REFERENCES

Carmichael NM, Dostrovsky JO, Charlton MP (2010) Peptide-mediated transdermal delivery of botulinum neurotoxin type A reduces neurogenic inflammation in the skin. *Pain* 149:316–24

Chan J, Smoller BR, Raychauduri SP *et al.* (1997) Intraepidermal nerve fiber expression of calcitonin gene-related peptide, vasoactive intestinal peptide and substance P in psoriasis. *Arch Dermatol Res* 289:611–6

Dewing SB (1971) Remission of psoriasis associated with cutaneous nerve section. *Arch Dermatol* 104:220–1

Farber EM, Lanigan SW, Boer J (1990) The role of cutaneous sensory nerves in the maintenance of psoriasis. *Int J Dermatol* 29:418–20

Griffiths CE, Richards HL (2001) Psychological influences in psoriasis. *Clin Exp Dermatol* 26:338–42

Jiang W-Y, Raychaudhuri SP, Farber EM (1998) Double-labeled immunofluorescence study of cutaneous nerves in psoriasis. *Int J Dermatol* 37:572–4

Joachim RA, Kuhlmei A, Dinh QT *et al.* (2007) Neuronal plasticity of the ''brain-skin connection'': stress-triggered up-regulation of neuropeptides in dorsal root ganglia and skin via nerve growth factor-dependent pathways. *J Mol Med* 85:1369–78

Joseph T, Kurian J, Warwick DJ *et al.* (2005) Unilateral remission of psoriasis following traumatic nerve palsy. *Br J Dermatol* 152:185–6

Meng J, Wang J, Lawrence G *et al.* (2007) Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. *J Cell Sci* 120:2864–74

Naukkarinen A, Nickoloff BJ, Farber EM (1989) Quantification of cutaneous sensory nerves and their substance P content in psoriasis. *J Invest Dermatol* 92:126–9

Ostrowski SM, Belkadi A, Loyd CM *et al.* (2011) Cutaneous denervation of psoriasiform mouse skin improves acanthosis and inflammation in a sensory neuropeptide-dependent manner. *J Invest Dermatol* 131:1530–8

Perlman HH (1972) Remission of psoriasis vulgaris from the use of nerve-blocking agents. *Arch Dermatol* 105:128–9

Remrod C, Lonne-Rahm S, Nordlind K (2007) Study of substance P and its receptor neurokinin-1 in psoriasis and their relation to chronic stress and pruritus. *Arch Dermatol Res* 299:85–91

Stratigos AJ, Katoulis AK, Stavrianeas NG (1998) Spontaneous clearing of psoriasis after stroke. *J Am Acad Dermatol* 38:768–70

Zanchi M, Favot F, Bizzarini M *et al.* (2008) Botulinum toxin type-A for the treatment of inverse psoriasis. *J Eur Acad Dermatol Venereol* 22:431–6

Interactions between Genetic Variants of *FLG* and Chromosome 11q13 Locus Determine Susceptibility for Eczema Phenotypes

Journal of Investigative Dermatology (2012) **132,** 1930–1932; doi:10.1038/jid.2012.62; published online 15 March 2012

TO THE EDITOR

Eczema is caused by complex gene–environmental interactions. The gene encoding filaggrin (*FLG*) on chromosome 1q21 reported initially by genome-wide linkage scan has been the most consistently replicated one in Caucasian children (Palmer *et al.*, 2006; Brown and McLean, 2009). Such finding was confirmed in a recent meta-analysis (van den Oord and Sheikh, 2009). Nevertheless, all five known *FLG* mutations were rare in our southern Chinese children (Ching *et al.*, 2009), whereas ethnic-specific *FLG* mutations were found in the Japanese (Nomura *et al.*, 2008), Singaporean Chinese (Chen *et al.*, 2011), and Taiwanese (Hsu *et al.*, 2009). A recent study reported 10 *FLG* mutations, which to our knowledge were previously

Table 1. Multi-locus interaction models by GMDR for plasma total IgE concentration and circulating eosinophil percentage

Combination of SNPs	CVC	Test accuracy	*P*[1]
Plasma total IgE concentration			
rs2155219	9	0.565	0.0002
rs1933064_rs2155219	10	0.577	<0.0001
rs1933064_rs2155219_rs1892951	6	0.597	<0.0001
rs1933064_rs3862807_rs10793175_rs17135034	2	0.573	0.0016
Circulating eosinophil percentage			
rs2155219	10	0.571	0.0006
rs2155219_rs7927894	8	0.575	0.0004
rs1933064_rs2155219_rs17135034	3	0.581	<0.0001
rs11584427_rs2155219_rs7927894_rs10751256	8	0.592	0.0002

Abbreviations: CVC, cross-validation consistency; GMDR, generalized multifactor dimensionality reduction; SNP, single-nucleotide polymorphism.
[1]Based on 5,000 permutations.

Abbreviations: eos%, circulating eosinophil percentage; FLG, *filaggrin; GMDR, generalized multifactor dimensionality reduction; GWAS, genome-wide association study; logIgE, logarithm-transformed plasma total IgE concentration; MAF, minor allele frequency; SNP, single-nucleotide polymorphism*

unreported, for eczema in Han Chinese (Zhang *et al.*, 2011). We postulated that eczema is also related to its single-nucleotide polymorphisms (SNPs). The first genome-wide association study (GWAS) for eczema found a common noncoding variant, rs7927894, on chromosome 11q13 to have the strongest association with eczema in German children (Esparza-Gordillo *et al.*, 2009). Such association was replicated in the Irish population (O'Regan *et al.*, 2010). Nevertheless, there are no data on the interaction between *FLG* and 11q13 locus for eczema susceptibility.

In this case–control study, Chinese children aged ⩽18 years with physician-diagnosed eczema and non-allergic controls were recruited to investigate the relationship between childhood eczema phenotypes and tagging SNPs of *FLG* and 11q13. Their total plasma and allergen-specific IgE concentrations and circulating eosinophil percentage (eos%) were also measured (see Supplementary Materials online). Total IgE was log-transformed (logIgE) before analysis. Subjects and their parents gave informed written consent. This study was approved by our clinical research ethics committee and performed according to the Declaration of Helsinki Principles.

Genotypic data of SNPs spanning 20-kb flanking region of rs7927894 on 11q13 and 10 kb upstream and downstream of *FLG* on 1q21 were retrieved from HapMap (McVean *et al.*, 2005). The details of tagging SNP selection and genotyping were described in Supplementary Materials online, and the linkage disequilibrium patterns of SNPs in various ethnic groups are provided in Supplementary Figures S1–S5 online. Rs11584427 was in complete linkage disequilibrium ($r^2 = 1$) with two SNPs reported in an eczema GWAS in Han Chinese (Sun *et al.*, 2011). The associations between SNP and childhood eczema phenotypes were analyzed by logistic or linear regression using SPSS v.17 (SPSS, Chicago, IL), with level of significance being 0.003 (0.05/17) to correct for multiple statistical comparisons. The interactions among SNPs for eczema phenotypes were analyzed by generalized multifactor dimensionality reduction (GMDR; see Supplementary Materials online), and significant findings were confirmed by generalized linear model for normally distributed logIgE or linear regression for eos%, which did not follow normal data distribution. One-way ANOVA and Kruskal–Wallis test with *post-hoc* tests were used to compare logIgE and eos% among GMDR-defined risk groups.

A total of 1,230 Chinese eczema patients and 1,113 controls were recruited. Supplementary Table S1 online summarizes their clinical and laboratory features. Fifteen SNPs on 11q13 and two SNPs of *FLG* with ⩾90% genotyping efficiency and in Hardy–Weinberg equilibrium were analyzed (Supplementary Table S2 online). Two *FLG* SNPs rs11584427 and rs1933064 were in complete linkage disequilibrium. Eczema diagnosis was not associated with any single SNP. However, moderate-to-severe eczema was associated with rs11584427 of *FLG* (Supplementary Table S3 online). Supplementary Tables S4 and S5 online summarize results of linear regression for logIgE and eos%, respectively. LogIgE was associated with rs7124842 and rs3862807, and subjects homozygous for major alleles of these SNPs had higher total IgE levels. Eos% was associated with rs2155219 (Supplementary Table S6 online). GMDR ana-

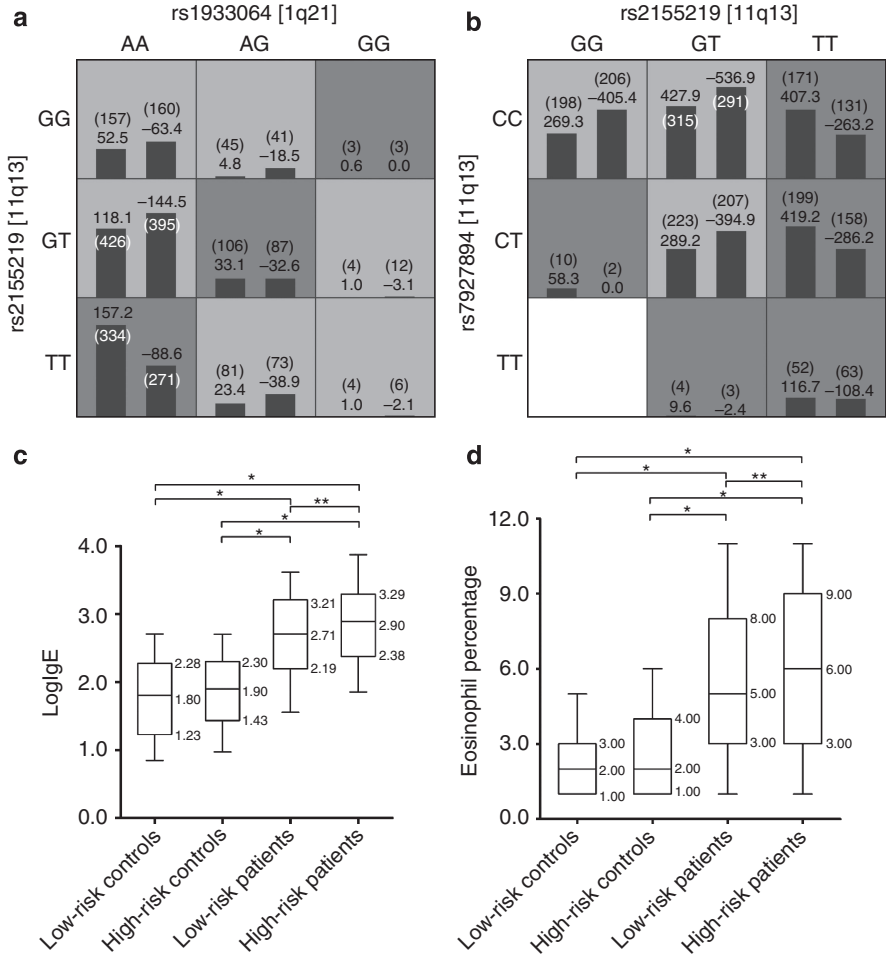

Figure 1. Interactions between filaggrin (FLG) and 11q13 locus for eczema phenotypes. Generalized multifactor dimensionality reduction (GMDR) analyses for single-nucleotide polymorphism (SNP)–SNP interactions showing the best two-locus models for (**a**) plasma total IgE concentration (logIgE) and (**b**) circulating eosinophil percentage (eos%). Left bars in grids represent cases, whereas the right ones are controls. Grids in dark are of the high-risk group and those in gray are of the low-risk group. The white grid is unclassified. For *post-hoc* analyses, box plots for high- and low-risk groups as defined by GMDR are provided for the interactions (**c**) between rs1933064 and rs2155219 for logIgE and (**d**) between rs7927894 and rs2155219 for eos%. The median (25th–75th percentiles) values for the four groups are shown on the right sides of the respective boxes. *$P<0.001$; **$P<0.005$.

lyses revealed the best interaction model for logIgE to be the two-way combination of rs1933064 of *FLG* and rs2155219 on 11q13 with the highest cross-validation consistency (10 out of the 10-fold cross-validation), which was confirmed by the generalized linear model ($P = 1.1 \times 10^{-7}$; Table 1). For eos%, rs2155219/rs7927894 on 11q13 was the best two-locus model, confirmed by linear regression ($P = 1.5 \times 10^{-4}$), whereas rs11584427/rs2155219/rs7927894/rs10751256 was the best four-locus model. Figure 1 illustrates the assignment of subjects into high-risk or low-risk groups. Total IgE levels were significantly different among the four groups ($P < 0.001$), whereas eos% was higher in high-risk than low-risk subjects ($P < 0.001$) among both patients and controls.

This study found that moderate-to-severe childhood eczema was associated with rs11584427 of *FLG*, whereas rs1933064 of *FLG* and rs2155219 on 11q13 interacted to determine total IgE and rs2155219 and rs7927894 on 11q13 interacted to determine eos%. Such results support both *FLG* and 11q13 to be candidate loci for childhood eczema. Palmer *et al.* (2006) showed that loss-of-function variants R510X and 2282del4 of *FLG* were strong predisposing factors for childhood eczema. *FLG* also conferred susceptibility to other allergies such as asthma, hay fever, and atopic sensitization (Bisgaard *et al.*, 2008; Marenholz *et al.*, 2009; Schuttelaar *et al.*, 2009). There was strong synergistic interaction between *FLG*-null alleles and early food sensitization in the transition from eczema to asthma (Marenholz *et al.*, 2009). These findings support the importance of *FLG* in susceptibility for allergies. The first GWAS reported noncoding rs7927894 on 11q13 to be associated with eczema in German children (Esparza-Gordillo *et al.*, 2009). However, we could not replicate such association possibly because of lower minor allele frequency (MAF) in our Chinese population (0.23) than that in Caucasians (0.36–0.41). However, rs2155219 on 11q13 was associated with eos% and interacted with rs1933064 of *FLG* for total IgE levels and with rs7927894 for eos%. With regard to *FLG*, rs11584427 was associated with moderate-to-severe childhood eczema. Another SNP (rs1933064) of *FLG* interacted with rs2155219 on 11q13 to modulate total IgE levels. These findings support the importance of 11q13 and *FLG* in the pathogenesis of childhood eczema.

Our sample size of 1,230 cases and 1,113 controls had 80% power to detect a risk allele with odds ratio 1.35 for eczema at MAF 0.2 with 95% confidence, but 70% power for SNP with MAF 0.1 (EpiInfo, Center for Disease Control and Prevention, Atlanta, GA). Despite this, this study is adequately powered to replicate the risk of 1.47 for rs7927894 on 11q13, as initially reported (Esparza-Gordillo *et al.*, 2009).

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

This study was funded by Research Grants Council General Research Fund (#469908) of Hong Kong SAR.

Susan Shuxin Wang[1,5], Kam Lun Hon[1,5], Hing Yee Sy[1], Alice Pik-Shan Kong[2], Iris Hiu-Shuen Chan[3], Lai Yin Tse[1], Christopher Wai-Kei Lam[3,4], Gary Wing-Kin Wong[1], Juliana Chung-Ngor Chan[2] and Ting Fan Leung[1]

[1]Department of Pediatrics, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; [2]Department of Medicine and Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; [3]Department of Chemical Pathology, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong and [4]Macau Institute for Applied Research in Medicine and Health, Macau University of Science and Technology, Taipa, Macau
E-mail: tfleung@cuhk.edu.hk
[5]These authors contributed equally to this work.

SUPPLEMENTARY MATERIAL

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

REFERENCES

Bisgaard H, Simpson A, Palmer CN *et al.* (2008) Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. *PLoS Med* 5:e131

Brown SJ, McLean WH (2009) Eczema genetics: current state of knowledge and future goals. *J Invest Dermatol* 129:543–52

Chen H, Common JE, Haines RL *et al.* (2011) Wide spectrum of filaggrin-null mutations in atopic dermatitis highlights differences between Singaporean Chinese and European populations. *Br J Dermatol* 165:106–14

Ching GK, Hon KL, Ng PC *et al.* (2009) Filaggrin null mutations in childhood atopic dermatitis among the Chinese. *Int J Immunogenet* 36:251–4

Esparza-Gordillo J, Weidinger S, Fölster-Holst R *et al.* (2009) A common variant on chromosome 11q13 is associated with atopic dermatitis. *Nat Genet* 41:596–601

Hsu CK, Akiyama M, Nemoto-Hasebe I *et al.* (2009) Analysis of Taiwanese ichthyosis vulgaris families further demonstrates differences in FLG mutations between European and Asian populations. *Br J Dermatol* 161: 448–51

Marenholz I, Kerscher T, Bauerfeind A *et al.* (2009) An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. *J Allergy Clin Immunol* 123:911–6

McVean G, Spencer CC, Chaix R. (2005) Perspectives on human genetic variation from the HapMap Project. *PLoS Genet* 1:e54

Nomura T, Akiyama M, Sandilands A *et al.* (2008) Specific filaggrin mutations cause ichthyosis vulgaris and are significantly associated with atopic dermatitis in Japan. *J Invest Dermatol* 128:1436–41

O'Regan GM, Campbell LE, Cordell HJ *et al.* (2010) Chromosome 11q13.5 variant associated with childhood eczema: an effect supplementary to filaggrin mutations. *J Allergy Clin Immunol* 125:170–4

Palmer CN, Irvine AD, Terron-Kwiatkowski A *et al.* (2006) Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 38:441–6

Schuttelaar ML, Kerkhof M, Jonkman MF *et al.* (2009) Filaggrin mutations in the onset of eczema, sensitization, asthma, hay fever and the interaction with cat exposure. *Allergy* 64:1758–65

Sun L-D, Xiao F-L, Li Y *et al.* (2011) Genome-wide association study identifies two new susceptibility loci for atopic dermatitis in the Chinese Han population. *Nat Genet* 43:690–6

van den Oord RA, Sheikh A. (2009) Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ* 339:b2433

Zhang H, Guo Y, Wang W *et al.* (2011) Mutations in the filaggrin gene in Han Chinese patients with atopic dermatitis. *Allergy* 66:420–7