

Association of *KIF3A*, but not *OVOL1* and *ACTL9*, with atopic eczema in Italian patients

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Summary

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Conflicts of interest

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Background Atopic eczema (AE) (OMIM %603165) is the most common chronic inflammatory skin disease characterized by xerosis, pruritus, and erythematous lesions with increased transepidermal water loss. It's a complex disease due to the interaction between environmental and genetics factors. To date, different loci have been related to the disease.

Objectives To verify the association, between AE and rs479844, rs2164983, and rs2897442, target for OVOLI (11q13), ACTL9 (19p13.2), and in KIF3A (5q31) genes in the Italian population. Recently, these SNPs have been validated as associated to the disease.

Methods A case-control study testing a cohort of 359 AE cases and 778 controls.

Results We confirmed the association between rs2897442 in KIF3A gene and the disease at both allele and genotype level (P-value: 4.8×10^{-4} and P-value: 6.3×10^{-4} , respectively). The C allele of the SNP showed an Odds Ratio (OR) of 1.46 (95% CI 1.18–1.82), moreover the CC genotype achieved an OR of 2.77 (95% CI 1.66–4.61). We failed to reveal association between AE and the other two SNPs tested.

Conclusions Our study indicated KIF3A as a novel gene implicated in the development of AE in the Italian population.

Atopic eczema (AE) (OMIM %603165) is the most common chronic inflammatory skin disease and is characterized by xerosis, pruritus and erythematous lesions with increased transepidermal water loss.¹ Regarding the genetics of the disease, different loci, from ATOD1 to ATOD9, have been related to the development of AE. Recently, Paternoster et al.² performed a genome-wide association meta-analysis that revealed three different single nucleotide polymorphisms (SNPs) associated with the disease: rs479844, rs2164983 and rs2897442 near OVOLI (11q13), ACTL9 (19p13.2) and in KIF3A (5q31) genes, respectively. It is well known that null mutations within the filaggrin gene (FLG) in the ATOD2 locus are the main susceptibility factor of AE.^{3,4} In our previous work, we demonstrated that these null mutations in the FLG gene do not confer susceptibility to the disease in the Italian population.⁵ Moreover, the recent full sequencing of the gene did not reveal associated variants, suggesting that FLG should not be considered to be a major risk factor for AE in the Italian population and supporting the existence of genetic heterogeneity across Europe.

Herein, we tested the association between the new variants detected by Paternoster et al.² and the disease to verify the

existence of other susceptibility alleles involved in the development of AE in Italian patients. A case-control study has been performed in our cohort of 359 Italian patients with AE (recruited by IDI – Istituto Dermopatico dell'Immacolata and Fatebenefratelli Hospital) and 778 healthy subjects (recruited in a wide cohort of blood donors originating from the same geographical area as the samples). The diagnosis of AE in our case cohort was made by experienced dermatologists or by a paediatric allergologist. The cohort consisted of 85% of cases with the intrinsic subtype and 15% with the extrinsic form of AE. Further clinical details of Italian patients are available in Bergboer et al.⁶ Written consent was obtained from all patients or their parents. The study was approved by the ethics committee of each participating institute and complied with the guidelines of the Declaration of Helsinki.

Genomic DNA was extracted from peripheral blood using standard procedures. Genotyping was performed by TaqMan[®] assays (Applied Biosystems, Foster City, CA, U.S.A.). Reactions were run in an AB7500 Fast real-time polymerase chain reaction (PCR) machine (Applied Biosystems) and interpreted using Sequence Detection System 2.1 software (Applied

Table 1 Allele and genotype association between atopic eczema and rs479844, rs2164983 and rs2897442

rs479844			rs2164983			rs2897442		
Allele frequency	P	OR (95% CI)	Allele frequency	P	OR (95% CI)	Allele frequency	P	OR (95% CI)
Cases								
A: 0.48	0.123	1.16 (0.95–1.41)	A: 0.15	0.851	1.04 (0.79–1.36)	C: 0.37	4.8×10^{-4}	1.46 (1.18–1.82)
G: 0.52			C: 0.85			T: 0.63		
Controls								
A: 0.44			A: 0.15			C: 0.28		
G: 0.56			C: 0.85			T: 0.72		
Genotype frequency	P	OR (95% CI)	Genotype frequency	P	OR (95% CI)	Genotype frequency	P	OR (95% CI)
Cases								
AA: 0.24	0.139	AA: 1.36 (0.92–2.02)	AA: 0.01	0.791	AA: 0.60 (0.20–1.82)	CC: 0.16	6.3×10^{-4}	CC: 2.77 (1.66–4.61)
AG: 0.48			AC: 0.27			CT: 0.42		
GG: 0.28		AG: 1.05 (0.76–1.46)	CC: 0.72		AC: 1.03 (0.75–1.41)	TT: 0.42		CT: 1.15 (0.85–1.57)
Controls								
AA: 0.19			AA: 0.03			CC: 0.07		
AG: 0.50		GG: Reference	AC: 0.26		CC: Reference	CT: 0.43		TT: Reference
GG: 0.31			CC: 0.71			TT: 0.50		

CI, confidence interval; OR, odds ratio; P, P-value of Cochran–Armitage test.

Biosystems). No departure from Hardy–Weinberg equilibrium was detected.

Statistical analyses were performed using a standard 2×2 table and Fisher's exact tests. The odds ratio (OR) was calculated using <http://www.hutchon.net/ConfidOR.htm> (last accessed 28 December 2012). Statistical power was calculated using <http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html> (last accessed 28 December 2012).

While we detected a significant association between rs2897442 in the KIF3A gene and AE at both the allele and genotype level, we failed to reveal a significant P-value between the disease and the other variants tested. As shown in Table 1, we detected an allele P-value of 4.8×10^{-4} for this variant. The C allele of rs2897442 has a frequency of 0.37 in cases and 0.28 in controls, achieving an odds ratio (OR) of 1.46 [95% confidence interval (CI) 1.18–1.82]. At genotype level, we obtained a P-value of 6.3×10^{-4} . The CC genotype shows a frequency of 0.16 in AE samples and 0.07 in controls, with an OR of 2.77 (95% CI 1.66–4.61). The TT genotype shows a frequency of 0.42 in AE samples and 0.50 in controls and a protective OR of 0.36 (95% CI 0.22–0.60). Moreover, no significant association was detected for rs479844 and rs2164983 at genotype level. In this respect, it is important to note that the low statistical power (<0.8) for rs479844 and rs2164983 cannot exclude that negative results could be explained by population heterogeneity. Moreover, the frequency of the associated allele of rs2897442 is higher in Italian patients with respect to other published data (statistical power = 1.00). In this study, we confirmed a role of rs2897442 as a susceptibility factor in the development of the disease in our population, while we failed to replicate the association between rs479844 and rs2164983 and AE.

The rs2897442 is an intronic SNP located in the KIF3A gene (kinesin family protein 3A). The gene encodes a subunit of the kinesin II complex and is implicated in the assembly of primary cilia.⁷ It maps in the same region as one of the susceptibility loci to atopic eczema, ATOD6.⁸ The region is characterized by a complex linkage disequilibrium (LD) pattern and, within it, a cluster of immune-related and cytokine genes. In particular, the IL13 gene has been recently associated with the disease.^{9,10} The LD pattern of 5q31 does not allow unique identification of the real susceptibility gene or variant that predisposes to the development of AE. Indeed, the association between AE and rs2897442 suggests a potential susceptibility role for KIF3A or for genes/variants in complete LD with it in the same region. We previously proposed that FLG should not be considered to be a major risk factor for AE in the Italian population, making possible the existence of a population-specific gradient across Europe,¹ which also appeared in a recent Ethiopian study that failed to reveal an association between AE and FLG.¹¹ On the basis of these results, the KIF3A gene can be considered a risk factor for AE in Italian population.

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