

LETTER TO THE EDITOR

Association of distinct IL-31 polymorphisms with pruritus and severity of atopic dermatitis

Editor

Interleukin-31 (IL-31) is a recently discovered four-helix bundle cytokine expressed in low abundance in a wide variety of human tissues.^{1,2} The activated CD4 + CD45RO + CLA + T cells have been IL-31's main source.³ IL-31 acts through a heterodimeric receptor composed of IL-31 receptor α (IL-31RA) and oncostatin M receptor β (OSMR) coexpressed on keratinocytes and activated monocytes.^{1,4,5} IL-31 interacts with Janus tyrosine kinase (JAK), which results in activation of numerous signal transduction pathways, including STAT (Signal transducers and activators of transcription), MAPK (mitogen-activated protein kinase), PI-3K/AKT (phosphatidylinositol 3-kinase/AKT) and p38 mitogen-activated protein kinases.⁴

There have been very few reports demonstrating the correlation between the genetic polymorphisms of IL-31 and atopic dermatitis (AD).^{6–8} The aim of the study was to compare the frequency of IL-31 –2057G/A, –1066G/A, IVS 2 + 12A/G gene polymor-

phisms and to demonstrate their relation to the IL-31 serum level, degree of pruritus and AD severity.

Sixty patients with AD (age range: 13–56 years; mean age 26.4 ± 11.38) without history of immunosuppressive treatment or immunotherapy and 59 healthy controls (age range: 18–52 years; mean age 27.8 ± 7.58) without any allergic diseases were included in this study. Assessment of severity of pruritus was performed using Visual Analogue Scale (VAS; 0–3, mild; >3–7, moderate; >7–9, severe; >9, very severe pruritus) and severity of AD using SCORAD index: severe (>60, $n = 22$), moderate (25–60, $n = 34$) and mild (<25, $n = 4$).

The variants gene polymorphisms were analysed using amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) method. Serum IL-31 levels were measured using ELISA standard kits (Bender MedSystems GmbH, Vienna, Austria). The results were evaluated by the Pearson's chi-squared test, Student's *t*-test, the Mann–Whitney *U* test, logistic regression model (OR) and the Spearman's rank correlation.

The frequency of the GA genotype for the IL-31 –2057 was higher in AD than those in controls (66.67% vs. 47.46%) and was linked to a slightly increased risk of AD development (OR = 2.21; $P = 0.034$). The same was with AA genotype for the –1066

Table 1 Genotype and allele frequencies of IL-31 –2057G/A, –1066G/A, IVS2 + 12A/G gene polymorphism in atopic dermatitis (AD) patients and healthy control group

IL-31 gene polymorphism	Genotype and allele frequencies	AD <i>N</i> = 60 (%)	Control <i>N</i> = 59 (%)	<i>P</i> -value	Odds ratio (OR)	<i>P</i> -value
–2057G/A <i>P</i> = 0.04*	GG	20 (33.33)	28 (47.46)	NS	NS	NS
	GA	40 (66.67)	28 (47.46)	0.03	2.21	0.034
	AA	0	3 (5.08)	0.08	NS	NS
	G	80 (66.67)	84 (71.2)	NS	NS	NS
	A	40 (33.33)	34 (28.8)			
–1066G/A <i>P</i> = 0.0025*	GG	11 (18.33)	25 (42.37)	0.004	0.30	0.004
	GA	27 (45.00)	26 (44.07)	NS	NS	NS
	AA	22 (36.67)	8 (13.56)	0.004	3.69	0.003
	G	49 (40.83)	76 (64.41)	NS	NS	NS
	A	71 (59.17)	42 (35.59)	0.0003	3.28	0.004
IVS2 + 12A/G <i>P</i> = 0.78**	AA	17 (28.33)	15 (25.42)	NS	NS	NS
	AG	41 (68.33)	43 (72.88)			
	GG	2 (3.33)	1 (1.69)			
	A	75 (62.5)	73 (61.9)	NS	NS	NS
	G	45 (37.5)	45 (38.1)			

P-value < 0.05 - statistically significant

*Pearson's chi-squared test from 2 × 3 contingency tables for genotype and 2 × 2 contingency tables for allele

**inconsistent with the HWD

NS = not significant.

Table 2 Genotype frequencies of distinct IL-31 gene polymorphisms and their relationships to pruritus, severity of AD (SCORAD), as well as to serum IL-31 concentrations

IL-31 gene polymorphism	Genotype frequencies	AD IL31 pg/mL mean $\pm$ SD	Controls IL31 pg/mL mean $\pm$ SD	P-value	Itch 0–10 scale mean $\pm$ SD	P-value	SCORAD mean $\pm$ sd	P-value
–2057G/A	GG	2.81 $\pm$ 1.63	0.031 $\pm$ 0.2	0.00001	3.80 $\pm$ 2.76	0.003	42.37 $\pm$ 19.19	0.004
	GA	3.99 $\pm$ 3.15	0.41 $\pm$ 0.98	0.00001	5.32 $\pm$ 2.43		56.45 $\pm$ 15.78	
	AA	–	–	–	–		–	
–1066G/A	GG	4.42 $\pm$ 2.45	0.12 $\pm$ 0.5	0.00001	4.18 $\pm$ 2.93	NS	50.35 $\pm$ 22.15	NS
	GA	3.70 $\pm$ 3.54	0.36 $\pm$ 0.91	0.00001	5.22 $\pm$ 2.58		55.18 $\pm$ 16.70	
	AA	3.07 $\pm$ 1.65	0	0.0001	4.64 $\pm$ 2.57		48.26 $\pm$ 17.71	
IVS2 + 12A/G	AA	5.23 $\pm$ 3.77	0.24 $\pm$ 0.72	0.00001	5.12 $\pm$ 2.74	NS	58.25 $\pm$ 19.33	0.03
	AG	2.94 $\pm$ 1.96	0.20 $\pm$ 0.72	0.00001	4.51 $\pm$ 2.50		48.28 $\pm$ 16.57	
	GG	3.36 $\pm$ 3.49	0	NS	8.50 $\pm$ 2.12		67.90 $\pm$ 25.60	

P-value < 0.05 - statistically significant.

(36.67% AD vs. 13.56% controls; OR = 3.69; P = 0.003) and allele A (OR = 3.28; P = 0.004) (Table 1).

The genotypes of studied variants were associated with moderate AD severity. A statistically significant correlation between moderate pruritus and genotype GG (3.80 $\pm$ 2.76) and GA (5.32 $\pm$ 2.43) –2057G/A (P = 0.003) was found (Table 2). The mean IL-31 levels in healthy controls sera were stated as 0.21 $\pm$ 0.71 pg/mL (range: 0–4.1) and in the patients group 3.6 $\pm$ 2.78 pg/mL (range: 0–18.19) (P < 0.00001). VAS >7 was associated with severe AD (P = 0.000007) and the mean serum concentrations of IL-31 were significantly higher in severe AD (4.71 $\pm$ 3.70) vs. SCORAD <60 (2.96 $\pm$ 1.85) (P = 0.04; OR = 1.34; P = 0.01); however, no positive correlation was found between IL-31 and severity of pruritus (P = 0.38).

The pathophysiological mechanism and genetic susceptibility of AD are still insufficiently understood. Sonkoly *et al.*² confirmed that IL-31 mRNA is significantly upregulated in skin of patients with pruritic dermatoses but not with non-pruritic forms of chronic inflammation. Ezzat *et al.*⁹ demonstrated positive correlation between IL-31 serum levels and the AD severity in children. Schulz *et al.*⁶ showed the association of specific haplotype A of IL-31 gene with non-atopic eczema. However, Hong *et al.*⁷ have found that two IL-31 SNPs were not associated with development of extrinsic AD suggesting that only the non-atopic eczema is associated with different IL-31 SNPs. Lan *et al.*⁸ revealed specific allele of IL-31 gene associated with increased risk of development of atopic eczema, but not of non-atopic hand dermatitis.

In conclusion, we hypothesize that an altered regulation of IL-31 gene expression influence clinical course of AD. The available published data and our results lend support to an important role of IL-31 gene polymorphism in AD pathogenesis; however, further investigation on the subject is required.

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