

LETTER TO THE EDITOR

Variation in the *COL29A1* gene in German patients with atopic dermatitis, asthma and chronic obstructive pulmonary disease

Dear Editor,

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by dry, itchy skin lesions that usually presents in early childhood.¹ The prevalence is approximately 5–15% in Western Europe.² AD belongs to the group of allergic disorders also including food allergy, allergic rhinitis and asthma. It is supposed to be a multifactorial disorder influenced by environmental as well as genetic factors.³ A genome-wide screen in European families reported linkage to a region on chromosome 3q21.⁴ Recently, Söderhäll *et al.*⁵ further investigated this region in a family-based association analysis using microsatellite markers and single nucleotide polymorphisms (SNP). They were able to narrow down the critical region and identified eight SNPs that showed allelic and haplotypic association with AD, with the strongest association results for SNP rs4688761. Subsequently, the findings were replicated in a second independent family cohort. A novel gene was identified in the critical region that contains a collagenous domain and therefore was classified as collagen 29A1 (*COL29A1*).⁵ Expression analysis of *COL29A1* showed highest expression in the skin, but also in other epithelial tissues such as lung and gastrointestinal tract, which are the main manifestation sites of allergic disorders. Taken together, the *COL29A1* gene represents the first AD gene that was identified by positional cloning. Expression analysis indicated that variation in *COL29A1* may not only play a role in AD pathogenesis but also in the pathogenesis of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma.

For replication of these findings, we genotyped four selected SNPs in *COL29A1* in a German case–control cohort comprising 465 patients with AD and 350

healthy controls and evaluated them for allelic and haplotypic association with AD. Additionally, we also analyzed these polymorphisms in 215 German patients with COPD and 130 children with asthma. Genotyping was performed by polymerase chain reaction (PCR) with subsequent restriction enzyme digestion (restriction fragment length polymorphism).

Genotype and allele frequencies did not differ between cases and controls (Table 1). Only in the small group of asthmatic children one SNP, rs13095825, showed a tendency towards a significant association (uncorrected $P = 0.02$), but this weak association did not withstand Bonferroni correction. Haplotype analysis did not yield significant associations in any of the analyzed groups either (Table 2). To our knowledge, this is the first attempt at replicating association of variation in *COL29A1*, the first AD gene identified by positional cloning, with AD in an independent cohort. However, we were unable to replicate the association of *COL29A1* variation with AD in our German case–control cohort. Further, we did not find evidence that the investigated polymorphisms may play a substantial role in the pathogenesis of COPD or asthma. The discrepancy between our findings and the results of the original study by Söderhäll *et al.* may be explained by differences in study population and design. Although the majority (60%) of the 199 families in the Söderhäll study were Germans as in our cohort, patients originating from other European countries such as Italy, Sweden and the Netherlands were also included. Recruitment was restricted to patients with an age of onset under 2 years, while in our study age of onset was recorded, but not used as an inclusion or exclusion criterion. However, when we restricted the analysis to the group of patients with an age of onset below

Correspondence: Susanne Stemmler, M.D., Ruhr-University, Department of Human Genetics, Universitätsstrasse 150, 44801 Bochum, Germany.
Email: susanne.stemmler@rub.de

Table 1. Allele and genotype frequencies of *COL29A1* polymorphisms in AD, asthma and COPD patients and controls

Polymorphism	Genotype	Allele	AD	Asthma	COPD	Controls
rs13095825	T/T		204 (44.1%)	54 (41.5%)	88 (41.4%)	147 (42.2%)
	T/C		209 (45.1%)	55 (42.3%)	100 (46.9%)	173 (49.8%)
	C/C		50 (10.8%)	21 (16.2%)	25 (11.7%)	28 (8.0%)
	<i>n</i>		463	130	213	348
	<i>P</i> -value*		0.27	0.02	0.34	–
rs10212372		T	617 (66.7%)	163 (62.7%)	276 (64.8%)	467 (67.1%)
		C	309 (33.3%)	97 (37.3%)	150 (35.2%)	229 (32.9%)
		<i>P</i> -value*	0.84	0.20	0.43	–
	A/A		278 (59.6%)	78 (59.5%)	126 (59.4%)	211 (60.5%)
	A/G		164 (35.2%)	49 (37.4%)	79 (37.3%)	125 (35.8%)
rs4688761	G/G		24 (5.2%)	4 (3.1%)	7 (3.3%)	13 (3.7%)
	<i>n</i>		466	131	212	349
	<i>P</i> -value*		0.63	0.78	0.75	–
		A	720 (77.3%)	205 (78.2%)	331 (78.0%)	547 (78.4%)
		G	212 (22.7%)	57 (21.8%)	93 (22.0%)	151 (21.6%)
rs9883988		<i>P</i> -value*	0.59	0.97	0.91	–
	T/T		255 (54.7%)	69 (52.3%)	114 (53.0%)	184 (52.5%)
	T/C		177 (38.0%)	57 (43.2%)	93 (43.3%)	150 (42.7%)
	C/C		34 (7.3%)	6 (4.5%)	8 (3.7%)	17 (4.8%)
	<i>n</i>		466	132	215	351
rs9883988	<i>P</i> -value*		0.19	0.99	0.82	–
		T	687 (73.7%)	195 (73.9%)	321 (77.6%)	518 (73.8%)
		C	245 (26.3%)	69 (26.1%)	109 (25.4%)	184 (26.2%)
		<i>P</i> -value*	0.97	0.98	0.75	–
	G/G		423 (90.6%)	117 (90.0%)	196 (90.7%)	323 (91.7%)
rs9883988	G/A		43 (9.2%)	13 (10.0%)	20 (9.3%)	27 (7.7%)
	A/A		1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
	<i>n</i>		467	130	216	352
	<i>P</i> -value*		0.44	0.42	0.52	–
		G	889 (95.2%)	247 (95.0%)	412 (95.4%)	673 (95.6%)
rs9883988		A	45 (4.8%)	13 (5.0%)	20 (4.6%)	31 (4.4%)
		<i>P</i> -value*	0.69	0.69	0.86	–

*Uncorrected *P*-values are presented here (threshold of significance after Bonferroni correction: $P < 0.0125$). AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease.

Table 2. *COL29A1* haplotype frequencies in AD, asthma and COPD patients and controls

Haplotype	Controls	AD	Asthma	COPD
TATG	59.3%	57.9% ($P = 0.57$)	56.1% ($P = 0.35$)	57.3% ($P = 0.49$)
CGCG	11.3%	10.1% ($P = 0.44$)	8.9% ($P = 0.26$)	9.1% ($P = 0.24$)
CATG	7.1%	8.1% ($P = 0.48$)	9.5% ($P = 0.20$)	7.9% ($P = 0.57$)
CACG	7.7%	7.6% ($P = 0.93$)	9.7% ($P = 0.32$)	8.5% ($P = 0.61$)
CGTG	4.8%	5.6% ($P = 0.47$)	7.0% ($P = 0.19$)	7.0% ($P = 0.13$)
Other infrequent	8.8%	9.8%	7.8%	8.5%

AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease.

2 years ($n = 292$), we did not find any significant result either. Further, Söderhäll *et al.* used family-based association tests while the present study followed a case-control design, comparing unrelated AD patients and controls. Thus, we were unable to evaluate the parent-of-origin effect (significant over-

transmission of the maternal alleles) observed by Söderhäll *et al.* at this locus. Another difference in study design is that we only genotyped four polymorphisms in the *COL29A1* instead of the complete replication data set used in the original study (comprising eight SNPs), and thus may have missed association

with one of the other SNPs in this gene. However, we chose the SNPs that showed highest significant association, and because they were in high linkage disequilibrium (LD) with the remaining four SNPs of this set, we feel confident that we have not missed substantial information with this approach. Taken together, we could not support the role of *COL29A1* as an AD gene in our German cohort. Further, we did not find evidence that the investigated polymorphisms may play a substantial role in the pathogenesis of COPD or asthma. Because both gene–gene and gene–environment interactions have been postulated as important factors in the pathogenesis of AD,⁶ integrating these mechanisms into genetic analysis in the future may contribute to a more profound insight into the role of *COL29A1* variation in AD.

Additional studies in large cohorts of patients with AD, COPD and asthma are needed to clarify the role of *COL29A1* variation for allergic and respiratory diseases.

ACKNOWLEDGMENTS

We thank Natascha Wirkus for technical assistance and the patients for participating in the study.

Monika HARAZIN,¹ Kumar PARWEZ,²
Elisabeth PETRASCH-PARWEZ,³ Joerg T. EPPLEN,¹
Umut ARINIR,^{1,4} Sabine HOFFJAN,¹
Susanne STEMMLER¹

¹Department of Human Genetics, Ruhr-University, Bochum, Germany,
²Private Medical Practice, Gladbeck, Germany, ³Department of Neuroanatomy
and Molecular Brain Research, Ruhr-University Bochum, Germany, and
⁴Department of Internal Medicine III, Pneumology, Allergology and Sleep
Medicine, University Hospital Bergmannsheil, Bochum, Germany

REFERENCES

- 1 Chien YH, Hwu WL, Chiang BL. The genetics of atopic dermatitis. *Clin Rev Allergy Immunol* 2007; **33**: 178–190.
- 2 Peroni DG, Piacentini GL, Bodini A, Rigotti E, Pigozzi R, Boner AL. Prevalence and risk factors for atopic dermatitis in preschool children. *Br J Dermatol* 2008; **158**: 539–543.
- 3 Wuthrich B, Cozzio A, Roll A, Senti G, Kundig T, Schmid-Grendelmeier P. Atopic eczema: genetics or environment? *Ann Agric Environ Med* 2007; **14**: 195–201.
- 4 Lee YA, Wahn U, Kehrt R *et al.* A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat Genet* 2000; **26**: 470–473.
- 5 Söderhäll C, Marenholz I, Kerscher T *et al.* Variants in a novel epidermal collagen gene (*COL29A1*) are associated with atopic dermatitis. *PLoS Biol* 2007; **5**: e242.
- 6 Vercelli D. Advances in asthma and allergy genetics in 2007. *J Allergy Clin Immunol* 2008; **122**: 267–271.