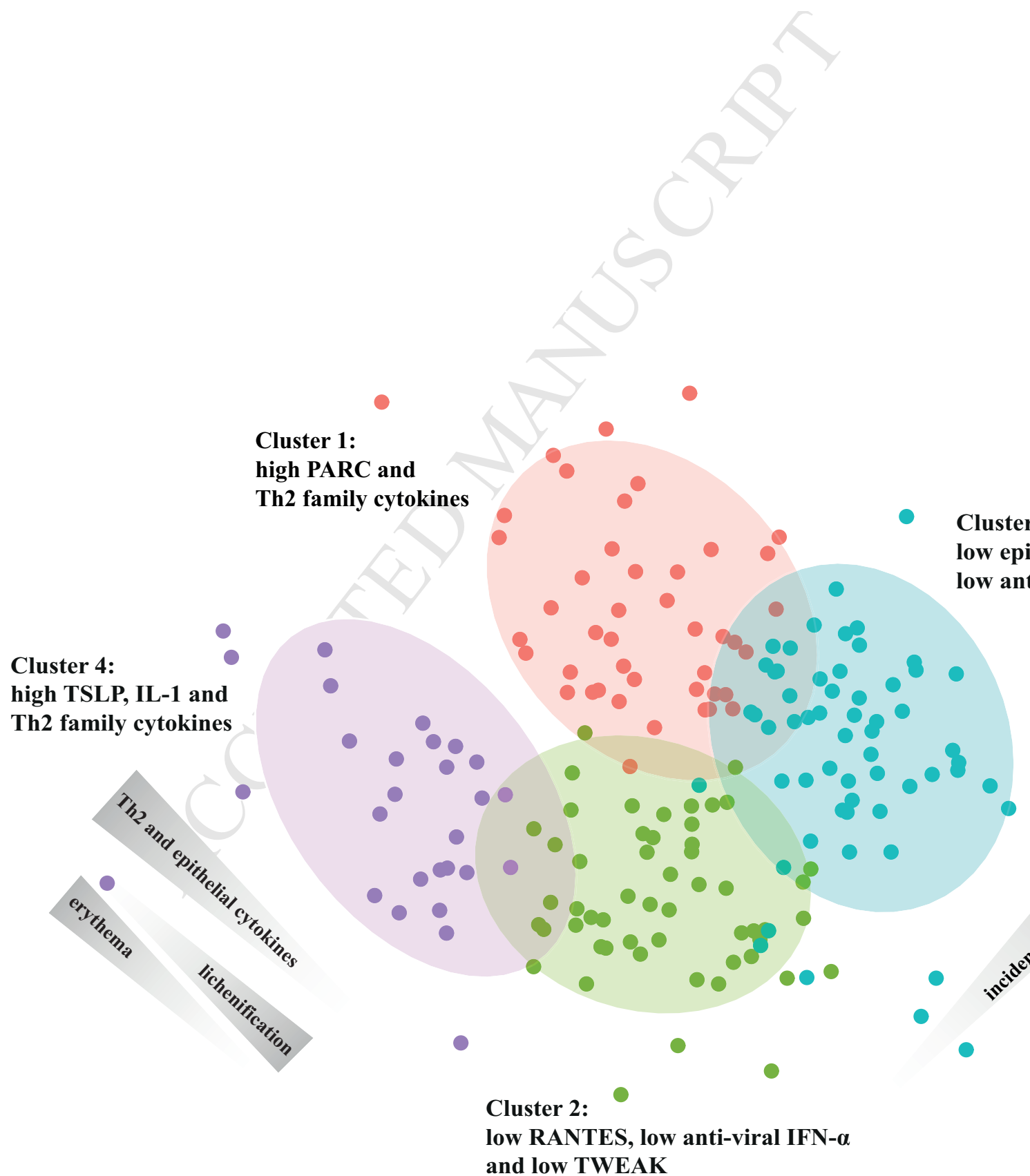
A: PCA of Box-Cox normalized serum data reveals presence of four likely clusters. Blue ovals are illustrative annotation representing four likely clusters.

B. Eight PCs describe 50% of the variance and 57 PCs describe 90% of the variance in the Box-Cox normalized serum dataset

C. Generation of four clusters of AD patients by unsupervised k-means clustering of the 57 most important PCs into four clusters using a predefined seed value. Clinical characteristics (not included in the clusters analysis) were analysed between the four clusters (**Table 2**), and averages of serum analytes per cluster were calculated and tabulated to characterise the clusters (**see Table E2 and E3 in the Online Repository**). This figure shows the characterisation of the four AD clusters.







Moving towards endotypes in atopic dermatitis: identification of patient clusters based on serum biomarker analysis

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Measurement of serum mediators

Luminex. Multiplex Luminex immunoassays were performed using a panel of 147 analytes (see **Table E1 in the Online Repository**). Uniquely color-coded magnetic beads (MagPlex Microspheres, Luminex, Austin, Texas) were conjugated to antibodies specific for the reported analytes and incubated with 50 μ L of standard dilutions or sample for 1 hour (continuous shaking at room temperature in the dark). Samples were diluted in High Performance Elisa buffer (HPE; Sanquin, The Netherlands). Pre-treatment of samples included filtration (0.22 μ m pore size) and incubation with HeteroBlock to prevent interference by binding of heterophilic antibodies. Plates were washed (Bio-Plex Pro II Wash Station; Bio-Rad, Hercules, CA, USA) and a corresponding cocktail of biotinylated detection antibodies was added for 1 hour (continuous shaking at room temperature in the dark). Repeated washings were followed by a 10-minute streptavidin-phycoerythrin (PE) incubation (continuous shaking at room temperature in the dark). Fluorescence intensity of PE was measured using a Flexmap 3D system (Luminex) and analysed using BioPlex Manager software version 6.1; (Bio-Rad, Hercules, CA, USA) using 5-parameter curve fitting.

Periostin. Periostin was measured using an in-house ELISA-based assay. In brief, Mesoscale discovery (MSD®) assay plates (MSD®, Rockville, MA, USA) were coated overnight at 4 °C with anti-human periostin antibody (MedImmune, clone 4B4.B11). Unbound antibody was washed off and plates were blocked with 0.2% I-Block Buffer (IBB; Applied Biosystems, Bedford, USA, cat# T2015) for 1 hour at room temperature after which standards (rh periostin, R&D Systems, Abingdon, UK, cat# 3548-F2) and serum samples (1:10 dilution) in IBB were incubated for 1 hour at room temperature with gentle agitation. Plates were washed off and then incubated with Sulfo-TAG (MSD, cat #R91AN) labelled anti-human periostin antibody (MedImmune, clone 7B5.C4) for 1 hour at room temperature, bound periostin detected using MSD Read Buffer T (MSD cat# R92TC) and analysed using an MSD Sector Imager 6000.

Dipeptidyl peptidase-4 (DPP4). DPP4 was measured using a commercial ELISA as per manufacturer's instructions (R&D Systems, Minneapolis, MN, USA).

Staphylococcus aureus (S. aureus) binding or neutralising antibodies. Measurement of anti-S. aureus alpha toxin antibodies was measured using an in house ELISA based assay. Briefly, ELISA plates (Nunc, Thermo Fisher Scientific Inc., Uppsala, Sweden) were coated with purified, native alpha-toxin in carbonate/bicarbonate coating buffer (Thermo Fisher Scientific Inc., Uppsala, Sweden, cat# 28382) and incubated overnight, 4°C. Plates were blocked with 5% BSA in 1 X PBS, 0.1% Tween 20, for 1 hour. A titration of an anti-alpha toxin IgG antibody (MedImmune, MEDI4893) was

used to generate a standard curve. Standards and samples (50 μ l /well) were added to the plates and incubate at room temperature for 1 hour. Bound antibodies detected with mouse anti-human IgG Fc-
HRP (SouthernBiotech, Birmingham, AL, USA; cat.no. 9040-05) and then developed with TMB
substrate (Sigma-Aldrich, St. Louis, MO, USA, cat# T4444). Neutralising anti-*Staphylococcus aureus*
alpha toxin antibodies were measured using an in house bioassay. In brief purified *Staphylococcus*
aureus alpha toxin was incubated with cells in the presence of AD patient serum. Neutralisation was
measured as a percentage reduction of cell death, as measured using a lactate dehydrogenase (LDH)
release using the Cytotox 96 non-radioactive assay kit (Promega, USA).

IgE (total and specific). Total IgE levels were determined using ImmunoCAP (Thermo Fisher
Scientific Inc., Uppsala, Sweden) according to the manufacturer's instructions. Specific IgEs were
measured using a multiplex immuno-solid phase allergen chip (ISAC)(Thermo Fisher Scientific Inc.,
Uppsala, Sweden) containing 112 allergens from 50 allergen sources according to the manufacturer's
instructions.

Statistical analysis

Statistical analyses were performed with R Project software (version 3.2.3; www.R-project.org)¹
using the R packages “caret”², “e1071”³ and “ggplot2”⁴. 200 AD patient samples were profiled against
the serum biomarker panel, but only 193 were from unique individuals and so these 193 were carried
forward for analysis. Patient demographics and sample characteristics were evaluated by an unpaired
t-test. Serum mediator data was cleansed of patients with any missing data (five patients were
removed), and subjected to Box-Cox transformation of the data. The transformed serum data was
analysed using a PCA followed by unsupervised k-means cluster analysis of the principal
components. Serum analyte levels between the four patient clusters and healthy controls were
compared using an one-way ANOVA, followed by pairwise t-tests with Holm’s correction for
multiple comparisons. According to distribution pattern of data means (M) are given for normally
distributed data, medians (Med) for log-non normally distributed data and geometric means (GM) for
log-normally distributed data. Numbers shown in brackets after measure of central tendency are 95%
confidence intervals (for mean and geomean) or quartile 1 and quartile 3 (median). Adjusted p-values
of <0.05 were considered statistically significant.

Table E1. Categorization of serum mediators based on their function.

Serum mediators		
Apoptosis biomarkers	Growth factors	Leukocyte migration biomarkers
Fas	ANG-1	ICAM-1
Fas-L	ANG-2	P-selectin
KIM-1	DKK-1	
	EGF	Neutrophil/granulocyte biomarkers
Atopic biomarker	FGF β	Elastase
Total IgE	HGF	ENA-78 (CXCL5)
	IL-7	GCP-2 (CXCL6)
Chemokines	SCF	GCSF
BLC (CXCL13)	Thrombopoietin	GM-CSF
BRAC (CXCL14)		GRO- α (CXCL1)
CTACK (CCL27)	Immunomodulatory cytokines	IL-6
MPIF (CCL23)	IL-2	NAP-2 (CXCL7)
Eotaxin (CCL11)	IL-10	S100A8
Eotaxin-3 (CCL26)	IL-12	
I-309 (CCL1)	IL-18	Proteases and protease inhibitors
IP-10 (CXCL10)	IL-21	Cathepsin B
ITAC (CXCL11)	IL-22	Cathepsin L
MCP-1 (CCL2)	IL-23	Cathepsin S
MCP-2 (CCL8)	IL-26	Cystatin C
MCP-3 (CCL7)	IL-27	SLPI
MCP-4 (CCL13)	IL-37	MMP-8
MDC (CCL22)	LAIR-1	MMP-9
MPIF (CCL23)	LIF	
MIG (CXCL9)	NGF	
MIP-1 α (CCL3)	Oncostatin	Remodelling biomarkers
MIP-1 β (CCL4)	Osteoprotegerin	Endoglin
MIP-3 α (CCL20)	PD1	GDF (MIC-1)
PARC (CCL18)	Resistin	LAP (TGF- β)
PF4 (CXCL4)		LIGHT
RANTES (CCL5)	Inflammatory biomarkers	MMP-1
SDF-1 (CXCL12)	sCD163	MMP-3
SRPSOX (CXCL16)	M-CSF	TIMP-1
TARC (CCL17)	E-selectin	
TECK (CCL25)	IL-1 α	Th2 cytokines
XCL-1	IL-1 β	DPP4
	IL-1R1	IL-4
Complement pathway	IL-1R2	IL-5
C5a	IL-1R4	IL-9
	IL-1Ra	IL-13
Epithelial cytokines	sIL-2R α	Periostin
IL-25	IL-3	
IL-33	IL-8 (CXCL8)	Vascular regulation
S100A12	IL-11	PAI-1
TSLP	IL-17	PLGF
	IL-18BP α	TIE-2
Galectins	IL-19	VEGF
Galectin-1	IL-20	sVEGF-R1
Galectin-3	IL-31	
Galectin-9	Osteopontin	Viral response
	SAA1	IFN- α
Glucose regulation	sSCFR	IFN- β
Adiponectin	TNF- α	IFN- γ
Adipsin	TACI	IL-15
Apelin	TNF-R1	IL-29
Chemerin 4	TNF-R2	TNF- β
Leptin	TREM1	
RBP4	TWEAK	Other
	VCAM-1	ACE
	YKL-40 (CHI3L1)	BDNF
		Cathepsin S
	Innate immunity biomarkers	EPO-R
	sCD14	SOST
	%Neutralisation of α -toxin-induced lysis	
	Serum Ig targeting alpha toxin	

Table E2. Summary of differentially expressed serum mediators that characterise the 4 AD disease clusters.

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Healthy controls
Apoptosis biomarkers					
Fas ^{GM}	2229.7 ^{>N,2,3} (1988.6, 2499.7)	1845.1 ^{>N, <1,4} (1701.7, 2000.6)	1717 ^{>N, <1,4} (1551, 1900.8)	2255.4 ^{>N,2,3} (2013.4, 2526.5)	840.9 ^{<1,2,3,4} (721.8, 979.7)
Fas-L ^{Med}	40.3 (29.5, 58.4)	54.0 ^{>3} (41.3, 67.4)	30.1 ^{<2,4} (19.2, 56.1)	57.5 ^{>3} (36.5, 93.6)	32.8 (31.0, 37.5)
KIM-1 ^{GM}	7.3x10 ¹ (4.0x10 ¹ , 3.0x10 ²)	8.1x10 ¹⁻³ (5.5x10 ¹ , 1.2x10 ²)	3.3x10 ^{1-2,4} (2.2x10 ¹ , 4.9x10 ¹)	1.0x10 ²⁻³ (5.8x10 ¹ , 1.9x10 ²)	4.4x10 ¹ (2.6x10 ¹ , 7.4x10 ¹)
Chemokines					
BLC ^M	68.7 ^{>N,2,3, <4} (55.6, 58.2)	42.4 ^{>3, <1,4} (36.1, 49.4)	28.2 ^{<N,1,2,4} (24.0, 33.0)	116.4 ^{>N,1,2,3} (83.9, 161.5)	43.8 ^{<1,4, >3} (32.9, 58.2)
BRAC ^{Med}	541.8 ^{<4} (318.5, 872.7)	574.5 ^{>N} (389.3, 814.0)	473.7 ^{<4} (243.5, 747.3)	774.7 ^{>N,1,3} (678.3, 1131.9)	310.3 ^{<2,4} (195.5, 487.2)
CTACK ^{Med}	432.4 ^{>3N} (237.6, 720.6)	451.5 ^{>3,N} (287.0, 774.2)	292.5 ^{<2,3,4} (153.9, 555.4)	446.6 ^{>3,N} (283, 821)	2.5 ^{<1,2,3,4} (2.5, 4.3)
Eotaxin ^{Med}	915.3 ^{>N,2,3,<4} (770.5, 1087.4)	543.2 ^{>3,N,<1,4} (458.0, 644.2)	258.3 ^{>N,<1,2,4} (220.8, 302.2)	1747.1 ^{>N,1,2,3} (1407.4, 2168.7)	73.6 ^{<1,2,3,4} (61.4, 88.3)
Eotaxin-3 ^{GM}	1.7 (1.7, 1.7)	1.7 (1.7, 1.7)	1.7 (1.7, 1.7)	1.7 ^{>N,3} (1.7, 6.6)	1.7 ^{<4} (1.7, 1.7)
I309 ^{GM}	75.4 ^{>N,2,3} (61.0, 93.2)	29.4 ^{>N, <1,4} (22.8, 37.9)	25.7 ^{>N, <1,4} (19.2, 34.4)	67 ^{>N,2,3} (47.9, 93.8)	2.1 ^{<1,2,3,4} (2.1, 2.1)
IP-10 ^{GM}	503.7 ^{>N} (442.5, 573.4)	435.7 ^{>N, <4} (397.3, 477.8)	426.4 ^{>N, <4} (383.3, 474.4)	561 ^{>N,2,3} (496.6, 670.1)	280.6 ^{<1,2,3,4} (239.9, 328.1)
ITAC ^{GM}	127.0 ^{>N} (100.5, 160.5)	91.5 ^{>N, <4} (75.6, 110.7)	105.1 ^{>N, <4} (87.2, 126.6)	165.4 ^{>N,2,3} (121.8, 224.6)	38.5 ^{<1,2,3,4} (29.9, 49.4)
MCP-1 ^{GM}	198.4 ^{>N} (177.9, 221.3)	179.2 ^{>N} (164.6, 195.2)	205.0 ^{>N} (186.3, 225.5)	214.2 ^{>N} (190.4, 240.9)	79.1 ^{<1,2,3,4} (67.9, 92.2)
MCP-3 ^{Med}	5.5 ^{<4} (5.5, 39.6)	22.0 ^{<4, >3} (16.8, 49.9)	5.5 ^{<2,4} (5.5, 5.5)	117.8 ^{>N,1,2,3} (27.5, 195)	5.5 ^{<4} (5.5, 29.9)
MCP-4 ^{Med}	55.9 (44.2, 88.8)	61.0 (41.3, 103.5)	57.1 ^{<N} (24.2, 99.1)	67.2 (46.3, 111.1)	103.8 ^{>3} (53.4, 136.7)
MIG ^{GM}	232.4 ^{>N,2,3} (201.6, 268.0)	112.0 ^{<1,4, >3} (98.1, 127.7)	73.1 ^{<N,1,2,4} (60.7, 88.1)	282.7 ^{>N,2,3} (245.5, 325.6)	97.2 ^{<1,4, >3} (90.2, 104.8)
MIP-1 α ^{Med}	116.2 ^{>N, <4} (72.7, 154.7)	106.1 ^{>N, <4} (77.6, 152.9)	86.9 ^{>N, <4} (57.4, 143.2)	144.9 ^{>N,1,2,3} (117.1, 191.9)	16.5 ^{<1,2,3,4} (16.5, 16.5)
MIP-3 α ^{Med}	10.7 ^{>N,3} (6.5, 15.8)	7.7 ^{>N, <4} (5.4, 10.2)	6.1 ^{>N, <1,4} (2.9, 10.7)	13 ^{>N,2,3} (7.7, 17)	0.6 ^{<1,2,3,4} (0.6, 0.6)
PARC ^{Med}	8.7x10 ⁶ ^{>N,2,3,4} (3.9x10 ⁶ , 8.7x10 ⁶)	6.3x10 ⁵ ^{<1} (2.7x10 ⁵ , 2.5x10 ⁶)	1.0x10 ⁶ ^{<1} (3.7x10 ⁵ , 8.7x10 ⁶)	9.3x10 ⁵ ^{<1} (3.8x10 ⁵ , 3.5x10 ⁶)	4.7x10 ⁵ ^{<1} (2.8x10 ⁵ , 7.1x10 ⁵)
SDF-1 α ^{Med}	7.2x10 ² ^{>2,4} (4.3x10 ² , 1.1x10 ³)	2.6x10 ¹ ^{<N,1,3} (2.6x10 ¹ , 2.6x10 ¹)	7.7x10 ² ^{>2,4} (4.5x10 ² , 1.3x10 ³)	2.6x10 ¹ ^{<N,1,3} (2.6x10 ¹ , 1.3x10 ²)	3.1x10 ² ^{>2,4} (2.4x10 ² , 5.3x10 ²)
TARC ^{Med}	6294.8 ^{>N,2,3} (1765.1, 8943.8)	2880.2 ^{>N, <1} (612.1, 8943.8)	2194.6 ^{>N, <1} (961.4, 8943.8)	2508.1 ^{>N} (1204.2, 5125.6)	96.5 ^{<1,2,3,4} (67.7, 137.1)
TECK ^{Med}	513.5 ^{<N} (323.4, 742.3)	411.3 ^{<N} (286.8, 578.6)	394.9 ^{<N} (292.5, 634.1)	507.5 (412.7, 674.6)	915.9 ^{>1,2,3} (562.1, 1324.1)
XCL-1 ^{Med}	8.5 ^{<N,2,4} (8.5, 8.5)	32.7 ^{>N,1,3, <4} (8.5, 61.3)	8.5 ^{<N,2,4} (8.5, 8.5)	71.9 ^{>N,1,2,3} (50, 118.1)	8.5 ^{>1,3, <4} (8.5, 61.5)
Complement pathway					
C5a ^{GM}	1.7x10 ⁵ ^{>2,3,N} (1.4x10 ⁵ , 2.2x10 ⁵)	8.4x10 ⁴ ^{<1,4,>N} (7.2x10 ⁴ , 9.8x10 ⁴)	1.1x10 ⁵ ^{<1,>N} (8.5x10 ⁴ , 1.3x10 ⁵)	1.4x10 ⁵ ^{>N} (1.1x10 ⁵ , 1.8x10 ⁵)	5.2x10 ⁴ ^{<1,2,3,4} (4.3x10 ⁴ , 6.3x10 ⁴)
Epithelial cytokines					
IL-25 ^{Med}	1.5x10 ⁴ ^{>N,2,3} (1.0x10 ⁴ , 2.2x10 ⁴)	6.7x10 ³ ^{>N,3, <1,4} (4.9x10 ³ , 9.8x10 ³)	4.5x10 ³ ^{>N, <1,2,4} (1.6x10 ³ , 6.2x10 ³)	1.8x10 ⁴ ^{>N,2,3} (1.5x10 ⁴ , 2.4x10 ⁴)	8.2x10 ¹ ^{<1,2,3,4} (8.2x10 ¹ , 5.8x10 ²)
IL-33 ^{GM}	92.8 ^{>N,2,3} (73.2, 117.8)	38.7 ^{>N,3, <1,4} (31.6, 47.4)	22.5 ^{>N, <1,2,4} (18.8, 27.0)	119.8 ^{>N,2,3} (93.5, 153.5)	9.2 ^{<1,2,3,4} (6.0, 14.1)
S100A12 ^{Med}	4.0x10 ⁶ ^{<2,4} (3.4x10 ⁶ , 5.3x10 ⁶)	7.9x10 ⁶ ^{>1,3} (6.5x10 ⁶ , 8.7x10 ⁶)	3.7x10 ⁶ ^{<2,4} (2.5x10 ⁶ , 5.0x10 ⁶)	8.5x10 ⁶ ^{>1,3} (6.6x10 ⁶ , 9.4x10 ⁶)	NA
TSLP ^{GM}	24.4 ^{>N,2,3, <4} (20.9, 28.4)	16.4 ^{>N,3, <1,4} (14.3, 18.7)	6.9 ^{>N, <1,2,4} (5.6, 8.5)	57.0 ^{>N,1,2,3} (45.5, 71.3)	3.3 ^{<1,2,3,4} (1.6, 6.7)

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Healthy controls
Galectins					
Galectin-1 ^M	2.8x10 ⁴ > ^{N,3} (2.6x10 ⁴ , 3.0x10 ⁴)	2.8x10 ⁴ > ^{N,3} (2.6x10 ⁴ , 3.0x10 ⁴)	2.4x10 ⁴ > ^{N, <1,2} (2.3x10 ⁴ , 2.6x10 ⁴)	2.8x10 ⁴ > ^N (2.5x10 ⁴ , 3.1x10 ⁴)	1.9x10 ⁴ < ^{1,2,3,4} (1.6x10 ⁴ , 2.1x10 ⁴)
Galectin-9 ^{Med}	1x10 ¹ < ^N (1x10 ¹ , 1x10 ¹)	1x10 ¹ < ^{N, >1,3} (1x10 ¹ , 1x10 ⁵)	1x10 ¹ < ^N (1x10 ¹ , 1x10 ⁵)	1x10 ¹ < ^{N, >1,3} (1x10 ¹ , 1x10 ⁵)	3.2x10 ³ > ^{1,2,3,4} (2.3x10 ³ , 4.4x10 ³)
Glucose regulation					
Adipsin ^{Med}	1.7x10 ⁴ < ⁴ (1.5x10 ⁴ , 1.7x10 ⁴)	1.7x10 ⁴ > ^{N,3} (1.6x10 ⁴ , 1.8x10 ⁴)	1.6x10 ⁴ < ^{2,4} (1.5x10 ⁴ , 1.7x10 ⁴)	1.9x10 ⁴ > ^{N,1,3} (1.8x10 ⁴ , 2.0x10 ⁴)	1.5x10 ⁴ < ^{2,4} (1.4x10 ⁴ , 1.7x10 ⁴)
Chemerin 4 ^{Med}	6.8x10 ³ < ^{N,4} (6.8x10 ³ , 2.0x10 ⁴)	1.5x10 ⁴ < ^N (6.8x10 ³ , 2.1x10 ⁴)	6.8x10 ³ < ^{N,4} (6.8x10 ³ , 1.6x10 ⁴)	2.0x10 ⁴ > ^{1,3} (6.8x10 ³ , 2.8x10 ⁴)	1.9x10 ⁴ > ^{1,2,3} (1.7x10 ⁴ , 2.5x10 ⁴)
RBP4 ^{Med}	2.7x10 ⁷ (2.5x10 ⁷ , 3.0x10 ⁷)	2.5x10 ⁷ < ^N (2.2x10 ⁷ , 2.6x10 ⁷)	2.6x10 ⁷ < ^N (2.3x10 ⁷ , 2.9x10 ⁷)	2.7x10 ⁷ (2.5x10 ⁷ , 2.9x10 ⁷)	2.8x10 ⁷ > ^{2,3} (2.7x10 ⁷ , 2.9x10 ⁷)
Growth factors					
EGF ^{GM}	23.0 ^{>2,3} (20.4, 25.8)	12.6 ^{<N,1,4} (11.0, 14.5)	9.5 ^{<N,1,4} (8.3, 10.9)	27.1 ^{>2,3} (23.5, 31.1)	24.3 ^{>2,3} (12.2, 48.6)
FGFb ^{Med}	7.8 ^{<4} (7.8, 7.8)	7.8 ^{<4} (7.8, 7.8)	7.8 ^{<4} (7.8, 7.8)	7.8 ^{>N,1,2,3} (7.8, 136.6)	7.8 ^{<4} (7.8, 7.8)
HGF ^{GM}	1237.5 ^{>N, >2,3} (1118.1, 1369.6)	824.1 ^{>N, <1,4} (754.3, 901.1)	844.0 ^{>N, <1,4} (770.8, 924.0)	1426.1 ^{>N,2,3} (1249.4, 1627.8)	629.1 ^{<1,2,3,4} (521.8, 758.6)
IL-7 ^M	46.8 ^{>N,2,3} (42.2, 51.4)	30.7 ^{>N, <1,4} (28.3, 33.2)	27.7 ^{>N, <1,4} (25.2, 30.1)	51.6 ^{>N,2,3} (46.0, 57.2)	5.2 ^{<1,2,3,4} (3.8, 6.6)
SCF	29.0 ^{<N,2,4} (16.8, 35.6)	40.4 ^{>1,3} (32.3, 52.1)	22.0 ^{<N,2,4} (14.0, 31.2)	53.6 ^{>1,3} (44.2, 70.0)	50.8 ^{>1,3} (37.7, 59)
Immunomodulatory cytokines					
IL-2 ^{Med}	2.1 ^{<N} (2.1, 2.1)	2.1 (2.1, 2.1)	2.1 ^{<N} (2.1, 2.1)	2.1 ^{>1,2,3} (2.1, 5.4)	2.1 ^{>1,3} (2.1, 2.1)
IL-10 ^{Med}	1.7 ^{<2,4} (1.7, 1.7)	6.4 ^{>N,1,3} (4.4, 8.6)	1.7 ^{<2,4} (1.7, 1.7)	9.0 ^{>N,1,3} (5.5, 12.8)	1.7 ^{<2,4} (1.7, 1.7)
IL-12 ^{Med}	102.7 ^{>N,2,3} (62.3, 154.9)	54.1 ^{>N,3, <1,4} (43.5, 77.3)	29.5 ^{>N, <1,2,4} (11.8, 44.2)	135 ^{>N,2,3} (112.5, 169.2)	3.3 ^{<1,2,3,4} (3.3, 11.7)
IL-18 ^{GM}	370.0 ^{>N,2,3} (318.4, 430.1)	214.2 ^{>N, <1,4} (179.1, 256.2)	284.4 ^{>N, <1} (211.8, 291.3)	314.9 ^{>N,2} (245.3, 404.3)	82.5 ^{<1,2,3,4} (66.4, 102.4)
IL-21 ^{GM}	7.5x10 ³ > ^{N,3, <4} (6.6x10 ³ , 8.4x10 ³)	6.3x10 ³ > ^{N,3, <4} (5.7x10 ³ , 3.7x10 ³)	2.4x10 ³ > ^{N, <1,2,4} (1.7x10 ³ , 3.5x10 ³)	1.7x10 ⁴ > ^{N,1,2,3} (1.4x10 ⁴ , 2.2x10 ⁴)	3.5x10 ² < ^{1,2,3,4} (1.1x10 ² , 1.2x10 ³)
IL-22 ^{Med}	341.5 ^{>N} (58.4, 554.7)	254.5 ^{>N,3} (106.6, 523.1)	117.0 ^{>N, <2} (31.9, 368.9)	280.8 ^{>N} (104.7, 420.5)	1.8 ^{<1,2,3,4} (1.8, 1.8)
IL-23 ^{Med}	6.8x10 ² > ^{N,3} (1.1x10 ² , 1.7x10 ³)	2.3x10 ² > ^{N,3} (1.5x10 ² , 9.6x10 ²)	9.8x10 ¹ > ^{1, <4} (1.5x10 ¹ , 7.3x10 ²)	1.3x10 ³ > ^{N,3} (2.5x10 ² , 4.9x10 ³)	1.5x10 ¹ < ^{1,2,4} (1.5x10 ¹ , 6.9x10 ¹)
IL-26 ^{Med}	5.7x10 ² < ^{2,4, >3} (3.8x10 ¹ , 2.2x10 ³)	5.8x10 ³ > ^{N,1,3} (4.5x10 ³ , 6.9x10 ³)	3.8x10 ¹ < ^{N,1,2,4} (3.8x10 ¹ , 4.2x10 ²)	8.6x10 ³ > ^{N,1,3} (6.5x10 ³ , 9.9x10 ³)	6.5x10 ² < ^{2,4, >3} (1.4x10 ² , 1.5x10 ³)
IL-27 ^{Med}	1.6x10 ¹ < ^N (1.6x10 ¹ , 1.6x10 ¹)	1.6x10 ¹ < ^{N, >3} (1.6x10 ¹ , 1.9x10 ⁴)	1.6x10 ¹ < ^N (1.6x10 ¹ , 1.6x10 ¹)	1.6x10 ¹ < ^N (1.6x10 ¹ , 1.9x10 ⁴)	1.4x10 ³ (4.7x10 ² , 2.7x10 ³)
IL-37 ^{Med}	1397.3 ^{>N,2,3, <4} (829.1, 2333.5)	950.9 ^{>N,3, <1,4} (554.2, 1276.3)	44.2 ^{>1,2,4} (44.2, 360.4)	2540.7 ^{>N,1,2,3} (2081.5, 3156)	44.2 ^{<1,2,4} (44.2, 44.2)
LAIR-1 ^{Med}	182.1 ^{<4} (182.1, 182.1)	182.1 ^{<4} (182.1, 182.1)	182.1 ^{<4} (182.1, 182.1)	966.4 ^{>N,1,2,3} (182.1, 2330.2)	182.1 ^{<4} (182.1, 182.1)
LIF ^{Med}	4.8 ^{<2,4} (4.8, 4.8)	4.8 ^{>N,1,3} (4.8, 26.2)	4.8 ^{<2,4} (4.8, 4.8)	13.5 ^{>N,1,3} (4.8, 36.9)	4.8 ^{<2,4} (4.8, 4.8)
NGF ^{Med}	4.4 ^{<2,4} (1.8, 10.1)	8.6 ^{<4, >N,1,3} (2.2, 14.5)	1.8 ^{<2,4} (1.8, 5.7)	18.5 ^{>N,1,2,3} (10.4, 24.7)	2.8 ^{<2,4} (1.8, 6.7)
Oncostatin M ^{Med}	11.4 ^{<N} (3.3, 36.7)	20.8 ^{>N} (7.0, 47.7)	3.3 ^{<2,4} (3.3, 11.9)	41.1 ^{>3,N} (14.3, 59.2)	3.3 ^{<1,2,4} (3.3, 3.3)
Osteopontin ^{Med}	2091.7 ^{>N} (1885.7, 2388.2)	2738.5 ^{>N,3, <4} (2220.4, 3078.4)	1949.5 ^{>N, <2} (1345.1, 2188.7)	2781.8 ^{>N,2} (2201.4, 3140.6)	7.6 ^{<1,2,3,4} (7.6, 7.6)
PD1 ^{Med}	4.6x10 ⁰ (4.6x10 ⁰ , 5.8x10 ³)	2.3x10 ² (4.6x10 ⁰ , 5.0x10 ³)	4.6x10 ⁰ < ⁴ (4.6x10 ⁰ , 3.5x10 ²)	3.1x10 ² > ³ (9.5x10 ¹ , 2.3x10 ³)	2.1x10 ¹ (4.6x10 ⁰ , 2.0x10 ²)
Resistin ^{Med}	9.8x10 ³ > ^{2,3} (8.4x10 ³ , 1.2x10 ⁴)	6.5x10 ³ < ^{N,1,4} (5.6x10 ³ , 7.6x10 ³)	6.2x10 ³ < ^{N,1} (4.9x10 ³ , 8.1x10 ³)	8.7x10 ³ > ^{2,3} (7.1x10 ³ , 9.8x10 ³)	9.4x10 ³ (8.9x10 ³ , 1.0x10 ⁴)
Inflammatory biomarkers					
E-selectin ^{Med}	2.3x10 ⁴ (1.8x10 ⁴ , 3.4x10 ⁴)	2.2x10 ⁴ < ^N (1.5x10 ⁴ , 2.8x10 ⁴)	2.1x10 ⁴ < ^N (1.6x10 ⁴ , 3.1x10 ⁴)	2.2x10 ⁴ < ^N (1.7x10 ⁴ , 2.8x10 ⁴)	6.4x10 ⁴ > ^{2,3,4} (4.3x10 ⁴ , 8.5x10 ⁴)

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Healthy controls
IL-1 α ^{Med}	22.5 ^{>N,3,<2,4} (8.3, 43.7)	34.6 ^{>N,1,3,<4} (25.4, 50.5)	10.4 ^{<1,2,4} (1.1, 20.1)	77.4 ^{>N,1,2,3} (57.2, 89.5)	4.7 ^{<1,2,4} (3.1, 8.1)
IL-1 β ^{GM}	22.7 ^{>N,2,3,<4} (19.7, 26.2)	10.9 ^{>N,3,<1,4} (9.5, 12.4)	7.4 ^{>N,<1,2,4} (6.4, 8.6)	35.5 ^{>N,1,2,3} (28.8, 43.9)	1.1 ^{<1,2,3,4} (0.7, 1.9)
IL-1R1 ^{Med}	88.4 ^{>N,3,<4} (65.2, 112.6)	89.7 ^{>N,3,<4} (68.1, 109.0)	37.2 ^{>N,<1,2,4} (18.8, 55.3)	160.5 ^{>N,1,2,3} (145.6, 201.3)	5.6 ^{<1,2,3,4} (2.7, 7.5)
IL-1R2 ^{Med}	2046.8 (1400.9, 2356.7)	1865.4 ^{>N} (1441.7, 2275.3)	1688.5 (1215.7, 2576.7)	1745 (1366.4, 2120.5)	1473.4 ^{<2} (842.3, 2059.5)
IL-1R4 ^{Med}	3.0 ^{<4} (0.6, 11.6)	9.1 ^{>3} (0.6, 17.2)	0.6 ^{<2,4} (0.6, 9.0)	14.6 ^{>N,3} (4.3, 22.8)	0.6 ^{<4} (0.6, 12.8)
IL-1Ra ^{Med}	37.1 ^{<2,4,>3} (17.3, 69.4)	50.9 ^{>N,1,3,<4} (42.8, 74.0)	4.2 ^{<N,1,2,4} (4.2, 11.2)	118.0 ^{>N,1,2,3} (92.9, 163.0)	4.2 ^{<2,3,4} (4.2, 88.0)
sIL-2R α ^{Med}	23.5 ^{<N,4} (23.5, 23.5)	23.5 (23.5, 23.5)	23.5 ^{<N,4} (23.5, 23.5)	23.5 ^{>1,3} (23.5, 465.4)	23.5 ^{>1,3} (23.5, 335.7)
IL-6 ^{Med}	13.7 ^{>N,<4} (8.9, 28.5)	23.0 ^{>N,3} (14.9, 51.5)	7.8 ^{>N,<2,4} (3.4, 20.8)	29.7 ^{>N,1,3} (22.6, 53.7)	1.4 ^{<1,2,3,4} (1.4, 10.2)
IL-8 ^{GM}	20.0 ^{>3,<4} (14.2, 28.1)	15.0 ^{<4} (11.4, 17.9)	8.6 ^{<N,1,4} (6.1, 12.0)	68.1 ^{>N,1,2,3} (43.0, 107.9)	20.9 ^{>3,<4} (12.6, 34.4)
IL-11 ^{Med}	4.0 ^{>N,<2,4} (4.0, 26.1)	70.3 ^{>N,1,3} (30.9, 108.8)	4.0 ^{>N,<2,4} (4.0, 9.6)	113.7 ^{>N,1,2,3} (83.5, 227.7)	4 ^{<1,2,3,4} (4, 4)
IL-17 ^{Med}	2.8 ^{<2,4} (2.8, 6.2)	7.7 ^{>N,1,3,<4} (2.8, 17.1)	2.8 ^{<2,4} (2.8, 2.8)	24 ^{>N,1,2,3} (15, 35.4)	2.8 ^{<2,4} (2.8, 2.8)
IL-18BP α ^{Med}	2535.7 ^{>N} (1880.6, 3002.2)	2435.6 ^{<4} (1791.8, 2868.9)	2091.2 ^{<4} (1580.6, 2767.5)	2816.9 ^{>N,2,3} (2604.1, 3281.5)	1416.3 ^{<1,4} (1121.3, 1740.4)
IL-19 ^{Med}	1715.6 ^{>2,3} (1272.7, 2164.4)	1184.9 ^{>3,<1,4} (896.0, 1543.2)	733.7 ^{<1,2,4} (422.2, 911.4)	2316.8 ^{>2,3} (1921.1, 2714.7)	NA
IL-20 ^{Med}	42.4 ^{>N,<4} (42.4, 42.4)	42.4 ^{>N,<4} (42.4, 42.4)	42.4 ^{>N,<4} (42.4, 42.4)	122.2 ^{>N,1,2,3} (102.1, 160.5)	42.4 ^{<1,2,3} (42.4, 42.4)
TNF- α ^{Med}	1.1 ^{<2,4} (1.1, 1.1)	3.6 ^{>N,1,3,<4} (1.1, 6.7)	1.1 ^{<2,4} (1.1, 1.1)	9.3 ^{>N,1,2,3} (2.5, 24.8)	1.1 ^{<2,4} (1.1, 1.1)
TNF-R1 ^M	6.4x10 ^{3>N,2} (5.8x10 ³ , 7.0x10 ³)	5.1x10 ^{3>N,<1} (4.7x10 ³ , 5.5x10 ³)	5.7x10 ^{3>N} (5.2x10 ³ , 6.1x10 ³)	5.5x10 ^{3>N} (4.6x10 ³ , 6.4x10 ³)	5.9x10 ^{2<1,2,3,4} (2.8x10 ² , 9.1x10 ²)
TNF-R2 ^M	2324.9 ^{>N,2,3} (2106.0, 2543.8)	1993.2 ^{>N,<1} (1875.4, 2110.9)	1876.2 ^{>N,<1,4} (1722.1, 2030.4)	2310 ^{>N,3} (2067.3, 2552.6)	1476.4 ^{<1,2,3,4} (1351.6, 1601.1)
TREM1 ^{GM}	8.3x10 ^{1>N,3,<4} (6.3x10 ¹ , 1.1x10 ²)	8.7x10 ^{1>N,3,<4} (6.9x10 ¹ , 1.1x10 ²)	2.4x10 ^{1>N,3,<1,2,4} (1.8x10 ¹ , 3.3x10 ¹)	1.7x10 ^{2>N,1,2,3} (1.4x10 ² , 1.9x10 ²)	1.4x10 ^{1<1,2,3,4} (9.3x10 ⁰ , 2.1x10 ¹)
YKL40 ^{Med}	5.6x10 ^{4>2} (4.4x10 ⁴ , 8.8x10 ⁴)	3.8x10 ^{4<1} (3.2x10 ⁴ , 4.4x10 ⁴)	4.8x10 ⁴ (3.3x10 ⁴ , 6.7x10 ⁴)	3.9x10 ⁴ (3.2x10 ⁴ , 5.8x10 ⁴)	5.0x10 ⁴ (4.5x10 ⁴ , 6.6x10 ⁴)
Innate immunity biomarkers					
sCD14 ^{Med}	2.0x10 ^{6>2,3,4} (1.5x10 ⁶ , 2.5x10 ⁶)	1.2x10 ^{6<N,1} (1.1x10 ⁶ , 1.3x10 ⁶)	1.6x10 ^{6<N,1} (1.1x10 ⁶ , 2.0x10 ⁶)	1.3x10 ^{6<N,1} (1.1x10 ⁶ , 1.7x10 ⁶)	2.3x10 ^{6>2,3,4} (2.1x10 ⁶ , 2.5x10 ⁶)
%Neutralisation of α -toxin-induced lysis ^{Med}	50.1 ^{>N,3} (28.8, 86.1)	25.1 ^{>N} (15.9, 48.0)	34.0 ^{>N,<1} (9.0, 57.0)	28.6 ^{>N} (14.0, 72.5)	10.8 ^{<1,2,3,4} (0.9, 20.5)
Leukocyte migration biomarkers					
ICAM-1 ^{Med}	6.2x10 ^{5>N,2,3} (5.3x10 ⁵ , 7.7x10 ⁵)	4.1x10 ^{5<1,>N} (3.7x10 ⁵ , 4.9x10 ⁵)	4.9x10 ^{5<1,>N} (3.8x10 ⁵ , 6.7x10 ⁵)	4.8x10 ^{5>N} (3.9x10 ⁵ , 5.6x10 ⁵)	2.9x10 ^{5<1,2,3,4} (2.2x10 ⁵ , 3.4x10 ⁵)
P-selectin	3.6x10 ⁵ (2.0x10 ⁵ , 1.4x10 ⁶)	3.8x10 ^{5<N} (2.1x10 ⁵ , 5.7x10 ⁵)	2.9x10 ^{5<N} (2.0x10 ⁵ , 4.7x10 ⁵)	3.7x10 ⁵ (2.7x10 ⁵ , 5.8x10 ⁵)	5.5x10 ^{5>2,3} (3.5x10 ⁵ , 1.4x10 ⁶)
Neutrophil/Granulocyte biomarkers					
Elastase ^{Med}	2.7x10 ^{4<4,>N} (1.3x10 ⁴ , 8.6x10 ⁴)	2.3x10 ^{4<4,>N} (1.4x10 ⁴ , 8.6x10 ⁴)	2.2x10 ^{4<4,>N} (1.0x10 ⁴ , 8.6x10 ⁴)	8.6x10 ^{4>1,2,3,N} (8.6x10 ⁴ , 8.6x10 ⁴)	1.2x10 ^{4<1,2,3,4} (7.1x10 ³ , 1.6x10 ⁴)
GCP-2 ^{GM}	160.3 ^{>N,<4} (120.9, 212.6)	127.1 ^{>N,<4} (101.5, 159.1)	102.6 ^{<4} (77.1, 136.6)	399.8 ^{>N,1,2,3} (304.8, 524.5)	64.2 ^{<1,2,4} (34.4, 119.8)
GM-CSF ^{Med}	7.6 ^{<4,>N} (7.6, 7.6)	7.6 ^{<4,>N} (7.6, 7.6)	7.6 ^{<4,>N} (7.6, 7.6)	17.3 ^{>N,1,2,3} (7.6, 35.3)	7.6 ^{<1,2,3,4} (7.6, 7.6)
GRO- α ^{GM}	125.5 ^{>3,<4} (110.8, 142.3)	110.3 ^{>3,<4} (102.2, 118.9)	74.7 ^{<1,2,4} (67.3, 82.8)	245.1 ^{>1,2,3} (198.0, 303.4)	NA
S100A8 ^{Med}	1.3x10 ^{5>N} (1.2x10 ⁵ , 1.6x10 ⁵)	1.6x10 ^{5>N,3} (1.4x10 ⁵ , 1.8x10 ⁵)	1.3x10 ^{5>N,<2} (1.1x10 ⁵ , 1.5x10 ⁵)	1.6x10 ^{5>N} (1.5x10 ⁵ , 1.9x10 ⁵)	1.2x10 ^{4<1,2,3,4} (8.4x10 ³ , 1.6x10 ⁴)
Proteases and protease inhibitors					
Cathepsin S ^{Med}	1.6x10 ^{4>2,3} (1.4x10 ⁴ , 2.0x10 ⁴)	1.3x10 ^{4<N,1} (1.1x10 ⁴ , 1.4x10 ⁴)	1.3x10 ^{4<N,1} (1.1x10 ⁴ , 1.6x10 ⁴)	1.4x10 ⁴ (1.2x10 ⁴ , 1.7x10 ⁴)	1.7x10 ^{4>2,3} (1.6x10 ⁴ , 1.9x10 ⁴)

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Healthy controls
SLPI ^{Med}	9.4x10 ³ >N, <2,4 (8.2x10 ³ , 1.9x10 ⁴)	1.9x10 ⁴ >N,1,3 (1.9x10 ⁴ , 1.9x10 ⁴)	9.2x10 ³ >N, <2,4 (8.1x10 ³ , 1.9x10 ⁴)	1.9x10 ⁴ >N,1,3 (1.9x10 ⁴ , 1.9x10 ⁴)	6.4x10 ³ <1,2,3,4 (5.9x10 ³ , 7.2x10 ³)
MMP-8 ^{GM}	1.9x10 ⁵ <N, >2,3 (1.6x10 ⁵ , 2.2x10 ⁵)	1.0x10 ⁵ <N,1,4 (8.9x10 ⁴ , 1.2x10 ⁵)	9.5x10 ⁴ <N,1,4 (8.5x10 ⁴ , 1.1x10 ⁵)	1.6x10 ⁵ <N, >2,3 (1.3x10 ⁵ , 1.8x10 ⁵)	3.0x10 ⁵ >1,2,3,4 (2.7x10 ⁵ , 3.2x10 ⁵)
Remodelling biomarkers					
Endoglin ^{GM}	3.2x10 ³ >N,2 (2.9x10 ³ , 3.6x10 ³)	2.3x10 ³ >N, <1,3 (2.0x10 ³ , 2.5x10 ³)	2.8x10 ³ >N,2 (2.5x10 ³ , 3.1x10 ³)	2.8x10 ³ >N (2.4x10 ³ , 3.2x10 ³)	1.2x10 ³ <1,2,3,4 (1.1x10 ³ , 1.3x10 ³)
LAP-TGF α ^{GM}	3.0x10 ⁵ >N, <2,4 (2.8x10 ⁵ , 3.2x10 ⁵)	3.5x10 ⁵ >N,1,3 (3.4x10 ⁵ , 3.7x10 ⁵)	2.9x10 ⁵ >N, <2,4 (2.7x10 ⁵ , 3.1x10 ⁵)	3.7x10 ⁵ >N,1,3 (3.4x10 ⁵ , 4.0x10 ⁵)	1.5x10 ⁵ <1,2,3,4 (1.4x10 ⁵ , 1.7x10 ⁵)
LIGHT ^{Med}	4.0 ^{<N,2,4} (4.0, 4.0)	151.7 ^{>1,3, <4} (4.0, 257.3)	4.0 ^{<N,2,4} (4.0, 4.0)	331.3 ^{>N,1,2,3} (209.9, 610.4)	29.8 ^{>1,3, <4} (4, 73.3)
MMP-1 ^{GM}	6.0x10 ⁴ >N,2 (5.2x10 ⁴ , 6.9x10 ⁴)	3.40x10 ⁴ <1,3 (2.5x10 ⁴ , 3.5x10 ⁴)	4.5x10 ⁴ >2 (3.6x10 ⁴ , 5.5x10 ⁴)	4.0x10 ⁴ (3.2x10 ⁴ , 5.0x10 ⁴)	3.5x10 ⁴ <1 (2.8x10 ⁴ , 4.3x10 ⁴)
TIMP-1 ^M	6.0x10 ⁵ >N,2,3,4 (5.7x10 ⁵ , 6.3x10 ⁵)	4.3x10 ⁵ <N,1,3,4 (4.2x10 ⁵ , 4.5x10 ⁵)	5.3x10 ⁵ <1, >2 (5.0x10 ⁵ , 5.6x10 ⁵)	4.8x10 ⁵ <1, >2 (4.5x10 ⁵ , 5.0x10 ⁵)	5.0x10 ⁵ <1, >2 (4.8x10 ⁵ , 5.2x10 ⁵)
Th2 cytokines					
IL-4 ^{Med}	6.7 ^{>N,2,3, <4} (4.1, 9.5)	3.6 ^{>N,3, <1,4} (2.5, 5.5)	1.4 ^{>N, <1,2,4} (0.3, 2.2)	10.2 ^{>N,1,2,3} (7.8, 14.1)	0.3 ^{<1,2,3,4} (0.3, 0.3)
IL-5 ^{GM}	323.7 ^{>N,2,3} (278.9, 375.6)	171.9 ^{>N, <1,4} (151.2, 195.6)	124.9 ^{>N, <1,4} (101.6, 153.6)	506.8 ^{>N,2,3} (415.4, 618.3)	5.0 ^{<1,2,3,4} (2.6, 9.6)
IL-9 ^{GM}	145.9 ^{>N,2,3, <4} (122.0, 174.4)	75.7 ^{>N,3, <1,4} (64.4, 89.0)	34.3 ^{>N, <1,2,4} (25.5, 46.1)	349.2 ^{>N,1,2,3} (265.6, 459)	12.2 ^{<1,2,3,4} (4.8, 31.3)
IL-13 ^{GM}	97.1 ^{>N,2,3, <4} (83.8, 112.6)	51.9 ^{>N,3, <1,4} (45.9, 58.6)	39.9 ^{>N, <1,4} (34.2, 46.7)	170.3 ^{>N,1,2,3} (134.2, 216.2)	23.3 ^{<1,2,3,4} (10.3, 52.8)
Periostin ^{GM}	18.6 ^{>N} (14.5, 24.0)	13.2 ^{>N} (11.4, 15.4)	15.0 ^{>N} (13.1, 17.3)	11.8 (9.4, 14.8)	6.7 ^{<1,2,3} (3.4, 13.4)
Vascular regulation					
PAI-1 ^{Med}	8.7x10 ⁵ >4 (7.4x10 ⁵ , 1.2x10 ⁶)	1.0x10 ⁵ <N,1,3 (4.4x10 ⁴ , 1.0x10 ⁵)	8.6x10 ⁵ >2,3 (6.9x10 ⁵ , 1.1x10 ⁶)	4.4x10 ⁵ <N,1,3 (4.4x10 ⁴ , 7.8x10 ⁵)	9.5x10 ⁵ >2,4 (6.6x10 ⁵ , 1.3x10 ⁶)
PLGF ^{Med}	40.5 ^{<4} (10.6, 54.2)	45.4 ^{<4} (16.1, 59.7)	31.0 ^{<4} (16.7, 52.3)	64.3 ^{>1,2,3} (40.2, 89.7)	40.8 (26.7, 61.6)
TIE-2 ^M	9.6x10 ³ >N,2 (8.6x10 ³ , 1.1x10 ⁴)	7.8x10 ³ >N, <1 (7.3x10 ³ , 8.3x10 ³)	8.6x10 ³ >N (7.9x10 ³ , 9.2x10 ³)	8.5x10 ³ >N (7.9x10 ³ , 9.1x10 ³)	2.6x10 ³ <1,2,3,4 (2.3x10 ³ , 2.8x10 ³)
VEGF ^{Med}	873.5 ^{>N,2} (687.4, 1295.9)	493.1 ^{>N, <1,3,4} (317.1, 871.3)	793.0 ^{>N,2} (439.4, 1295.8)	945.5 ^{>N,2} (535.5, 1278.7)	346.4 ^{<1,2,3,4} (170.2, 602.5)
sVEGF-R1 ^{GM}	1.6x10 ³ >3, <4 (1.3x10 ³ , 1.8x10 ³)	1.2x10 ³ <4 (1.1x10 ³ , 1.5x10 ³)	1.1x10 ³ <N,1,4 (9.7x10 ² , 1.2x10 ³)	2.2x10 ³ >N,1,2,3 (1.9x10 ³ , 2.5x10 ³)	1.5x10 ³ >3, <4 (1.2x10 ³ , 1.9x10 ³)
Viral response					
IFN- α ^{Med}	95.1 ^{>N,2} (82.0, 100.2)	41.5 ^{>N, <1,3,4} (30.3, 51.2)	93.3 ^{>N,2} (81.8, 101.0)	63.2 ^{>N,2} (55.5, 110.1)	0.7 ^{<1,2,3,4} (0.7, 2.9)
IFN- β ^{Med}	9.4x10 ¹ <N,2,4, >3 (9.7x10 ⁰ , 1.9x10 ²)	1.9x10 ² <N,4, >1,3 (1.4x10 ² , 2.9x10 ²)	9.7x10 ⁰ <N,1,2,4 (9.7x10 ⁰ , 4.2x10 ¹)	6.5x10 ² >1,2,3 (3.4x10 ² , 1.1x10 ³)	3.2x10 ² >1,2,3 (1.5x10 ² , 9.1x10 ²)
IFN- γ ^{Med}	4.4 ^{<2,4} (4.4, 4.4)	11.0 ^{<4, >1,3} (4.4, 27.0)	4.4 ^{<2,4} (4.4, 4.4)	95.2 ^{>N,1,2,3} (28.4, 178.2)	4.4 ^{<4} (4.4, 4.4)
IL-15 ^{Med}	174.9 ^{>N,2,3, <4} (101.7, 238.8)	84.6 ^{>N,3, <1,4} (63.0, 132.4)	44.6 ^{>N, <1,2,4} (22.2, 65.4)	242.7 ^{>N,1,2,3} (213, 354.1)	3.7 ^{<1,2,3,4} (1.5, 6.4)
IL-29 ^{Med}	1.0x10 ¹ (1.0x10 ¹ , 1.0x10 ¹)	1.0x10 ¹ >3 (1.0x10 ¹ , 1.1x10 ²)	1.0x10 ¹ <2,4 (1.0x10 ¹ , 1.0x10 ¹)	1.0x10 ¹ >3 (1.0x10 ¹ , 2.0x10 ¹)	1.0x10 ¹ (1.0x10 ¹ , 1.0x10 ¹)
TNF- β ^{Med}	1.5 ^{<4} (1.5, 1.5)	3.5 ^{<4} (1.5, 10.3)	1.5 ^{<N,4} (1.5, 1.5)	44.2 ^{>N,1,2,3} (5.3, 118.6)	1.5 ^{<3,4} (1.5, 12.8)
Other					
ACE ^{GM}	3.6x10 ⁵ >2,3 (3.2x10 ⁵ , 4.1x10 ⁵)	2.6x10 ⁵ <N,1 (2.4x10 ⁵ , 2.9x10 ⁵)	2.7x10 ⁵ <N,1 (2.3x10 ⁵ , 3.2x10 ⁵)	2.9x10 ⁵ (2.5x10 ⁵ , 3.4x10 ⁵)	4.0 x10 ⁵ >2,3 (3.6 x10 ⁵ , 4.3 x10 ⁵)
BDNF ^M	2.3x10 ⁵ <N (2.2x10 ⁵ , 2.5x10 ⁵)	2.3x10 ⁵ <N (2.1x10 ⁵ , 2.4x10 ⁵)	2.0x10 ⁵ <N,4 (1.8x10 ⁵ , 2.2x10 ⁵)	2.6x10 ⁵ <N (2.5x10 ⁵ , 2.8x10 ⁵)	5.5x10 ⁵ >1,2,3,4 (4.7x10 ⁵ , 6.2x10 ⁵)
EPO-R ^{Med}	13.7 ^{<4} (13.7, 225.1)	26.0 ^{<4} (13.7, 473.0)	13.7 ^{<4} (13.7, 45.3)	914.5 ^{>N,1,2,3} (123.9, 1935.1)	13.7 ^{<4} (13.7, 13.7)
MIF ^{GM}	4.4x10 ³ <N, >2,3 (3.8x10 ³ , 5.0x10 ³)	2.6x10 ³ <N,1,4 (2.2x10 ³ , 3.1x10 ³)	2.2x10 ³ <N,1,4 (2.0x10 ³ , 2.5x10 ³)	4.4x10 ³ <N, >2,3 (3.8x10 ³ , 5.2x10 ³)	7.0x10 ³ >1,2,3,4 (5.2x10 ³ , 9.3x10 ³)
NAP-2 ^{Med}	4.0x10 ⁷ >2,3 (3.3x10 ⁷ , 4.0x10 ⁷)	1.5x10 ⁷ <1 (1.3x10 ⁷ , 1.6x10 ⁷)	2.8x10 ⁷ <1 (1.5x10 ⁷ , 4.0x10 ⁷)	1.6x10 ⁷ (1.5x10 ⁷ , 1.7x10 ⁷)	1.9x10 ⁷ (1.7x10 ⁷ , 4.0x10 ⁷)

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Healthy controls
SOST ^{Med}	11.7 ^{<N,2,4} (11.7, 11.7)	11.7 ^{<N,4, >1,3} (11.7, 11.7)	11.7 ^{<N,2,4} (11.7, 11.7)	272.6 ^{>N,1,2,3} (104, 389.5)	11.7 ^{<4, >1,2,3} (11.7, 87.7)
Trappin-2 ^{Med}	37.1 ^{<N,2,4} (14.9, 90.3)	236.4 ^{<N,>1,3} (164.9, 384.5)	36.4 ^{<N,2,4} (13.2, 77.9)	181.5 ^{<N,>1,3} (162.0, 240.0)	2226.0 (1923.7, 2576.3)

Variable types are shown in superscript next to variable name; M (mean) for normally distributed data, Med (median) for log-non normally distributed data, GM (geometric mean) for log-normally distributed data. Numbers shown in brackets after measure of central tendency are 95% confidence intervals (for mean and geomean) or interquartile range (median). Superscript numbers after measure of central tendency are groups that are significantly different.

Supplemental table E3. Table showing analytes that do not significantly differ between clusters.

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Healthy controls
Adiponectin ^{Med}	1.9x10 ⁸ (1.1x10 ⁸ , 4.2x10 ⁸)	1.3x10 ⁸ (8.6x10 ⁷ , 1.7x10 ⁸)	1.8x10 ⁸ (9.6x10 ⁷ , 4.2x10 ⁸)	1.5x10 ⁸ (1.3x10 ⁸ , 1.8x10 ⁸)	1.3x10 ⁸ (9.0x10 ⁷ , 1.6x10 ⁸)
Ang1 ^{Med}	5.4x10 ⁴ (4.2x10 ⁴ , 7.0x10 ⁴)	4.9x10 ⁴ (4.2x10 ⁴ , 5.6x10 ⁴)	5.5x10 ⁴ (4.3x10 ⁴ , 7.1x10 ⁴)	6.2x10 ⁴ (5.0x10 ⁴ , 7.0x10 ⁴)	4.4x10 ⁴ (3.6x10 ⁴ , 6.0x10 ⁴)
Ang2 ^{Med}	1.4x10 ⁴ < ^N (1.3x10 ⁴ , 1.6x10 ⁴)	1.2x10 ⁴ < ^N (1.1x10 ⁴ , 1.4x10 ⁴)	1.3x10 ⁴ < ^N (1.1x10 ⁴ , 1.6x10 ⁴)	1.3x10 ⁴ < ^N (1.2x10 ⁴ , 1.5x10 ⁴)	1.9x10 ⁴ > ^{1,2,3,4} (1.8x10 ⁴ , 2.8x10 ⁴)
Apelin ^{Med}	6.5x10 ⁴ > ^N (6.1x10 ⁴ , 7.0x10 ⁴)	6.1x10 ⁴ > ^N (5.7x10 ⁴ , 6.4x10 ⁴)	6.4x10 ⁴ > ^N (5.8x10 ⁴ , 6.8x10 ⁴)	6.4x10 ⁴ > ^N (6.3x10 ⁴ , 6.6x10 ⁴)	4.7x10 ⁴ < ^{1,2,3,4} (3.8x10 ⁴ , 5.2x10 ⁴)
Cathepsin B ^M	1.7x10 ⁴ > ^N (1.5x10 ⁴ , 1.9x10 ⁴)	1.6x10 ⁴ > ^N (1.4x10 ⁴ , 1.7x10 ⁴)	1.7x10 ⁴ > ^N (1.5x10 ⁴ , 1.9x10 ⁴)	1.6x10 ⁴ > ^N (1.3x10 ⁴ , 1.8x10 ⁴)	9.9x10 ³ < ^{1,2,3,4} (8.5x10 ³ , 1.1x10 ⁴)
Cathepsin L ^{Med}	1.3x10 ³ > ^{2,3} , < ^N (1.1x10 ³ , 1.7x10 ³)	9.5x10 ² < ¹ , < ^N (6.6x10 ² , 1.2x10 ³)	1.1x10 ³ < ¹ , < ^N (7.3x10 ² , 1.4x10 ³)	1.1x10 ³ < ^N (8.2x10 ² , 1.3x10 ³)	6.4x10 ³ > ^{1,2,3,4} (5.0x10 ³ , 8.0x10 ³)
Cystatin C ^{Med}	2.1x10 ⁵ > ^N (1.9x10 ⁵ , 2.4x10 ⁵)	1.9x10 ⁵ > ^N (1.7x10 ⁵ , 2.1x10 ⁵)	2.0x10 ⁵ > ^N (1.7x10 ⁵ , 2.2x10 ⁵)	1.9x10 ⁵ > ^N (1.6x10 ⁵ , 2.1x10 ⁵)	1.2x10 ⁵ < ^{1,2,3,4} (8.4x10 ⁴ , 1.5x10 ⁵)
DKK-1 ^M	2299.1 (2179.8, 2418.4)	2177.0 (2117.5, 2236.4)	2391.9 (2320.5, 2463.4)	2282.3 (2205, 2359.7)	2403.4 (1913.3, 2893.4)
DPP4 ^{GM}	614.4 (557.0, 678.3)	586.2 (541.2, 634.8)	619.2 (578.8, 662.4)	570.9 (504.2, 646.5)	539.3 (498.5, 583.3)
ENA-78 ^{Med}	2.5x10 ³ > ^N (1.9x10 ³ , 4.0x10 ³)	2.1x10 ³ > ^N (1.2x10 ³ , 2.8x10 ³)	2.7x10 ³ > ^N (2.1x10 ³ , 4.0x10 ³)	3.7x10 ³ > ^N (2.4x10 ³ , 5.3x10 ³)	7.4x10 ² < ^{1,2,3,4} (4.8x10 ² , 1.2x10 ³)
Galectin-3 ^M	2.2x10 ⁴ > ³ (1.9x10 ⁴ , 2.6x10 ⁴)	2.1x10 ⁴ < ^N (1.8x10 ⁴ , 2.3x10 ⁴)	1.8x10 ⁴ < ^{N,1,4} (1.6x10 ⁴ , 1.9x10 ⁴)	2.4x10 ⁴ > ³ (2.1x10 ⁴ , 2.8x10 ⁴)	2.8x10 ⁴ > ^{2,3} (2.6x10 ⁴ , 3.0x10 ⁴)
GCSF ^{GM}	8.4x10 ³ > ^N (6.4x10 ³ , 1.5x10 ⁴)	8.6x10 ³ > ^N (6.3x10 ³ , 1.5x10 ⁴)	7.0x10 ³ > ^N (5.4x10 ³ , 1.1x10 ⁴)	1.1x10 ⁴ > ^N (8.3x10 ³ , 1.9x10 ⁴)	1.8x10 ³ < ^{1,2,3,4} (1.8x10 ³ , 1.8x10 ³)
GDF ^{Med}	1.1x10 ³ > ² (8.4x10 ² , 1.6x10 ³)	7.4x10 ² < ¹ (6.7x10 ² , 9.9x10 ²)	1.0x10 ³ (7.3x10 ² , 1.6x10 ³)	8.8x10 ² (7.6x10 ² , 1.1x10 ³)	1.2x10 ³ (1.0x10 ³ , 1.3x10 ³)
IL-3 ^{Med}	2.5 > ^N (2.5, 283.2)	2.5 > ^N (2.5, 400.9)	2.5 > ^N (2.5, 242.4)	167.7 > ^N (2.5, 536.1)	2.5 < ^{1,2,3,4} (2.5, 2.5)
IL-16 ^M	2.0x10 ³ (1.7x10 ³ , 2.3x10 ³)	1.9x10 ³ (1.7x10 ³ , 2.1x10 ³)	1.2x10 ³ (1.1x10 ³ , 1.4x10 ³)	2.1x10 ³ (1.9x10 ³ , 2.3x10 ³)	2.0x10 ³ (6.8x10 ² , 3.4x10 ³)
IL-31 ^{Med}	1.2x10 ¹ (1.2x10 ¹ , 3.1x10 ³)	1.2x10 ¹ (1.2x10 ¹ , 2.5x10 ³)	1.2x10 ¹ (1.2x10 ¹ , 1.2x10 ¹)	1.2x10 ¹ (1.2x10 ¹ , 4.6x10 ¹)	1.2x10 ¹ (1.2x10 ¹ , 2.5x10 ¹)
Leptin ^{Med}	8.0x10 ² < ^N (8.0x10 ² , 2.4x10 ³)	8.0x10 ² < ^N (8.0x10 ² , 1.4x10 ³)	8.0x10 ² < ^N (8.0x10 ² , 1.4x10 ³)	8.0x10 ² < ^N (8.0x10 ² , 2.0x10 ³)	3.6x10 ³ > ^{1,2,3,4} (2.8x10 ³ , 5.4x10 ³)
MCP-2 ^{Med}	50.4 (42.2, 62.7)	41.8 (34.5, 56.9)	45.4 (33.6, 56.6)	53 > ^N (46.1, 65.8)	36.5 < ⁴ (28.7, 44.2)
MCSF ^{GM}	7.6 (7.6, 7.6)	7.6 (7.6, 7.6)	7.6 (7.6, 7.6)	7.6 (7.6, 7.6)	7.6 (7.6, 7.6)
MDC ^{Med}	3352.0 > ^N (2210.0, 9001.0)	2493.3 > ^N (1764.5, 4146.5)	2330.7 > ^N (1784.7, 4040.4)	2975.6 > ^N (2125.7, 4217.4)	737.8 < ^{1,2,3,4} (681.2, 873.9)
MIP-1β ^{GM}	138.2 > ^N (119.8, 159.4)	108.3 > ^N (95.0, 123.4)	127.7 > ^N (112.7, 144.7)	132.6 > ^N (105.4, 166.9)	41.0 < ^{1,2,3,4} (32.8, 51.4)
MIP-3β ^{Med}	1.6x10 ⁰ (1.6x10 ⁰ , 1.2x10 ¹)	1.6x10 ⁰ (1.6x10 ⁰ , 1.1x10 ⁴)	1.6x10 ⁰ (1.6x10 ⁰ , 1.6x10 ⁰)	1.6x10 ⁰ (1.6x10 ⁰ , 1.5x10 ¹)	6.6x10 ¹ (3.9x10 ¹ , 1.1x10 ²)
MMP-3 ^{GM}	3.5x10 ⁴ > ² (3.0x10 ⁴ , 4.2x10 ⁴)	2.4x10 ⁴ < ¹ (2.1x10 ⁴ , 2.8x10 ⁴)	2.6x10 ⁴ (2.2x10 ⁴ , 3.2x10 ⁴)	2.8x10 ⁴ (2.2x10 ⁴ , 3.5x10 ⁴)	2.5x10 ⁴ (2.1x10 ⁴ , 3.0x10 ⁴)
MMP-9 ^{Med}	1.6x10 ⁶ (1.6x10 ⁶ , 1.6x10 ⁶)	1.6x10 ⁶ (1.6x10 ⁶ , 1.6x10 ⁶)	1.6x10 ⁶ (1.6x10 ⁶ , 1.6x10 ⁶)	1.6x10 ⁶ (1.6x10 ⁶ , 1.6x10 ⁶)	1.6x10 ⁶ (1.6x10 ⁶ , 1.6x10 ⁶)
MPIF ^{Med}	480.4 > ^N (287.2, 643.2)	341.6 > ^N (198.3, 536.6)	398.4 > ^N (254.9, 491.8)	362.8 > ^N (173.4, 508)	94.4 < ^{1,2,3,4} (40.9, 170.8)
Osteopontin ^{GM}	3.5x10 ⁴ < ^N (3.1x10 ⁴ , 4.1x10 ⁴)	3.2x10 ⁴ < ^N (2.7x10 ⁴ , 3.7x10 ⁴)	3.6x10 ⁴ < ^N (3.0x10 ⁴ , 4.3x10 ⁴)	3.6x10 ⁴ < ^N (3.1x10 ⁴ , 4.3x10 ⁴)	1.2x10 ⁴ > ^{1,2,3,4} (9.2x10 ³ , 1.5x10 ⁴)
PF4 ^{Med}	2.0x10 ⁶ < ^N (2.0x10 ⁶ , 2.0x10 ⁶)	2.0x10 ⁶ < ^N (2.0x10 ⁶ , 2.0x10 ⁶)	2.0x10 ⁶ < ^N (2.0x10 ⁶ , 2.0x10 ⁶)	2.0x10 ⁶ < ^N (2.0x10 ⁶ , 2.0x10 ⁶)	4.7x10 ⁶ > ^{1,2,3,4} (3.2x10 ⁶ , 6.6x10 ⁶)

RANTES ^{Med}	1.6×10^5 ^{<N, >2,3} (1.3×10^5 , 2.5×10^5)	8.4×10^4 ^{<N,1,3,4} (4.8×10^4 , 1.4×10^5)	1.4×10^5 ^{<N,1, >2} (6.3×10^4 , 2.2×10^5)	1.6×10^5 ^{<N, >2} (1.1×10^5 , 2.1×10^5)	6.4×10^5 ^{>1,2,3,4} (4.0×10^5 , 9.1×10^5)
SAA1 ^{Med}	1.0×10^8 (1.0×10^8 , 1.0×10^8)	1.0×10^8 (1.0×10^8 , 1.0×10^8)	1.0×10^8 (1.0×10^8 , 1.0×10^8)	1.0×10^8 (1.0×10^8 , 1.0×10^8)	1.0×10^8 (5.2×10^7 , 1.0×10^8)
sCD163 ^{Med}	4.3×10^4 ^{<N} (4.3×10^4 , 4.3×10^4)	4.3×10^4 ^{<N} (4.3×10^4 , 4.3×10^4)	4.3×10^4 ^{<N} (4.3×10^4 , 4.3×10^4)	4.3×10^4 ^{<N} (4.3×10^4 , 4.3×10^4)	1.4×10^5 ^{>1,2,3,4} (1.2×10^5 , 1.7×10^5)
Serum Ig targeting alpha toxin ^{GM}	93.9 ^{>N} (70.6, 125.0)	93.8 ^{>N} (65.5, 134.5)	65.7 ^{>N} (51.7, 83.3)	117.4 ^{>N} (71.6, 192.8)	11.2 ^{<1,2,3,4} (7.0, 18.0)
SRPSOX ^{Med}	8.9×10^2 (6.3×10^2 , 6.0×10^3)	8.6×10^2 (7.3×10^2 , 2.6×10^3)	8.0×10^2 (6.1×10^2 , 1.4×10^3)	8.3×10^2 (6.5×10^2 , 3.5×10^3)	NA
sSCFR ^{Med}	6.5×10^4 ^{>N} (5.8×10^4 , 8.0×10^4)	6.4×10^4 ^{>N} (4.9×10^4 , 7.6×10^4)	6.2×10^4 ^{>N} (4.9×10^4 , 8.4×10^4)	6.4×10^4 ^{>N} (5.4×10^4 , 7.5×10^4)	4.2×10^4 ^{<1,2,3,4} (3.8×10^4 , 4.4×10^4)
TACI ^{Med}	8.0×10^2 ^{<N} (8.0×10^2 , 8.0×10^2)	8.0×10^2 ^{<N} (8.0×10^2 , 8.0×10^2)	8.0×10^2 ^{<N} (8.0×10^2 , 8.0×10^2)	8.0×10^2 ^{<N} (8.0×10^2 , 8.0×10^2)	8.9×10^4 ^{>1,2,3,4} (6.6×10^4 , 1.1×10^5)
Thrombopoietin ^{Med}	1.2×10^6 ^{<N, >2,3,4} (9.8×10^5 , 1.8×10^6)	7.6×10^5 ^{<N,1,3,4} (5.6×10^5 , 9.0×10^5)	1.0×10^6 ^{<N,1, >2} (8.3×10^5 , 1.2×10^6)	9.2×10^5 ^{<N,1, >2} (7.1×10^5 , 1.2×10^6)	8.6×10^6 ^{>1,2,3,4} (8×10^6 , 9.1×10^6)
Total IgE ^{Med}	3.4×10^3 ^{>N} (1.1×10^3 , 1.0×10^4)	1.8×10^3 ^{>N} (3.1×10^2 , 5.1×10^3)	1.6×10^3 ^{>N} (5.1×10^2 , 5.9×10^3)	1.8×10^3 ^{>N} (2.3×10^2 , 6.3×10^3)	3.7×10^4 ^{<1,2,3,4} (1.5×10^4 , 1.8×10^4)
TWEAK ^{GM}	1.1×10^4 ^{<N, >2} (9.8×10^3 , 1.2×10^4)	8.5×10^3 ^{<N,1,3,4} (8.0×10^3 , 9.1×10^3)	1.0×10^4 ^{<N, >2} (9.5×10^3 , 1.1×10^4)	1.1×10^4 ^{<N, >2} (9.3×10^3 , 1.3×10^4)	1.6×10^4 ^{>1,2,3,4} (1.4×10^4 , 1.9×10^4)
VCAM-1 ^{Med}	2.4×10^6 ^{<N, >2,3} (2.1×10^6 , 3.1×10^6)	1.9×10^6 ^{<N,1} (1.6×10^6 , 2.2×10^6)	2.0×10^6 ^{<N,1} (1.6×10^6 , 2.5×10^6)	2.3×10^6 ^{<N} (2.0×10^6 , 2.6×10^6)	4.3×10^6 ^{>1,2,3,4} (3.7×10^5 , 5.3×10^6)

Healthy controls
Lower than healthy controls
Higher than healthy controls or one other cluster

Variable types are shown in superscript next to variable name; M (mean), Med (median), GM (geometric mean). Numbers shown in brackets after measure of central tendency are 95% confidence intervals (for mean and geomean) or interquartile

Supplemental table E4. Summary of serum mediators that are differentially regulated in atopic dermatitis versus healthy controls but do not associate with disease severity.

Variables where HC < AD	Healthy controls (n=30)	Moderate AD (n=95)	Severe AD (n=98)
Serum Ig targeting alpha toxin^{GM}	11.2 ^{<Mod,Sev} (7, 18)	75.7 ^{>HC} (62, 92)	99.4 ^{>HC} (77.5, 127.5)
Apelin^{Med}	4.7x10 ^{4<Mod,Sev} (3.8x10 ⁴ , 5.2x10 ⁴)	6.3x10 ^{4>HC} (5.8x10 ⁴ , 6.7x10 ⁴)	6.4x10 ^{4>HC} (5.8x10 ⁴ , 6.6x10 ⁴)
C5a^{GM}	5.2x10 ^{4<Mod,Sev} (4.3x10 ⁴ , 6.3x10 ⁴)	1.3x10 ^{5>HC} (1.1x10 ⁵ , 1.5x10 ⁵)	1.1x10 ^{5>HC} (9.4x10 ⁴ , 1.3x10 ⁵)
Cathepsin B^M	9.9x10 ^{3<Mod,Sev} (8.5x10 ³ , 1.1x10 ⁴)	1.6x10 ^{4>HC} (1.5x10 ⁴ , 1.8x10 ⁴)	1.7x10 ^{4>HC} (1.5x10 ⁴ , 1.8x10 ⁴)
Cystatin C^{Med}	1.2x10 ^{5<Mod,Sev} (8.4x10 ⁴ , 1.5x10 ⁵)	1.9x10 ^{5>HC} (1.7x10 ⁵ , 2.2x10 ⁵)	2.0x10 ^{5>HC} (1.7x10 ⁵ , 2.2x10 ⁵)
Elastase^{Med}	1.2x10 ^{4<Mod,Sev} (7.1x10 ³ , 1.6x10 ⁴)	2.3x10 ^{4>HC} (1.1x10 ⁴ , 8.6x10 ⁴)	3.2x10 ^{4>HC} (1.5x10 ⁴ , 8.6x10 ⁴)
ENA-78^{Med}	7.4x10 ^{2<Mod,Sev} (4.8x10 ² , 1.2x10 ³)	2.4x10 ^{3>HC} (1.6x10 ³ , 3.8x10 ³)	2.7x10 ^{3>HC} (1.9x10 ³ , 4.2x10 ³)
Endoglin^{GM}	1.2x10 ^{3<Mod,Sev} (1.1x10 ³ , 1.3x10 ³)	2.7x10 ^{3>HC} (2.5x10 ³ , 3.0x10 ³)	2.6x10 ^{3>HC} (2.4x10 ³ , 2.9x10 ³)
Eotaxin-1^{GM}	73.6 ^{<Mod,Sev} (61, 88)	525.3 ^{>HC} (439, 629)	610.5 ^{>HC} (509, 733)
Fas^{GM}	840.9 ^{<Mod,Sev} (721, 978)	1889.4 ^{>HC} (1756, 2033)	1987.3 ^{>HC} (1846, 2140)
GCP-2^{GM}	64.2 ^{<Mod,Sev} (34, 120)	148.7 ^{>HC} (121, 182)	147.6 ^{>HC} (119, 183)
GCSF^{Med}	1.8x10 ^{1<Mod,Sev} (1.8x10 ¹ , 1.8x10 ¹)	8.7x10 ^{3>HC} (6.2x10 ³ , 1.7x10 ⁴)	8.6x10 ^{3>HC} (6.2x10 ³ , 1.5x10 ⁴)
HGF^{GM}	629.1 ^{<Mod,Sev} (522, 759)	935.5 ^{>HC} (868, 1009)	1036.4 ^{>HC} (950, 1130)
ICAM-1^{Med}	2.9x10 ^{5<Mod,Sev} (2.2x10 ⁵ , 3.4x10 ⁵)	4.7x10 ^{5>HC} (3.7x10 ⁵ , 6.0x10 ⁵)	5.0x10 ^{5>HC} (4.0x10 ⁵ , 6.7x10 ⁵)
IFN-α^{Med}	0.7 ^{<Mod,Sev} (1, 3)	82.5 ^{>HC} (53, 99)	81.9 ^{>HC} (48, 98)
IL-1α^{Med}	4.7 ^{<Mod,Sev} (3, 8)	23.8 ^{>HC} (9, 39)	26.0 ^{>HC} (14, 53)
IL-1β^{GM}	1.1 ^{<Mod,Sev} (1, 2)	12.5 ^{>HC} (11, 15)	14.4 ^{>HC} (12, 17)
IL-1R1^{Med}	5.6 ^{<Mod,Sev} (3, 8)	76.2 ^{>HC} (39, 114)	79.1 ^{>HC} (52, 118)
IL-1R2^{Med}	1473.4 ^{<Sev} (842, 2060)	1615.2 (1218, 2126)	2002.6 ^{>HC} (1509, 2624)
IL-3^{Med}	2.5 ^{<Mod,Sev} (3, 3)	2.5 ^{>HC} (3, 420)	2.5 ^{>HC} (3, 339)
IL-4^{Med}	0.3 ^{<Mod,Sev} (0, 0)	3.6 ^{>HC} (2, 7)	3.7 ^{>HC} (2, 8)
IL-5^{Med}	5.0 ^{<Mod,Sev} (3, 10)	196.6 ^{>HC} (164, 236)	220.1 ^{>HC} (191, 254)
IL-6^{Med}	1.4 ^{<Mod,Sev} (1, 10)	18.3 ^{>HC} (10, 47)	18.4 ^{>HC} (8, 36)
IL-7^M	5.2 ^{<Mod,Sev} (4, 7)	35.4 ^{>HC} (32, 38)	38 ^{>HC} (34, 41)
IL-9^{GM}	12.2 ^{<Mod,Sev} (5, 31)	76.4 ^{>HC} (60, 98)	93 ^{>HC} (75, 116)
IL-10^{Med}	1.7 ^{<Mod} (2, 2)	1.7 ^{>HC} (2, 8)	1.7 (2, 7)
IL-11^{Med}	4.0 ^{<Mod,Sev} (4, 4)	19.7 ^{>HC} (4, 89)	30.6 ^{>HC} (4, 89)
IL-12^{Med}	3.3 ^{<Mod,Sev} (3, 12)	58.3 ^{>HC} (29, 109)	58.5 ^{>HC} (38, 104)
IL-13^{GM}	23.3 ^{<Mod,Sev} (10, 53)	62.6 ^{>HC} (54, 73)	67.7 ^{>HC} (58, 79)
IL-15^{Med}	3.7 ^{<Mod,Sev} (2, 6)	93.4 ^{>HC} (57, 182)	92.6 ^{>HC} (51, 181)
IL-20^{Med}	42.4 ^{<Mod,Sev} (42, 42)	42.4 ^{>HC} (42, 42)	42.4 ^{>HC} (42, 42)

IL-21 ^{GM}	3.5x10 ^{2<Mod,Sev} (1.5x10 ² , 1.2x10 ³)	5.5x10 ^{3>HC} (4.4x10 ³ , 6.8x10 ³)	5.6x10 ^{3>HC} (4.4x10 ³ , 7.2x10 ³)
IL-23 ^{Med}	1.5x10 ^{1<Mod,Sev} (1.5x10 ¹ , 6.9x10 ¹)	5.9x10 ^{2>HC} (9.6x10 ¹ , 1.4x10 ³)	2.7x10 ^{2>HC} (1.0x10 ² , 1.5x10 ³)
IL-25 ^{Med}	8.2x10 ^{1<Mod,Sev} (8.2x10 ¹ , 5.8x10 ²)	7.4x10 ^{3>HC} (4.3x10 ³ , 1.5x10 ⁴)	8.3x10 ^{3>HC} (4.7x10 ³ , 1.5x10 ⁴)
IL-33 ^{GM}	9.2 ^{<Mod,Sev} (6, 14)	42.4 ^{>HC} (34, 51)	50.9 ^{>HC} (42, 62)
IL-37 ^{Med}	44.2 ^{<Mod,Sev} (44, 44)	865.9 ^{>HC} (68, 1572)	801.1 ^{>HC} (305, 1645)
ITAC ^{GM}	38.5 ^{<Mod,Sev} (30, 49)	104.1 ^{>HC} (91, 119)	120.4 ^{>HC} (102, 142)
LAP-TGFβ ^M	1.5x10 ^{5<Mod,Sev} (1.4x10 ⁵ , 1.7x10 ⁵)	3.2x10 ^{5>HC} (3.1x10 ⁵ , 3.4x10 ⁵)	3.2x10 ^{5>HC} (3.1x10 ⁵ , 3.4x10 ⁵)
LIF ^{Med}	4.8 ^{<Mod,Sev} (5, 5)	4.8 ^{>HC} (5, 5)	4.8 ^{>HC} (5, 5)
MCP-1 ^{GM}	79.1 ^{<Mod,Sev} (68, 92)	191.1 ^{>HC} (179, 204)	201.7 ^{>HC} (187, 218)

Variables where HC < AD	Healthy controls (n=30)	Moderate AD (n=95)	Severe AD (n=98)
MCP-2 ^{Med}	36.5 ^{<Mod,Sev} (29, 44)	46.6 ^{>HC} (36, 57)	48.4 ^{>HC} (38, 61)
MIG ^{GM}	97.2 ^{<Sev} (90, 105)	119.7 (101, 142)	142.6 ^{>HC} (124, 165)
MIP-1β ^{Med}	41.0 ^{<Mod,Sev} (33, 51)	122.7 ^{>HC} (110, 137)	124.8 ^{>HC} (113, 138)
MPIF ^{Med}	94.4 ^{<Mod,Sev} (41, 171)	371.9 ^{>HC} (199, 530)	404.3 ^{>HC} (246, 562)
Osteopontin ^{Med}	7.6 ^{<Mod,Sev} (8, 8)	2109.0 ^{>HC} (1656, 2683)	2278.0 ^{>HC} (1888, 2850)
Oncostatin M ^{Med}	3.3 ^{<Mod,Sev} (3, 3)	7 ^{>HC} (3, 28)	15 ^{>HC} (3, 43)
%Neutralisation of α-toxin-induced lysis ^{Med}	10.8 ^{<Mod,Sev} (1, 21)	26.4 ^{>HC} (15, 56)	35.5 ^{>HC} (23, 80)
S100A8 ^{Med}	1.2x10 ^{4<Mod,Sev} (8.4x10 ³ , 1.6x10 ⁴)	1.5x10 ^{5>HC} (1.3x10 ⁵ , 1.7x10 ⁵)	1.5x10 ^{5>HC} (1.2x10 ⁵ , 1.7x10 ⁵)
SAA1 ^{Med}	1.0x10 ^{8<Mod,Sev} (5.2x10 ⁷ , 1.0x10 ⁸)	1.0x10 ^{8>HC} (1.0x10 ⁸ , 1.0x10 ⁸)	1.0x10 ^{8>HC} (1.0x10 ⁸ , 1.0x10 ⁸)
SLP1 ^{Med}	6.4x10 ^{3<Mod,Sev} (5.9x10 ³ , 7.2x10 ³)	1.9x10 ^{4>HC} (8.7x10 ³ , 1.9x10 ⁴)	1.9x10 ^{4>HC} (9.1x10 ³ , 1.9x10 ⁴)
sSCFR ^{Med}	4.2x10 ^{4<Mod,Sev} (3.8x10 ⁴ , 4.4x10 ⁴)	6.3x10 ^{4>HC} (4.9x10 ⁴ , 7.7x10 ⁴)	6.3x10 ^{4>HC} (5.3x10 ⁴ , 7.8x10 ⁴)
TIE-2 ^{GM}	2.6x10 ^{3<Mod,Sev} (2.3x10 ³ , 2.8x10 ³)	8.6x10 ^{3>HC} (8.1x10 ³ , 9.1x10 ³)	8.6x10 ^{3>HC} (8.1x10 ³ , 9.0x10 ³)
TNFR1 ^M	5.9x10 ^{2<Mod,Sev} (2.8x10 ² , 9.1x10 ²)	5.6x10 ^{3>HC} (5.2x10 ³ , 5.9x10 ³)	5.7x10 ^{3>HC} (5.3x10 ³ , 6.1x10 ³)
TREM-1 ^{GM}	1.4x10 ^{1<Mod,Sev} (9.3x10 ⁰ , 2.1x10 ¹)	5.8x10 ^{1>HC} (4.5x10 ¹ , 7.6x10 ¹)	6.6x10 ^{1>HC} (5.4x10 ¹ , 8.2x10 ¹)
TSLP ^{GM}	3.3 ^{<Mod,Sev} (2, 7)	15.1 ^{>HC} (12, 18)	17.0 ^{>HC} (14, 21)
VEGF ^{Med}	346.4 ^{<Mod,Sev} (170, 603)	685.1 ^{>HC} (372, 1085)	856.5 ^{>HC} (500, 1324)

Variables where HC > AD	Healthy controls (n=30)	Moderate AD (n=95)	Severe AD (n=98)
ACE ^{GM}	4.0x10 ^{5>Mod,Sev} (3.6 x10 ⁵ , 4.3 x10 ⁵)	2.8x10 ^{5<HC} (2.6x10 ⁵ , 3.1x10 ⁵)	3.0x10 ^{5<HC} (2.7x10 ⁵ , 3.3x10 ⁵)
Ang2 ^{Med}	1.9x10 ^{4>Mod,Sev} (1.8x10 ⁴ , 2.8x10 ⁴)	1.3x10 ^{4<HC} (1.1x10 ⁴ , 1.5x10 ⁴)	1.4x10 ^{4<HC} (1.2x10 ⁴ , 1.5x10 ⁴)
BDNF ^M	5.5x10 ^{5>Mod,Sev} (4.7x10 ⁵ , 6.2x10 ⁵)	2.2x10 ^{5<HC} (2.1x10 ⁵ , 2.4x10 ⁵)	2.3x10 ^{5<HC} (2.2x10 ⁵ , 2.4x10 ⁵)
Cathepsin S ^M	1.7x10 ^{4>Mod,Sev} (1.6x10 ⁴ , 1.9x10 ⁴)	1.3x10 ^{4<HC} (1.1x10 ⁴ , 1.6x10 ⁴)	1.4x10 ^{4<HC} (1.2x10 ⁴ , 1.7x10 ⁴)
Chemerin 4 ^{Med}	1.9x10 ^{4>Mod,Sev} (1.7x10 ⁴ , 2.5x10 ⁴)	6.8x10 ^{3<HC} (6.8x10 ³ , 2.1x10 ⁴)	1.4x10 ^{4<HC} (6.8x10 ³ , 2.2x10 ⁴)

EGF ^{GM}	24.3 ^{>Mod,Sev} (12, 49)	13.8 ^{<HC} (12, 16)	15.5 ^{<HC} (14, 18)
Galectin-3 ^{GM}	2.8x10 ^{4>Mod,Sev} (2.6x10 ⁴ , 3.0x10 ⁴)	2.0x10 ^{4<HC} (1.8x10 ⁴ , 2.1x10 ⁴)	2.1x10 ^{4<HC} (2.0x10 ⁴ , 2.3x10 ⁴)
Galectin-9 ^{Med}	3.2x10 ^{3>Mod,Sev} (2.3x10 ³ , 4.4x10 ³)	1.0x10 ^{1<HC} (1.0x10 ¹ , 8.1x10 ³)	1.0x10 ^{1<HC} (1.0x10 ¹ , 1.0x10 ¹)
IFN- β ^{Med}	3.2x10 ^{2>Mod,Sev} (1.5x10 ² , 9.1x10 ²)	1.4x10 ^{2<HC} (9.7x10 ⁰ , 3.4x10 ³)	1.4x10 ^{2<HC} (9.7x10 ⁰ , 2.8x10 ²)
IL-27 ^{Med}	1.4x10 ^{3>Mod,Sev} (4.7x10 ² , 2.7x10 ³)	1.6x10 ^{0<HC} (1.6x10 ⁰ , 1.9x10 ⁴)	1.6x10 ^{0<HC} (1.6x10 ⁰ , 1.6x10 ⁰)
Leptin-3 ^{Med}	3.6x10 ^{3>Mod,Sev} (2.8x10 ³ , 5.4x10 ³)	8.0x10 ^{2<HC} (8.0x10 ² , 1.9x10 ³)	8.0x10 ^{2<HC} (8.0x10 ² , 2.0x10 ³)
MIF ^{GM}	7.0x10 ^{3>Mod,Sev} (5.2x10 ³ , 9.3x10 ³)	2.8x10 ^{3<HC} (2.5x10 ³ , 3.1x10 ³)	3.2x10 ^{3<HC} (2.8x10 ³ , 3.6x10 ³)
PAI-1 ^{Med}	9.5x10 ^{5>Mod,Sev} (6.6x10 ⁵ , 1.3x10 ⁶)	6.9x10 ^{5<HC} (2.9x10 ⁵ , 9.6x10 ⁵)	7.5x10 ^{5<HC} (1.7x10 ⁵ , 1.0x10 ⁶)
P-selectin ^{Med}	5.5x10 ^{5>Mod,Sev} (3.5x10 ⁵ , 1.4x10 ⁶)	3.4x10 ^{5<HC} (2.0x10 ⁵ , 5.5x10 ⁵)	3.7x10 ^{5<HC} (2.2x10 ⁵ , 6.6x10 ⁵)
RBP-4 ^{Med}	2.8x10 ^{7>Mod,Sev} (2.7x10 ⁷ , 2.9x10 ⁷)	2.6x10 ^{7<HC} (2.4x10 ⁷ , 2.9x10 ⁷)	2.6x10 ^{7<HC} (2.4x10 ⁷ , 2.8x10 ⁷)
Resistin ^{Med}	9.4x10 ^{3>Mod,Sev} (8.9x10 ³ , 1.0x10 ⁴)	6.8x10 ^{3<HC} (5.7x10 ³ , 9.3x10 ³)	7.5x10 ^{3<HC} (6.0x10 ³ , 9.5x10 ³)
sCD14 ^{Med}	2.3x10 ^{6>Mod,Sev} (2.1x10 ⁶ , 2.5x10 ⁶)	1.3x10 ^{6<HC} (1.1x10 ⁶ , 1.8x10 ⁶)	1.5x10 ^{6<HC} (1.2x10 ⁶ , 2.0x10 ⁶)
sCD163 ^{Med}	1.4x10 ^{5>Mod,Sev} (1.2x10 ⁵ , 1.7x10 ⁵)	4.3x10 ^{4<HC} (4.3x10 ⁴ , 4.3x10 ⁴)	4.3x10 ^{4<HC} (4.3x10 ⁴ , 4.3x10 ⁴)
SCF ^{Med}	50.8 ^{>Mod,Sev} (38, 59)	31.5 ^{<HC} (20, 45)	34.5 ^{<HC} (21, 52)
sIL-2R α ^{Med}	23.5 ^{>Mod,Sev} (24, 336)	23.5 ^{<HC} (24, 24)	23.5 ^{<HC} (24, 24)
TACI ^{Med}	8.9x10 ^{4>Mod,Sev} (6.6x10 ⁴ , 1.1x10 ⁵)	8.0x10 ^{2<HC} (8.0x10 ² , 8.0x10 ²)	8.0x10 ^{2<HC} (8.0x10 ² , 8.0x10 ²)
TECK ^{Med}	915.9 ^{>Mod,Sev} (562, 1324)	405.0 ^{<HC} (294, 601)	481.3 ^{<HC} (306, 755)
TPO ^{Med}	8.6x10 ^{6>Mod,Sev} (8.0x10 ⁶ , 9.1x10 ⁶)	9.2x10 ^{5<HC} (7.2x10 ⁵ , 1.2x10 ⁶)	9.7x10 ^{5<HC} (7.6x10 ⁵ , 1.3x10 ⁶)

Variables where HC > AD	Healthy controls (n=30)	Moderate AD (n=95)	Severe AD (n=98)
Trappin-2 ^{Med}	2226.0 ^{>Mod,Sev} (1924, 2576)	123.1 ^{<HC} (27, 243)	99.8 ^{<HC} (29, 240)
TWEAK ^{GM}	1.6x10 ^{4>Mod,Sev} (1.4x10 ⁴ , 1.9x10 ⁴)	9.9x10 ^{3<HC} (9.3x10 ³ , 1.1x10 ⁴)	1.0x10 ^{4<HC} (9.3x10 ³ , 1.1x10 ⁴)
VCAM-1 ^{Med}	4.3x10 ^{6>Mod,Sev} (3.7x10 ⁶ , 5.3x10 ⁶)	2.0x10 ^{6<HC} (1.6x10 ⁶ , 2.5x10 ⁶)	2.2x10 ^{6<HC} (1.8x10 ⁶ , 2.6x10 ⁶)

Variable types are shown in superscript next to variable name; M (mean) for normally distributed data, Med (median) for log-non normally distributed data, GM (geometric mean) for log-normally distributed data. Numbers shown in brackets after measure of central tendency are 95% confidence intervals (for mean and geomean) or interquartile range (median). Superscript numbers after measure of central tendency are groups that are significantly different.

Supplemental table E5. Summary of serum mediators that are differentially regulated in atopic dermatitis versus healthy controls and associate with disease severity.

Variables where HC < AD	Healthy controls (n=30)	Moderate AD (n=95)	Severe AD (n=98)
BRAK1^{Med}	310.3 ^{<Mod,Sev} (196, 487)	522.6 ^{>HC, <Sev} (284, 690)	721.2 ^{>HC, Mod} (421, 948)
CTACK^{Med}	2.5 ^{<Mod,Sev} (3, 4)	297.6 ^{>HC, <Sev} (168, 521)	480.1 ^{>HC, Mod} (283, 863)
Galectin-1^M	1.9x10 ^{4<Mod,Sev} (1.6x10 ⁴ , 2.1x10 ⁴)	2.5x10 ^{4>HC, <Sev} (2.4x10 ⁴ , 2.7x10 ⁴)	2.8x10 ^{4>HC, Mod} (2.7x10 ⁴ , 3.0x10 ⁴)
I-309^{GM}	2.1 ^{<Mod,Sev} (2, 2)	29.4 ^{>HC, <Sev} (24, 37)	51.2 ^{>HC, Mod} (42, 62)
IL-18^{GM}	82.5 ^{<Mod,Sev} (66, 102)	220.9 ^{>HC, <Sev} (191, 255)	314.7 ^{>HC, Mod} (280, 354)
IL-18BP^{aMed}	1416.3 ^{<Mod,Sev} (1121, 1740)	2225.8 ^{>HC, <Sev} (1613, 2819)	2597.0 ^{>HC, Mod} (2000, 3135)
IL-22^{Med}	1.8 ^{<Mod,Sev} (2, 2)	110.2 ^{>HC, <Sev} (46, 300)	367 ^{>HC, Mod} (140, 602)
IP-10^{GM}	280.6 ^{<Mod,Sev} (240, 328)	426.4 ^{>HC, <Sev} (395, 460)	500 ^{>HC, Mod} (458, 546)
MDC^{Med}	737.8 ^{<Mod,Sev} (681, 874)	2218.2 ^{>HC, <Sev} (1529, 3169)	3730.3 ^{>HC, Mod} (2255, 9001)
MIP-1^{aMed}	16.5 ^{<Mod,Sev} (17, 17)	90.2 ^{>HC, <Sev} (69, 147)	129.5 ^{>HC, Mod} (85, 162)
MIP-3^{aMed}	0.6 ^{<Mod,Sev} (1, 1)	7.4 ^{>HC, <Sev} (4, 11)	9.5 ^{>HC, Mod} (6, 14)
Osteopontin^{GM}	1.2x10 ^{4<Mod,Sev} (9.2x10 ³ , 1.5x10 ⁴)	3.0x10 ^{4>HC, <Sev} (2.7x10 ⁴ , 3.4x10 ⁴)	3.9x10 ^{4>HC, Mod} (3.5x10 ⁴ , 4.4x10 ⁴)
PARC^{Med}	4.7x10 ^{5<Mod,Sev} (2.8x10 ⁵ , 7.1x10 ⁵)	7.7x10 ^{5>HC, <Sev} (3.3x10 ⁵ , 3.8x10 ⁶)	3.1x10 ^{6>HC, Mod} (5.8x10 ⁵ , 8.7x10 ⁶)
Periostin^{GM}	6.7 ^{<Mod,Sev} (3, 13)	12.0 ^{>HC, <Sev} (11, 13)	17.8 ^{>HC, Mod} (16, 21)
TARC^{Med}	96.5 ^{<Mod,Sev} (68, 137)	1504.5 ^{>HC, <Sev} (654, 3200)	3950.0 ^{>HC, Mod} (2104, 8944)
TNFR2^M	1476.4 ^{<Mod,Sev} (1352, 1601)	1968.9 ^{>HC, <Sev} (1836, 2102)	2167.0 ^{>HC, Mod} (2053, 2281)
Total IgE^{Med}	3.7x10 ^{1<Mod,Sev} (1.5x10 ¹ , 8.0x10 ¹)	1.0x10 ^{3>HC, <Sev} (2.5x10 ² , 3.2x10 ³)	4.2x10 ^{3>HC, Mod} (1.1x10 ³ , 9.4x10 ³)

Variables where HC > AD	Healthy controls (n=30)	Moderate AD (n=95)	Severe AD (n=98)
Cathepsin L^{Med}	6.4x10 ^{3>Mod,Sev} (5.0x10 ³ , 8.0x10 ³)	1.1x10 ^{3>HC, <Sev} (6.9x10 ² , 1.4x10 ³)	1.1x10 ^{3>HC, >Mod} (8.5x10 ² , 1.5x10 ³)
E-selectin^{Med}	6.4x10 ^{4>Mod,Sev} (4.3x10 ⁴ , 8.5x10 ⁴)	1.9x10 ^{4>HC, <Sev} (1.4x10 ⁴ , 2.5x10 ⁴)	2.7x10 ^{4>HC, >Mod} (1.9x10 ⁴ , 3.8x10 ⁴)
MCP-4^{Med}	103.8 ^{>Mod} (240, 328)	49.7 ^{>HC, <Sev} (29, 70)	76.9 ^{>Mod} (47, 134)
MMP8^{Med}	3.0x10 ^{5>Mod,Sev} (2.7x10 ⁵ , 3.2x10 ⁵)	1.1x10 ^{5>HC, <Sev} (1.0x10 ⁵ , 1.2x10 ⁵)	1.3x10 ^{5>HC, >Mod} (1.2x10 ⁵ , 1.5x10 ⁵)
RANTES^{Med}	6.4x10 ^{5>Mod,Sev} (4.0x10 ⁵ , 9.1x10 ⁵)	1.2x10 ^{5>HC, <Sev} (6.2x10 ⁴ , 1.8x10 ⁵)	1.5x10 ^{5>HC, >Mod} (7.7x10 ⁴ , 2.2x10 ⁵)

Variable types are shown in superscript next to variable name; M (mean) for normally distributed data, Med (median) for log-non normally distributed data, GM (geometric mean) for log-normally distributed data. Numbers shown in brackets after measure of central tendency are 95% confidence intervals (for mean and geomean) or interquartile range (median). Superscript numbers after measure of central tendency are groups that are significantly different.

Supplemental table E6. Summary of serum mediators that are not differentially regulated in atopic dermatitis versus healthy controls but associate with disease severity.

Variable	Healthy controls (n=30)	Moderate AD (n=95)	Severe AD (n=98)
GDF^{Med}	1.2x10 ³ (1.0x10 ³ , 1.3x10 ³)	8.4x10 ^{2<Sev} (7.1x10 ² , 1.1x10 ³)	9.6x10 ^{2>Mod} (7.4x10 ² , 1.5x10 ³)
MMP-1^{GM}	3.5x10 ⁴ (2.8x10 ⁴ , 4.3x10 ⁴)	3.7x10 ^{4<Sev} (3.1x10 ⁴ , 4.3x10 ⁴)	4.7x10 ^{4>Mod} (4.1x10 ⁴ , 5.3x10 ⁴)

Variable types are shown in superscript next to variable name; M (mean) for normally distributed data, Med (median) for log-non normally distributed data, GM (geometric mean) for log-normally distributed data. Numbers shown in brackets after measure of central tendency are 95% confidence intervals (for mean and geomean) or interquartile range (median). Superscript numbers after measure of central tendency are groups that are significantly different.

Supplemental table E7. Summary of serum mediators that are not differentially regulated in atopic dermatitis versus healthy controls.

Variable	Healthy controls (n=30)	Moderate AD (n=95)	Severe AD (n=98)
Adiponectin^{Med}	1.3x10 ⁸ (9.0x10 ⁷ , 1.6x10 ⁸)	1.6x10 ⁸ (1.2x10 ⁸ , 4.2x10 ⁸)	1.5x10 ⁸ (9.5x10 ⁷ , 4.2x10 ⁸)
Adipsin^{Med}	1.5x10 ⁴ (1.4x10 ⁴ , 1.7x10 ⁴)	1.7x10 ⁴ (1.5x10 ⁴ , 1.8x10 ⁴)	1.7x10 ⁴ (1.5x10 ⁴ , 1.8x10 ⁴)
Ang1^{Med}	4.4x10 ⁴ (3.6x10 ⁴ , 6.0x10 ⁴)	5.2x10 ⁴ (4.3x10 ⁴ , 6.2x10 ⁴)	5.4x10 ⁴ (4.3x10 ⁴ , 6.9x10 ⁴)
BLC^{GM}	43.8 (33, 58)	42.8 (36, 51)	53.4 (45, 64)
DKK-1^M	2403.4 (1913, 2893)	2260.6 (2195, 2326)	2321 (2268, 2373)
DPP-4^{GM}	539.3 (499, 583)	620.7 (583, 661)	584.6 (553, 618)
Eotaxin-3^{Med}	1.7 (1.7, 1.7)	1.7 (1.7, 1.7)	1.7 (1.7, 1.7)
EPO-R^{Med}	13.7 (13.7, 13.7)	13.7 (13.7, 623.1)	13.7 (13.7, 304.2)
FasL^{Med}	32.8 (31, 38)	45 (28, 68)	45 (26, 63)
FGFβ^{Med}	8 (8, 8)	8 (8, 8)	8 (8, 8)
GMCSF^{Med}	8 (8, 8)	8 (8, 8)	8 (8, 8)
GRO-α^{GM}	NA	106.7 (96, 119)	118.2 (105, 133)
IFN-γ^{Med}	4 (4,4)	4 (4,28)	4 (4,23)
IL1R4^{Med}	0.6 (1, 13)	4.3 (1, 14)	5.2 (1, 18)
IL1Ra^{Med}	4.2 (4, 88)	40.2 (4, 77)	43 (5, 77)
IL-2^{Med}	2.1 (2, 2)	2.1 (2, 2)	2.1 (2, 2)
IL-8^{GM}	20.9 (13, 34)	15.3 (12, 20)	18.0 (14, 24)
IL-16^M	2.0x10 ³ (6.8x10 ² , 3.4x10 ³)	1.6x10 ³ (1.5x10 ³ , 1.8x10 ³)	1.9x10 ³ (1.7x10 ³ , 2.0x10 ³)
IL-17^{Med}	2.8 (3, 3)	2.8 (3, 11)	2.8 (3, 12)
IL-19^{Med}	NA	1155.4 (787, 1815)	1241.7 (838, 1753)
IL-26^{Med}	6.5x10 ² (1.4x10 ² , 1.5x10 ³)	2.1x10 ³ (3.8x10 ¹ , 6.6x10 ³)	2.4x10 ³ (3.8x10 ¹ , 6.4x10 ³)
IL-29^{Med}	1.0x10 ¹ (1.0x10 ¹ , 1.0x10 ¹)	1.0x10 ¹ (1.0x10 ¹ , 1.0x10 ¹)	1.0x10 ¹ (1.0x10 ¹ , 1.0x10 ¹)
IL-31^{Med}	1.2x10 ¹ (1.2x10 ¹ , 2.5x10 ¹)	1.2x10 ¹ (1.2x10 ¹ , 3.1x10 ³)	1.2x10 ¹ (1.2x10 ¹ , 1.2x10 ¹)
KIM-1^{GM}	4.4x10 ¹ (2.6x10 ¹ , 7.4x10 ¹)	6.6x10 ¹ (4.6x10 ¹ , 9.4x10 ¹)	5.7x10 ¹ (4.2x10 ¹ , 7.8x10 ¹)
LAIR-1^{Med}	182.1 (182, 182)	182.1 (182, 182)	182.1 (182, 182)
LIGHT^{Med}	29.8 (4, 73)	4 (1, 128)	4 (4, 206)
MCP-3^{Med}	5.5 (6, 30)	14.4 (6, 53)	17.2 (6, 49)
MCSF^{Med}	7.6 (8, 8)	7.6 (8, 8)	7.6 (8, 8)
MIP-3β^{Med}	6.6x10 ¹ (3.9x10 ¹ , 1.1x10 ²)	1.6x10 ⁰ (1.6x10 ⁰ , 7.4x10 ³)	1.6x10 ⁰ (1.6x10 ⁰ , 1.6x10 ⁰)
MMP-3^{Med}	2.5x10 ⁴ (2.1x10 ⁴ , 3.0x10 ⁴)	2.8x10 ⁴ (2.4x10 ⁴ , 3.2x10 ⁴)	2.8x10 ⁴ (2.5x10 ⁴ , 3.2x10 ⁴)
NAP2^{Med}	1.9x10 ⁷ (1.7x10 ⁷ , 4.0x10 ⁷)	1.7x10 ⁷ (1.3x10 ⁷ , 4.0x10 ⁷)	1.7x10 ⁷ (1.5x10 ⁷ , 4.0x10 ⁷)

NGF^{Med}	2.8 (2, 7)	4.9 (2, 14)	6.4 (2, 13)
PDI^{Med}	2.1x10 ¹ (4.6x10 ⁰ , 2.0x10 ²)	4.6x10 ⁰ (4.6x10 ⁰ , 4.8x10 ³)	3.6x10 ¹ (4.6x10 ⁰ , 1.3x10 ³)
PLGF^{Med}	40.8 (27, 62)	41.5 (19, 59)	35.9 (19, 59)
S100A12^{Med}	NA	5.4x10 ⁶ (3.5x10 ⁶ , 7.8x10 ⁶)	5.3x10 ⁶ (3.6x10 ⁶ , 8.1x10 ⁶)
SDF-1α^{Med}	3.1x10 ² (2.4x10 ² , 5.3x10 ²)	3.7x10 ² (2.6x10 ¹ , 8.7x10 ²)	5.0x10 ² (2.6x10 ¹ , 1.1x10 ³)
SOST^{Med}	11.7 (12, 88)	11.7 (12, 12)	11.7 (12, 12)
SRPSOX^{Med}	NA	8.2x10 ² (6.3x10 ² , 2.9x10 ³)	8.6x10 ² (6.8x10 ² , 2.1x10 ³)
TIMP-1^M	5.0x10 ⁵ (4.8x10 ⁵ , 5.2x10 ⁵)	5.0x10 ⁵ (4.8x10 ⁵ , 5.3x10 ⁵)	5.2x10 ⁵ (4.9x10 ⁵ , 5.4x10 ⁵)
TNF-α^{Med}	1.1 (1, 1)	1.1 (1, 5)	1.1 (1, 5)
TNF-β^{Med}	1.5 (2, 13)	1.5 (2, 9)	1.5 (2, 9)
VEGFR^{GM}	1.5x10 ³ (1.2x10 ³ , 1.9x10 ³)	1.3x10 ³ (1.2x10 ³ , 1.5x10 ³)	1.4x10 ³ (1.3x10 ³ , 1.6x10 ³)
XCL-1^{Med}	8.5 (9, 62)	8.5 (9, 39)	8.5 (9, 50)
YKL40^{Med}	5.0x10 ⁴ (4.5x10 ⁴ , 6.6x10 ⁴)	4.3x10 ⁴ (3.3x10 ⁴ , 6.2x10 ⁴)	4.4x10 ⁴ (3.4x10 ⁴ , 6.3x10 ⁴)

Variable types are shown in superscript next to variable name; M (mean) for normally distributed data, Med (median) for log-non normally distributed data, GM (geometric mean) for log-normally distributed data. Numbers shown in brackets after measure of central tendency are 95% confidence intervals (for mean and geomean) or interquartile range (median). Superscript numbers after measure of central tendency are groups that are significantly different.

Supplemental table E8. ISAC sensitization pattern in healthy controls, moderate and severe AD patients.

Component	Sensitisation	Healthy controls (n=30)		Moderate AD (n=95)		Severe AD (n=97)	
		no. of patients	% of patients	no. of patients	% of patients	no. of patients	% of patients
actd1	Negative	29	96.7	81	85.3	79	81.4
	Positive	1	3.3	14	14.7	18	18.6
actd2	Negative	30	100.0	81	85.3	78	80.4
	Positive	0	0.0	14	14.7	19	19.6
actd5	Negative	30	100.0	93	97.9	95	97.9
	Positive	0	0.0	2	2.1	2	2.1
actd8	Negative	28	93.3	61	64.2	55	56.7
	Positive	2	6.7	34	35.8	42	43.3
alng1	Negative	27	90.0	36	37.9	38	39.2
	Positive	3	10.0	59	62.1	59	60.8
alta1	Negative	30	100.0	64	67.4	64	66.0
	Positive	0	0.0	31	63.6	33	34.0
alta6	Negative	30	100.0	85	89.5	82	84.5
	Positive	0	0.0	10	10.5	15	15.5
amba1	Negative	30	100.0	94	99.0	93	95.9
	Positive	0	0.0	1	1.0	4	4.1
anao2	Negative	30	100.0	88	92.6	86	88.7
	Positive	0	0.0	7	7.4	11	11.3
anis1	Negative	30	100.0	93	97.9	93	95.9
	Positive	0	0.0	2	2.1	4	4.1
anis3	Negative	29	96.7	91	95.8	84	86.6
	Positive	1	3.3	4	4.2	13	13.4
apig1	Negative	29	96.7	59	62.1	54	55.7
	Positive	1	3.3	36	37.9	43	44.3
apim1	Negative	30	100.0	91	95.8	90	92.8
	Positive	0	0.0	4	4.2	7	7.2
apim4	Negative	30	100.0	95	100.0	97	100.0
	Positive	0	0.0	0	0.0	0	0.0
arah1	Negative	30	100.0	86	90.5	86	88.7
	Positive	0	0.0	9	9.5	11	11.3
arah2	Negative	30	100.0	84	88.4	85	87.6
	Positive	0	0.0	11	11.6	12	12.4
arah3	Negative	30	100.0	85	89.5	87	89.7
	Positive	0	0.0	10	10.5	10	10.3
arah6	Negative	30	100.0	83	87.4	85	87.6
	Positive	0	0.0	12	12.6	12	12.4
arah8	Negative	28	93.3	41	43.2	42	43.3
	Positive	2	6.7	54	56.8	55	56.7
arah9	Negative	30	100.0	88	92.6	85	87.6
	Positive	0	0.0	7	7.4	12	12.4
artv1	Negative	30	100.0	89	93.7	84	86.6
	Positive	0	0.0	6	6.3	13	13.4
artv3	Negative	30	100.0	88	92.6	81	83.5
	Positive	0	0.0	7	7.4	16	16.5
aspf1	Negative	30	100.0	91	95.8	90	92.8
	Positive	0	0.0	4	4.2	7	7.2
aspf6	Negative	30	100.0	63	66.3	67	69.1
	Positive	0	0.0	32	33.7	30	30.9
aspf3	Negative	28	93.3	87	91.6	87	89.7
	Positive	2	6.7	8	8.4	10	10.3
bere1	Negative	30	100.0	93	97.9	95	97.9
	Positive	0	0.0	2	2.1	2	2.1
betv1	Negative	25	83.3	32	33.7	37	38.1
	Positive	5	16.7	63	66.3	60	61.9
betv2	Negative	30	100.0	84	88.4	81	83.5
	Positive	0	0.0	11	11.6	16	16.5
betv4	Negative	30	100.0	91	95.8	90	92.8
	Positive	0	0.0	4	4.2	7	7.2
blag1	Negative	30	100.0	91	95.8	91	93.8
	Positive	0	0.0	4	4.2	6	6.2
blag2	Negative	30	100.0	69	72.6	54	55.7
	Positive	0	0.0	26	27.4	43	44.3
blag5	Negative	29	96.7	95	100.0	96	99.0
	Positive	1	3.3	0	0.0	1	1.0
blag7	Negative	29	96.7	86	90.5	78	80.4
	Positive	1	3.3	9	9.5	19	19.6
blot5	Negative	29	96.7	75	79.0	64	66.0
	Positive	1	3.3	20	21.1	33	34.0
bosd4	Negative	30	100.0	86	90.5	93	95.9
	Positive	0	0.0	9	9.5	4	4.1
bosd5	Negative	30	100.0	83	87.4	86	88.7
	Positive	0	0.0	12	12.6	11	11.3
bosd6	Negative	30	100.0	89	93.7	86	88.7
	Positive	0	0.0	6	6.3	11	11.3
bosd8	Negative	30	100.0	79	83.2	79	81.4
	Positive	0	0.0	16	16.8	18	18.6
bosdlacto	Negative	30	100.0	93	97.9	88	90.7

canf1	Positive	0	0.0	2	2.1	9	9.3
	Negative	30	100.0	56	59.0	40	41.2
canf2	Positive	0	0.0	39	41.0	57	58.8
	Negative	30	100.0	71	74.7	60	61.9
canf3	Positive	0	0.0	24	25.3	37	38.1
	Negative	30	100.0	70	73.7	57	58.8
canf5	Positive	0	0.0	25	26.3	40	41.2
	Negative	30	100.0	63	66.3	59	60.8
chea1	Positive	0	0.0	32	33.7	38	39.2
	Negative	30	100.0	82	86.3	84	86.6
clah8	Positive	0	0.0	13	13.7	13	13.4
	Negative	30	100.0	83	87.4	86	88.7
cora1.0101	Positive	0	0.0	12	12.6	11	11.3
	Negative	27	90.0	36	37.9	41	42.3
cora1.0401	Positive	3	10.0	59	62.1	56	57.7
	Negative	26	86.7	35	36.8	35	36.1
cora8	Positive	4	13.3	60	63.2	62	63.9
	Negative	30	100.0	85	89.5	81	83.5
cora9	Positive	0	0.0	10	10.5	16	16.5
	Negative	30	100.0	89	93.7	86	88.7
cryj1	Positive	0	0.0	6	6.3	11	11.3
	Negative	29	96.7	81	85.3	71	73.2
cupa1	Positive	1	3.3	14	14.7	26	26.8
	Negative	29	96.7	80	84.2	68	70.1
cynd1	Positive	1	3.3	15	15.8	29	29.9
	Negative	27	90.0	38	40.0	31	32.0
derf1	Positive	3	10.0	57	60.0	66	68.0
	Negative	28	93.3	39	41.0	27	27.8
derf2	Positive	2	6.7	56	59.0	70	72.2
	Negative	27	90.0	35	36.8	34	35.0
derp1	Positive	3	10.0	60	63.2	63	65.0
	Negative	28	93.3	34	35.8	28	28.9
derp10	Positive	2	6.7	61	64.2	69	71.1
	Negative	29	96.7	50	52.6	36	37.1
derp2	Positive	1	3.3	45	47.4	61	62.9
	Negative	27	90.0	36	37.9	35	36.1
equc1	Positive	3	10.0	59	62.1	62	63.9
	Negative	30	100.0	66	69.5	59	60.8
equc3	Positive	0	0.0	29	30.5	38	39.2
	Negative	30	100.0	90	94.7	78	80.4
fage2	Positive	0	0.0	5	5.3	19	19.6
	Negative	30	100.0	93	97.9	96	99.0
feld1	Positive	0	0.0	2	2.1	1	1.0
	Negative	29	96.7	31	32.6	29	29.9
feld2	Positive	1	3.3	64	67.4	68	70.1
	Negative	30	100.0	87	91.6	76	78.3
feld4	Positive	0	0.0	8	8.4	21	21.6
	Negative	30	100.0	64	67.4	52	53.6
gadcl	Positive	0	0.0	31	32.6	45	46.4
	Negative	30	100.0	93	97.9	88	90.7
gald1	Positive	0	0.0	2	2.1	9	9.3
	Negative	30	100.0	78	82.1	71	73.2
gald2	Positive	0	0.0	17	17.9	26	26.8
	Negative	30	100.0	87	91.6	82	84.5
gald3	Positive	0	0.0	8	8.4	15	15.5
	Negative	30	100.0	42	44.2	33	34.0
gald5	Positive	0	0.0	53	55.8	64	66.0
	Negative	30	100.0	92	96.8	84	86.6
glym4	Positive	0	0.0	3	3.2	13	13.4
	Negative	28	93.3	52	54.7	47	48.5
glym5	Positive	2	6.7	43	45.3	50	51.5
	Negative	30	100.0	88	92.6	93	95.9
glym6	Positive	0	0.0	7	7.4	4	4.1
	Negative	30	100.0	85	89.5	86	88.7
hevb1	Positive	0	0.0	10	10.5	11	11.3
	Negative	30	100.0	92	96.8	91	93.8
hevb3	Positive	0	0.0	3	3.2	6	6.2
	Negative	30	100.0	94	99.0	89	91.8
hevb5	Positive	0	0.0	1	1.0	8	8.2
	Negative	30	100.0	94	99.0	93	95.9
hevb6.01	Positive	0	0.0	1	1.0	4	4.1
	Negative	30	100.0	83	87.4	78	80.4
hevb8	Positive	0	0.0	12	12.6	19	19.6
	Negative	30	100.0	82	86.3	77	79.4
jugr1	Positive	0	0.0	13	13.7	20	20.6
	Negative	30	100.0	89	93.7	86	88.7
jugr2	Positive	0	0.0	6	6.3	11	11.3
	Negative	30	100.0	81	85.3	63	65.0
jugr3	Positive	0	0.0	14	14.7	34	35.0
	Negative	29	96.7	85	89.5	86	88.7
lepd2	Positive	1	3.3	10	10.5	11	11.3
	Negative	29	96.7	67	70.5	61	62.9
mald1	Positive	1	3.3	28	29.5	36	37.1
	Negative	26	86.7	39	41.0	40	41.2
mera1	Positive	4	13.3	56	59.0	57	58.8
	Negative	30	100.0	85	89.5	81	83.5

musm1	Positive	0	0.0	10	10.5	16	16.5
	Negative	30	100.0	70	73.7	65	67.0
muxf3	Positive	0	0.0	25	26.3	32	33.0
	Negative	30	100.0	81	85.3	76	78.3
olee1	Positive	0	0.0	14	14.7	21	21.6
	Negative	29	96.7	76	80.0	78	80.4
olee7	Positive	1	3.3	19	20.0	19	19.6
	Negative	29	96.7	88	92.6	85	87.6
olee9	Positive	1	3.3	7	7.4	12	12.4
	Negative	30	100.0	57	60.0	41	42.3
parj2	Positive	0	0.0	38	40.0	56	57.7
	Negative	30	100.0	66	69.5	59	60.8
penm1	Positive	0	0.0	29	30.5	38	39.2
	Negative	29	96.7	90	94.7	82	84.5
penm2	Positive	1	3.3	5	5.3	15	15.5
	Negative	30	100.0	77	81.0	72	74.2
penm4	Positive	0	0.0	18	18.9	25	25.8
	Negative	30	100.0	92	96.8	92	94.8
phlp1	Positive	0	0.0	3	3.2	5	5.2
	Negative	26	86.7	35	36.8	32	33.0
phlp11	Positive	4	13.3	60	63.2	65	67.0
	Negative	29	96.7	78	82.1	80	82.5
phlp12	Positive	1	3.3	17	17.9	17	17.5
	Negative	29	96.7	85	89.5	80	82.5
phlp2	Positive	1	3.3	10	10.5	17	17.5
	Negative	29	96.7	56	59.0	56	57.7
phlp4	Positive	1	3.3	39	41.0	41	42.3
	Negative	29	96.7	38	40.0	29	29.9
phlp5	Positive	1	3.3	57	60.0	68	70.1
	Negative	28	93.3	53	55.8	45	46.4
phlp6	Positive	2	6.7	42	44.2	52	53.6
	Negative	28	93.3	61	64.2	55	56.7
phlp7	Positive	2	6.7	34	35.8	42	43.3
	Negative	30	100.0	81	85.3	83	85.6
plaa1	Positive	0	0.0	14	14.7	14	14.4
	Negative	30	100.0	93	97.9	91	93.8
plaa2	Positive	0	0.0	2	2.1	6	6.2
	Negative	30	100.0	73	76.8	55	56.7
plaa3	Positive	0	0.0	22	23.2	42	43.3
	Negative	30	100.0	86	90.5	84	86.6
plal1	Positive	0	0.0	9	9.5	13	13.4
	Negative	30	100.0	91	95.8	90	92.8
pold5	Positive	0	0.0	4	4.2	7	7.2
	Negative	29	96.7	90	94.7	85	87.6
phlp6.1	Positive	1	3.3	5	5.3	12	12.4
	Negative	28	93.3	61	64.2	55	56.7
phlp7.1	Positive	2	6.7	34	35.8	42	43.3
	Negative	30	100.0	81	85.3	83	85.6
plaa1.1	Positive	0	0.0	14	14.7	14	14.4
	Negative	30	100.0	93	97.9	91	93.8
plaa2.1	Positive	0	0.0	2	2.1	6	6.2
	Negative	30	100.0	73	76.8	55	56.7
plaa3.1	Positive	0	0.0	22	23.2	42	43.3
	Negative	30	100.0	86	90.5	84	86.6
plal1.1	Positive	0	0.0	9	9.5	13	13.4
	Negative	30	100.0	91	95.8	90	92.8
pold5.1	Positive	0	0.0	4	4.2	7	7.2
	Negative	29	96.7	90	94.7	85	87.6
prup1	Positive	1	3.3	5	5.3	12	12.4
	Negative	28	93.3	40	42.1	42	43.3
prup3	Positive	2	6.7	55	57.9	55	56.7
	Negative	30	100.0	57	60.0	46	47.4
salk1	Positive	0	0.0	38	40.0	51	52.6
	Negative	30	100.0	90	94.7	89	91.8
sesi1	Positive	0	0.0	5	5.3	8	8.2
	Negative	30	100.0	91	95.8	92	94.8
tria14	Positive	0	0.0	4	4.2	5	5.2
	Negative	30	100.0	91	95.8	81	83.5
tria19.0101	Positive	0	0.0	4	4.2	16	16.5
	Negative	30	100.0	95	100.0	92	94.8
triaaati	Positive	0	0.0	0	0.0	5	5.2
	Negative	30	100.0	92	96.8	89	91.8
vesv5	Positive	0	0.0	3	3.2	8	8.2
	Negative	28	93.3	90	94.7	80	82.5
	Positive	2	6.7	5	5.3	17	17.5

Supplemental table E9. ISAC sensitization pattern for each of the four cluster and healthy controls

Component	Sensitisation	Healthy controls (n=30)		Cluster 1 (n=44)		Cluster 2 (n=54)		Cluster 3 (n=62)		Cluster 4 (n=28)	
		No. of HC	% of HC	No. of patients	% of patients	No. of patients	% of patients	No. of patients	% of patients	No. of patients	% of patients
actd1	Negative	29	96.7	37	84.1	47	87.0	49	79.0	23	82.1
	Positive	1	3.3	7	15.9	7	13.0	13	21.0	5	17.9
actd2	Negative	30	100.0	33	75.0	45	83.3	55	88.7	55	78.6
	Positive	0	0.0	11	25.0	9	16.7	7	11.3	6	21.4
actd5	Negative	30	100.0	44	100.0	54	100.0	60	96.8	26	92.9
	Positive	0	0.0	0	0.0	0	0.0	2	3.2	2	7.1
actd8	Negative	28	93.3	23	52.3	33	61.1	41	66.1	15	53.6
	Positive	2	6.7	21	47.7	21	38.9	21	33.9	13	46.4
alng1	Negative	27	90.0	18	40.9	18	33.3	26	41.9	9	32.1
	Positive	3	10.0	26	59.1	36	66.7	36	58.1	19	67.9
alta1	Negative	30	100.0	30	68.2	31	57.4	49	79.0	16	57.1
	Positive	0	0.0	14	31.8	23	42.6	13	21.0	12	42.9
alta6	Negative	30	100.0	34	77.3	52	96.3	56	90.3	21	75.0
	Positive	0	0.0	10	22.7	2	3.7	6	9.7	7	25.0
amba1	Negative	30	100.0	41	93.2	54	100.0	62	100.0	26	92.9
	Positive	0	0.0	3	6.8	0	0.0	0	0.0	2	7.1
anao2	Negative	30	100.0	40	90.9	46	85.2	60	96.8	24	85.7
	Positive	0	0.0	4	9.1	8	14.8	2	3.2	4	14.3
anis1	Negative	30	100.0	41	93.2	54	100.0	61	98.4	26	92.9
	Positive	0	0.0	3	6.8	0	0.0	1	1.6	2	7.1
anis3	Negative	29	96.7	40	90.9	50	92.6	55	88.7	26	92.9
	Positive	1	3.3	4	9.1	4	7.4	7	11.3	2	7.1
apig1	Negative	29	96.7	19	43.2	31	57.4	41	66.1	18	64.3
	Positive	1	3.3	25	56.8	23	42.6	21	33.9	10	35.7
apim1	Negative	30	100.0	39	88.6	53	98.2	58	93.5	27	96.4
	Positive	0	0.0	5	11.4	1	1.8	4	6.4	1	3.6
apim4	Negative	30	100.0	44	100.0	54	100.0	62	100.0	28	100.0
	Positive	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
arah1	Negative	30	100.0	40	90.9	46	85.2	57	91.9	25	89.3
	Positive	0	0.0	4	9.1	8	14.8	5	8.1	3	10.7
arah2	Negative	30	100.0	37	84.1	45	83.3	59	95.2	25	89.3
	Positive	0	0.0	7	15.9	9	16.7	3	4.8	3	10.7
arah3	Negative	30	100.0	37	84.1	47	87.0	59	95.2	25	89.3
	Positive	0	0.0	7	15.9	7	13.0	3	4.8	3	10.7
arah6	Negative	30	100.0	35	79.5	46	85.2	58	93.5	25	89.3
	Positive	0	0.0	9	20.4	8	14.8	4	6.4	3	10.7
arah8	Negative	28	93.3	18	40.9	20	37.0	31	50.0	11	39.3
	Positive	2	6.7	26	59.1	34	63.0	31	50.0	17	60.7
arah9	Negative	30	100.0	37	84.1	51	94.4	57	91.9	24	85.7
	Positive	0	0.0	7	15.9	3	5.6	5	8.1	4	14.3
artv1	Negative	30	100.0	39	88.6	49	90.7	55	88.7	26	92.9
	Positive	0	0.0	5	11.4	5	9.3	7	11.3	2	7.1
artv3	Negative	30	100.0	36	81.8	50	92.6	56	90.3	23	82.1
	Positive	0	0.0	8	18.2	4	7.4	6	9.7	5	17.9
aspf1	Negative	30	100.0	41	93.2	53	98.2	57	91.9	26	92.9
	Positive	0	0.0	3	6.8	1	1.8	5	8.1	2	7.1
aspf6	Negative	30	100.0	27	61.4	39	72.2	42	67.7	19	67.9
	Positive	0	0.0	17	38.6	15	27.8	20	32.3	9	32.1
aspf3	Negative	28	93.3	39	88.6	47	87.0	59	95.2	26	92.9
	Positive	2	6.7	5	11.4	7	13.0	3	4.8	2	7.1
bere1	Negative	30	100.0	44	100.0	53	98.2	61	98.4	26	92.9
	Positive	0	0.0	0	0.0	1	1.8	1	1.6	2	7.1
betv1	Negative	25	83.3	16	36.4	16	29.6	27	43.5	7	25.0
	Positive	5	16.7	28	63.6	38	70.4	35	56.5	21	75.0
betv2	Negative	30	100.0	37	84.1	48	88.9	55	88.7	21	75.0
	Positive	0	0.0	7	15.9	6	11.1	7	11.3	7	25.0
betv4	Negative	30	100.0	40	90.9	52	96.3	59	95.2	27	96.4
	Positive	0	0.0	4	9.1	2	3.7	3	4.8	1	3.6
blag1	Negative	30	100.0	40	90.9	52	96.3	59	95.2	27	96.4
	Positive	0	0.0	4	9.1	2	3.7	3	4.8	1	3.6
blag2	Negative	30	100.0	22	50.0	33	61.1	45	72.6	19	67.9
	Positive	0	0.0	22	50.0	21	38.9	17	27.4	9	32.1
blag5	Negative	29	96.7	44	100.0	54	100.0	61	98.4	28	100.0
	Positive	1	3.3	0	0.0	0	0.0	1	1.6	0	0.0
blag7	Negative	29	96.7	36	81.8	49	90.7	51	82.3	24	85.7
	Positive	1	3.3	8	18.2	5	9.3	11	17.7	4	14.3
blot5	Negative	29	96.7	28	63.6	43	79.6	42	67.7	23	82.1
	Positive	1	3.3	16	36.4	11	20.4	20	32.3	5	17.9
bosd4	Negative	30	100.0	42	95.5	50	92.6	57	91.9	26	92.9
	Positive	0	0.0	2	4.5	4	7.4	5	8.1	2	7.1
bosd5	Negative	30	100.0	38	86.4	50	92.6	53	85.5	24	85.7
	Positive	0	0.0	6	13.6	4	7.4	9	14.5	4	14.3
bosd6	Negative	30	100.0	40	90.9	50	92.6	55	88.7	27	96.4

bosd8	Positive	0	0.0	4	9.1	4	7.4	7	11.3	1	3.6
	Negative	30	100.0	34	77.3	42	77.8	52	83.9	26	92.9
bosdlacto	Positive	0	0.0	10	22.7	12	22.2	10	16.1	2	7.1
	Negative	30	100.0	40	90.9	51	94.4	58	93.5	28	100.0
canf1	Positive	0	0.0	4	9.1	3	5.6	4	6.4	0	0.0
	Negative	30	100.0	16	36.4	29	53.7	33	53.2	14	50.0
canf2	Positive	0	0.0	28	63.6	25	46.3	29	46.8	14	50.0
	Negative	30	100.0	25	56.8	38	70.4	46	74.2	19	67.9
canf3	Positive	0	0.0	19	43.2	16	29.6	16	25.8	9	32.1
	Negative	30	100.0	25	56.8	38	70.4	42	67.7	18	64.3
canf5	Positive	0	0.0	19	43.2	16	29.6	20	32.3	10	35.7
	Negative	30	100.0	25	56.8	33	61.1	39	62.9	22	78.6
chea1	Positive	0	0.0	19	43.2	21	38.9	23	37.1	6	21.4
	Negative	30	100.0	36	81.8	45	83.3	55	88.7	26	92.9
clah8	Positive	0	0.0	8	18.2	9	16.7	7	11.3	2	7.1
	Negative	30	100.0	36	81.8	50	92.6	56	90.3	23	82.1
cora1	Positive	0	0.0	8	18.2	4	7.4	6	9.7	5	17.9
	Negative	27	90.0	18	40.9	19	35.2	27	43.5	10	35.7
cora1.0401	Positive	3	10.0	26	59.1	35	64.8	35	56.5	18	64.3
	Negative	26	86.7	15	34.1	19	35.2	23	37.1	10	35.7
cora8	Positive	4	13.3	29	65.9	35	64.8	39	62.9	18	64.3
	Negative	30	100.0	34	77.3	50	92.6	55	88.7	23	82.1
cora9	Positive	0	0.0	10	22.7	4	7.4	7	11.3	5	17.9
	Negative	30	100.0	39	88.6	50	92.6	59	95.2	23	82.1
cryj1	Positive	0	0.0	5	11.4	4	7.4	3	4.8	5	17.9
	Negative	29	96.7	34	77.3	42	77.8	55	88.7	18	64.3
cupa1	Positive	1	3.3	10	22.7	12	22.2	7	11.3	10	35.7
	Negative	29	96.7	32	72.7	39	72.2	55	88.7	18	64.3
cynd1	Positive	1	3.3	12	27.3	15	27.8	7	11.3	10	35.7
	Negative	27	90.0	11	25.0	12	22.2	31	50.0	11	39.3
derf1	Positive	3	10.0	33	75.0	42	77.8	31	50.0	17	60.7
	Negative	28	93.3	10	22.7	21	38.9	20	32.3	12	42.9
derf2	Positive	2	6.7	34	77.3	33	61.1	42	67.7	16	57.1
	Negative	27	90.0	13	29.6	22	40.7	18	29.0	13	46.4
derp1	Positive	3	10.0	31	70.5	32	59.3	44	71.0	15	53.6
	Negative	28	93.3	9	20.4	19	35.2	20	32.3	11	39.3
derp10	Positive	2	6.7	35	79.5	35	64.8	42	67.7	17	60.7
	Negative	29	96.7	15	34.1	26	48.1	28	45.2	13	46.4
derp2	Positive	1	3.3	29	65.9	28	51.9	34	54.8	15	53.6
	Negative	27	90.0	13	29.6	24	44.4	17	27.4	14	50.0
equc1	Positive	3	10.0	31	70.5	30	55.6	45	72.6	14	50.0
	Negative	30	100.0	23	52.3	36	66.7	45	72.6	17	60.7
equc3	Positive	0	0.0	21	47.7	18	33.3	17	27.4	11	39.3
	Negative	30	100.0	37	84.1	48	88.9	52	83.9	27	96.4
fage2	Positive	0	0.0	7	15.9	6	11.1	10	16.1	1	3.6
	Negative	30	100.0	42	95.5	53	98.2	62	100.0	28	100.0
feld1	Positive	0	0.0	2	4.5	1	1.8	0	0.0	0	0.0
	Negative	29	96.7	12	27.3	19	35.2	21	33.9	6	21.4
feld2	Positive	1	3.3	32	72.7	35	64.8	41	66.1	22	78.6
	Negative	30	100.0	36	81.8	45	83.3	53	85.5	25	89.3
feld4	Positive	0	0.0	8	18.2	9	16.7	9	14.5	3	10.7
	Negative	30	100.0	23	52.3	33	61.1	43	69.3	14	50.0
gadc1	Positive	0	0.0	21	47.7	21	38.9	19	30.6	14	50.0
	Negative	30	100.0	40	90.9	51	94.4	59	95.2	27	96.4
gald1	Positive	0	0.0	4	9.1	3	5.6	3	4.8	1	3.6
	Negative	30	100.0	31	70.5	42	77.8	47	75.8	25	89.3
gald2	Positive	0	0.0	13	29.6	12	22.2	15	24.2	3	10.7
	Negative	30	100.0	38	86.4	46	85.2	55	88.7	26	92.9
gald3	Positive	0	0.0	6	13.6	8	14.8	7	11.3	2	7.1
	Negative	30	100.0	14	31.8	25	46.3	19	30.6	14	50.0
gald5	Positive	0	0.0	30	68.2	29	53.7	43	69.3	14	50.0
	Negative	30	100.0	40	90.9	49	90.7	57	91.9	26	92.9
glym4	Positive	0	0.0	4	9.1	5	9.3	5	8.1	2	7.1
	Negative	28	93.3	21	47.7	27	50.0	34	54.8	14	50.0
glym5	Positive	2	6.7	23	52.3	27	50.0	28	45.2	14	50.0
	Negative	30	100.0	41	93.2	51	94.4	61	98.4	24	85.7
glym6	Positive	0	0.0	3	6.8	3	5.6	1	1.6	4	14.3
	Negative	30	100.0	39	88.6	47	87.0	59	95.2	22	78.6
hevb1	Positive	0	0.0	5	11.4	7	13.0	3	4.8	6	21.4
	Negative	30	100.0	41	93.2	49	90.7	62	100.0	27	96.4
hevb3	Positive	0	0.0	3	6.8	5	9.3	0	0.0	1	3.6
	Negative	30	100.0	42	95.5	49	90.7	61	98.4	27	96.4
hevb5	Positive	0	0.0	2	4.5	5	9.3	1	1.6	1	3.6
	Negative	30	100.0	43	97.7	52	96.3	62	100.0	26	92.9
hevb6.01	Positive	0	0.0	1	2.3	2	3.7	0	0.0	2	7.1
	Negative	30	100.0	39	88.6	44	81.5	51	82.3	23	82.1
hevb8	Positive	0	0.0	5	11.4	10	18.5	11	17.7	5	17.9
	Negative	30	100.0	36	81.8	42	77.8	56	90.3	21	75.0

juqr1	Positive	0	0.0	8	18.2	12	22.2	6	9.7	7	25.0
	Negative	30	100.0	40	90.9	49	90.7	58	93.5	24	85.7
	Positive	0	0.0	4	9.1	5	9.3	4	6.4	4	14.3
juqr2	Negative	30	100.0	32	72.7	41	75.9	47	75.8	20	71.4
	Positive	0	0.0	12	27.3	13	24.1	15	24.2	8	28.6
juqr3	Negative	29	96.7	39	88.6	48	88.9	56	90.3	24	85.7
	Positive	1	3.3	5	11.4	6	11.1	6	9.7	4	14.3
lepd2	Negative	29	96.7	27	61.4	39	72.2	34	54.8	25	89.3
	Positive	1	3.3	17	38.6	15	27.8	28	45.2	3	10.7
mald1	Negative	26	86.7	18	40.9	19	35.2	29	46.8	10	35.7
	Positive	4	13.3	26	59.1	35	64.8	33	53.2	18	64.3
mera1	Negative	30	100.0	37	84.1	47	87.0	57	91.9	21	75.0
	Positive	0	0.0	7	15.9	7	13.0	5	8.1	7	25.0
musm1	Negative	30	100.0	28	63.6	36	66.7	49	79.0	18	64.3
	Positive	0	0.0	16	36.4	18	33.3	13	21.0	10	35.7
muxf3	Negative	30	100.0	31	70.5	43	79.6	55	88.7	24	85.7
	Positive	0	0.0	13	29.6	11	20.4	7	11.3	4	14.3
olee1	Negative	29	96.7	33	75.0	41	75.9	54	87.1	22	78.6
	Positive	1	3.3	11	25.0	13	24.1	8	12.9	6	21.4
olee7	Negative	29	96.7	41	93.2	45	83.3	57	91.9	26	92.9
	Positive	1	3.3	3	6.8	9	16.7	5	8.1	2	7.1
olee9	Negative	30	100.0	17	38.6	29	53.7	35	56.5	14	50.0
	Positive	0	0.0	27	61.4	25	46.3	27	43.5	14	50.0
parj2	Negative	30	100.0	24	54.5	34	63.0	44	71.0	19	67.9
	Positive	0	0.0	20	45.5	20	37.0	18	29.0	9	32.1
penm1	Negative	29	96.7	39	88.6	48	88.9	56	90.3	25	89.3
	Positive	1	3.3	5	11.4	6	11.1	6	9.7	3	10.7
penm2	Negative	30	100.0	31	70.5	44	81.5	48	77.4	22	78.6
	Positive	0	0.0	13	29.6	10	18.5	14	22.6	6	21.4
penm4	Negative	30	100.0	44	100.0	51	94.4	58	93.5	27	96.4
	Positive	0	0.0	0	0.0	3	5.6	4	6.4	1	3.6
phlp1	Negative	26	86.7	12	27.3	10	18.5	32	51.6	9	32.1
	Positive	4	13.3	32	72.7	44	81.5	30	48.4	19	67.9
phlp11	Negative	29	96.7	35	79.5	40	74.1	55	88.7	24	85.7
	Positive	1	3.3	9	20.4	14	25.9	7	11.3	4	14.3
phlp12	Negative	29	96.7	38	86.4	46	85.2	57	91.9	20	71.4
	Positive	1	3.3	6	13.6	8	14.8	5	8.1	8	28.6
phlp2	Negative	29	96.7	23	52.3	26	48.1	45	72.6	14	50.0
	Positive	1	3.3	21	47.7	28	51.9	17	27.4	14	50.0
phlp4	Negative	29	96.7	11	25.0	10	18.5	30	48.4	13	46.4
	Positive	1	3.3	33	75.0	44	81.5	32	51.6	15	53.6
phlp5	Negative	28	93.3	19	43.2	23	42.6	37	59.7	16	57.1
	Positive	2	6.7	25	56.8	31	57.4	25	40.3	12	42.9
phlp6	Negative	28	93.3	23	52.3	26	48.1	46	74.2	17	60.7
	Positive	2	6.7	21	47.7	28	51.9	16	25.8	11	39.3
phlp7	Negative	30	100.0	36	81.8	45	83.3	57	91.9	22	78.6
	Positive	0	0.0	8	18.2	9	16.7	5	8.1	6	21.4
plaa1	Negative	30	100.0	42	95.5	50	92.6	61	98.4	27	96.4
	Positive	0	0.0	2	4.5	4	7.4	1	1.6	1	3.6
plaa2	Negative	30	100.0	22	50.0	37	68.5	45	72.6	20	71.4
	Positive	0	0.0	22	50.0	17	31.5	17	27.4	8	28.6
plaa3	Negative	30	100.0	36	81.8	49	90.7	57	91.9	24	85.7
	Positive	0	0.0	8	18.2	5	9.3	5	8.1	4	14.3
plal1	Negative	30	100.0	39	88.6	53	98.2	60	96.8	25	89.3
	Positive	0	0.0	5	11.4	1	1.8	2	3.2	3	10.7
pold5	Negative	29	96.7	40	90.9	48	88.9	56	90.3	28	100.0
	Positive	1	3.3	4	9.1	6	11.1	6	9.7	0	0.0
phlp6.1	Negative	28	93.3	23	52.3	26	48.1	46	74.2	17	60.7
	Positive	2	6.7	21	47.7	28	51.9	16	25.8	11	39.3
phlp7.1	Negative	30	100.0	36	81.8	45	83.3	57	91.9	22	78.6
	Positive	0	0.0	8	18.2	9	16.7	5	8.1	6	21.4
plaa1.1	Negative	30	100.0	42	95.5	50	92.6	61	98.4	27	96.4
	Positive	0	0.0	2	4.5	4	7.4	1	1.6	1	3.6
plaa2.1	Negative	30	100.0	22	50.0	37	68.5	45	72.6	20	71.4
	Positive	0	0.0	22	50.0	17	31.5	17	27.4	8	28.6
plaa3.1	Negative	30	100.0	36	81.8	49	90.7	57	91.9	24	85.7
	Positive	0	0.0	8	18.2	5	9.3	5	8.1	4	14.3
plal1.1	Negative	30	100.0	39	88.6	53	98.2	60	96.8	25	89.3
	Positive	0	0.0	5	11.4	1	1.8	2	3.2	3	10.7
pold5.1	Negative	29	96.7	40	90.9	48	88.9	56	90.3	28	100.0
	Positive	1	3.3	4	9.1	6	11.1	6	9.7	0	0.0
prup1	Negative	28	93.3	18	40.9	21	38.9	30	48.4	10	35.7
	Positive	2	6.7	26	59.1	33	61.1	32	51.6	18	64.3
prup3	Negative	30	100.0	17	38.6	29	53.7	39	62.9	14	50.0
	Positive	0	0.0	27	61.4	25	46.3	23	37.1	14	50.0
salk1	Negative	30	100.0	39	88.6	50	92.6	61	98.4	25	89.3
	Positive	0	0.0	5	11.4	4	7.4	1	1.6	3	10.7
sesi1	Negative	30	100.0	42	95.5	54	100.0	58	93.5	25	89.3

trial14	Positive	0	0.0	2	4.5	0	0.0	4	6.4	3	10.7
	Negative	30	100.0	41	93.2	49	90.7	55	88.7	23	82.1
trial19	Positive	0	0.0	3	6.8	5	9.3	7	11.3	5	17.9
	Negative	30	100.0	42	95.5	53	98.2	60	96.8	28	100.0
trialaati	Positive	0	0.0	2	4.5	1	1.8	2	3.2	0	0.0
	Negative	30	100.0	41	93.2	52	96.3	60	96.8	24	85.7
vesv5	Positive	0	0.0	3	6.8	2	3.7	2	3.2	4	14.3
	Negative	28	93.3	39	88.6	47	87.0	55	88.7	26	92.9
	Positive	2	6.7	5	11.4	7	13.0	7	11.3	2	7.1

Sensitisation is binominally displayed; sensitisation of >0.3 was classified as being positive

Supplemental Figure Legends**Supplemental Movie E10. Principal component analysis of AD patients.**

3D animation of the first three PCs showing the separation of the four patient clusters generated by unsupervised k-means cluster analysis (see Figure 1C). Patients in cluster 1 are represented by black dots, patients in cluster 2 by red dots, patients in cluster 3 by green dots and patients in cluster 4 by blue dots.

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