

Low-resolution teledermatology: reply from authors

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SIR, We thank Dr Strauss for his letter. First of all, we agree completely with his opinions. We would like to underline that our studies with personal digital assistants and cellular telephones^{1,2} were both only feasibility studies in teledermatology. The goal of both studies was to test the possibility of using these new devices in teledermatology, and clinical data were intentionally not provided in order to judge the genuine capacity of teleconsultants to formulate a diagnosis. Certainly, as Dr Strauss correctly outlined, the workflow for mobile teledermatology has yet to be designed and clinical information must be included in a practicable and reasonable way. We also agree that high-resolution cameras should preferably be used in mobile teledermatology.³ In fact, in a new study concerning mobile teledermoscopy, a new generation of cellular telephones with a high-resolution camera has been used and results are much more satisfying, indicating that mobile teledermatology is beginning to come of age.^{4,5}

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References

- 1 Massone C, Lozzi GP, Wurm E et al. Personal digital assistants in teledermatology. *Br J Dermatol* 2006; **154**:801–2.
- 2 Massone C, Lozzi GP, Wurm E et al. Cellular phones in clinical teledermatology. *Arch Dermatol* 2005; **141**:1319–20.
- 3 Strauss RM, Goulden V. Artefacts in digital whole-body photography. *J Telemed Telecare* 2004; **10**:307–8.
- 4 Massone C, Ahlgrimm-Siess V, Hofmann-Wellenhof R et al. Telediagnosis of pigmented skin lesions using cellular phones – feasibility study. *Dermatology* 2006; **212**:276.
- 5 Ebner C, Gabler G, Massone C et al. Mobile teledermatology coming in age. *Elektrotechnik und Informationstechnik* 2006; **123**:148–51.

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Filaggrin loss-of-function variant contributes to atopic dermatitis risk in the population of Northern Germany

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SIR, In March 2006, Smith et al.¹ demonstrated that two loss-of-function mutations (R501X and 2282del4) in the

gene encoding filaggrin (FLG) cause moderate or severe ichthyosis vulgaris, an autosomal semidominant scaling skin disorder. FLG encodes a filament-aggregating protein, which is essential for the formation of the stratum corneum.² FLG is located on chromosome 1q21 and the mutations R501X and 2282del4 in exon 3 both lead to complete loss of processed filaggrin products by stopping the protein translation within the first FLG repeat based on premature termination codons. Based on the well-known association of ichthyosis vulgaris with atopic diseases in general and in particular with atopic dermatitis (AD),³ FLG is also implicated to play a role in common skin disorders such as AD, which is known to have an essential genetic background. Shortly after the initial identification of FLG mutations in ichthyosis vulgaris, Palmer et al. identified the same two FLG variants as a major predisposing factor for AD in the Irish, Scottish and Danish population.⁴

To explore further the relevance of the variants for other populations of Western European descent, we typed each single nucleotide polymorphism in 272 patients with AD and 276 healthy control individuals of Northern German origin. In addition, we genotyped the mutation R501X in 338 mother–father–affected child trios for AD. All patients with AD were recruited from the dermatological outpatient ward between 2000 and 2005.⁵ The patients had a median age of 10 years and a female/male ratio of 1·2. The median age at onset was 1 year. The diagnosis of AD was established according to the criteria of Hanifin and Rajka.⁶ All control individuals were randomly selected from the population of Northern Germany as part of the PopGen project⁷ and had a female/male ratio of 1·1. All patients or parents of affected children and control individuals gave written informed consent to participation in the study.

Genotyping of the R501X variant was performed using the TaqMan allelic discrimination method (Applied Biosystems, Foster City, CA, U.S.A.) as reported by Palmer et al.⁴ Genotypes with the 2282del4 variant were determined by sizing a fluorescently labelled polymerase chain reaction fragment on an ABI3730 automated sequencer (Applied Biosystems) as described by Palmer et al.⁴ Each marker was tested for Hardy–Weinberg equilibrium in the control population using a χ^2 test. Genetic analyses were then performed at several levels. To test for association with AD, the R501X variant was subjected to single-locus transmission disequilibrium test (TDT) analysis as implemented in GENEHUNTER (Ver. 2.1).⁸ To assess significance of the TDT result for the variant we performed permutation tests using the same genotype data.⁸ For case–control analysis, allele frequencies were compared using Pearson χ^2 tests for the three genotype differences. Odds ratios (ORs) for dominant models were calculated using Fisher's exact test, genotype-based ORs were calculated using Fisher's contingency tables and association tested similarly.

We observed a significant overtransmission of the R501X risk allele to individuals with AD, with a transmitted/untransmitted ratio of 50 : 23 ($\chi^2 = 9\cdot99$, $P = 0\cdot0016$). Further-

more, the risk allele frequency for FLG R501X variant was 0.022 in the control population and 0.071 in the cohort of patients with AD, resulting in a highly significant association of $P = 0.0001$ and an OR of 3.39 (95% confidence interval, CI 1.75–6.58). When computing the OR for carriership, assuming a codominant mode of inheritance as proposed by Palmer et al.,⁴ the AD risk was estimated at OR 3.59 (95% CI 1.8–7.05). The allele frequency of the FLG 2282del4 variant was 0.017 in the control population compared with 0.11 in the AD study sample. Similar to the observations made by Palmer et al.,⁴ no homozygote carriers for the null allele were observed in the controls. The OR for AD susceptibility in carriers of at least one null allele was determined as 7.1 (95% CI 3.41–14.78, $P = 2.01 \times 10^{-8}$).

Our observation is in accordance with the report by Palmer et al.,⁴ and provides compelling evidence of FLG mutations as major predisposing factors for AD in Western European populations. According to our hypothesis that inflammatory barrier diseases may share disease genes,⁹ we have also tested the FLG variants in a large cohort of 681 patients with Crohn disease, 427 with ulcerative colitis and 546 with sarcoidosis, which have been described previously.^{10,11} We detected no association of the FLG mutations with any of these diseases. Thus it appears that FLG variants are specific to the epidermal barrier, but do not confer a general increased risk for chronic inflammatory diseases. It is conceivable that while some genetic variants, e.g. located in the peri-HLA region or on 5q31 (IBD5) or CARD15 are of general importance in chronic inflammatory diseases, variants in FLG appear to be more particular to the target organ. Future studies involving longitudinal phenotypic follow-up will further help to define lifetime health risk as well as the contribution of FLG mutations to coexisting clinical phenotypes including asthma, food allergy or house dust mite allergy.

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References

- Smith FJ, Irvine AD, Terron-Kwiatkowski A et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006; **38**:337–42.
- Dale BA, Resing KA, Lonsdale-Eccles JD. Filaggrin: a keratin filament associated protein. *Ann NY Acad Sci* 1985; **455**:330–42.
- Kuokkanen K. Ichthyosis vulgaris. A clinical and histopathological study of patients and their close relatives in the autosomal dominant and sex-linked forms of the disease. *Acta Derm Venereol (Stockh)* 1969; **62** (Suppl.) 1–72.
- Palmer CN, Irvine AD, Terron-Kwiatkowski A et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**:441–6.
- Fölster-Holst R, Stoll M, Koch WA et al. Lack of association of SPINK5 polymorphisms with nonsyndromic atopic dermatitis in the population of Northern Germany. *Br J Dermatol* 2005; **152**:1365–7.
- Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; **92** (Suppl.): 44–7.
- Krawczak M, Nikolaus S, von Eberstein H et al. PopGen: population-based recruitment of patients and controls for the analysis of complex genotype–phenotype relationships. *Community Genet* 2006; **9**:55–61.
- Markianos K, Daly MJ, Kruglyak L. Efficient multipoint linkage analysis through reduction of inheritance space. *Am J Hum Genet* 2001; **68**:963–77.
- Schreiber S, Rosenstiel P, Albrecht M et al. Genetics of Crohn disease, an archetypal inflammatory barrier disease. *Nat Rev Genet* 2005; **6**:376–88.
- Stoll M, Corneliussen B, Costello CM et al. Genetic variation in DLG5 is associated with inflammatory bowel disease. *Nat Genet* 2004; **36**:476–80.
- Valentonyte R, Hampe J, Huse K et al. Sarcoidosis is associated with a truncating splice site mutation in BTNL2. *Nat Genet* 2005; **37**:357–64.

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Proteus syndrome with agenesis of the rectus abdominis

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SIR, Proteus syndrome (PS)¹ is a sporadic genetic disorder. This rare mesodermal malformation syndrome has a prevalence of < 1 : 1 000 000 live births, and is estimated to affect 100–200 individuals worldwide.² Patients meeting all of the accepted general criteria and several specific criteria from different categories are diagnosed as having PS. General criteria include mosaic distribution of lesions, progressive course, and sporadic occurrence. Specific criteria are cerebiform connective tissue naevus, linear epidermal naevus, asymmetrical disproportionate overgrowth in variable tissues, specific tumours