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THE GENETIC ASSOCIATION OF THE *FPRL1* PROMOTER POLYMORPHISM WITH CHRONIC URTICARIA IN A KOREAN POPULATION

Chronic urticaria (CU) is a common immunologic disorder in the general population, but its pathogenic mechanisms are not fully understood. In general, mast cell activation has been considered to play a central role in CU.¹ A recent study² of urticaria suggested that neutrophil infiltration has a key role in its pathogenesis. Increased numbers of neutrophils were found in skin tissue from patients with chronic idiopathic urticaria.³ Moreover, the role of neutrophils has been suggested for other types of urticaria, including cholinergic⁴ and aspirin-intolerant urticaria.⁵

Formyl peptide receptor-like 1 (FPRL1) is a chemoattractant receptor and is mainly expressed on neutrophils, monocytes, and dendritic cells. FPRL1 plays an important role in the regulation of immune responses by the increasing migration of neutrophils and monocytes with the generation of reactive oxygen species.⁶ However, there have been no published reports, to our knowledge, regarding the relation between the *FPRL1* and CU. We hypothesized that the functional variability according to *FPRL1* gene polymorphisms may be associated with CU.

To investigate the genetic association of the *FPRL1* promoter polymorphism with CU, 193 patients with CU and 231 controls were enrolled from Ajou University Hospital, Suwon, Korea; they pro-

vided informed consent, and the study protocol was approved by the institutional review board of Ajou University Hospital. All the patients and controls belonged to the same ethnic group. Patients with CU were defined as having daily itchy wheals for more than 6 weeks. Controls with no personal or family history of allergic disease were recruited. Atopy was defined as 1 or more positive skin prick test reactions to 55 common aeroallergens (Bencard Co, West Sussex, United Kingdom). The total serum IgE level was measured using the UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden). Genomic DNA was extracted using the Puregene DNA Purification Kit (Gentra, Minneapolis, Minnesota). Three single nucleotide polymorphisms of the *FPRL1* gene (-6138C>T, -6136G>T, and -5840G>T) were genotyped using the SNaPshot Primer Extension kit (Applied Biosystems, Foster City, California). The sequences of the amplifying and extension primers were as follows: for *FPRL1*-61318C>T: forward, 5'-CAGGAAACAGCTATGACC-3'; reverse,

Table 1. Genotype and Haplotype Frequencies of *FPRL1* Genetic Polymorphisms^a

	Patients With Chronic Urticaria (n=193)	Controls (n=231)	P value
-6138C>T			
CC	142 (73.6)	155 (67.1)	.19
CT	48 (24.9)	69 (29.9)	.46
TT	3 (1.6)	7 (3.0)	.22
-6136G>T			
GG	89 (46.1)	126 (54.5)	.02 ^b
GT	73 (37.8)	89 (38.5)	.008 ^b
TT	31 (16.1)	16 (6.9)	.13
-5840G>T			
GG	68 (35.2)	65 (28.1)	.21
GT	92 (47.7)	117 (50.6)	.46
TT	33 (17.1)	49 (21.2)	.20
ht1[CGT]			
ht1/ht1	11 (5.7)	18 (7.8)	.35
ht1/-	96 (49.7)	121 (52.4)	.48
-/-	86 (44.6)	92 (39.8)	.39
ht2[CGG]			
ht2/ht2	16 (8.3)	15 (6.5)	.61
ht2/-	62 (32.1)	72 (31.2)	.60
-/-	115 (59.6)	144 (62.3)	.80
ht3[CTG]			
ht3/ht3	15 (7.8)	16 (6.9)	.19
ht3/-	87 (45.1)	86 (37.2)	.11
-/-	91 (47.2)	129 (55.8)	.88
ht4[TGT]			
ht4/ht4	3 (1.6)	6 (2.6)	.02 ^b
ht4/-	17 (8.8)	43 (18.6)	.01 ^b
-/-	173 (89.6)	182 (78.8)	.63
ht5[TGG]			
ht5/ht5			.28
ht5/-	16 (8.3)	27 (11.7)	.28
-/-	177 (91.7)	204 (88.3)	NA

Abbreviation: NA, not applicable.

^a Logistic regression analysis was used to analyze the single nucleotide polymorphisms and haplotypes controlling for age and sex as covariates with 3 alternative models, including codominant, dominant, and recessive model.

^b Statistically significant.

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5'-TGTAACGACGGCCAGT-3'; and extension, 5'-CCTGCGT-CAGCCTCCCGAG-3'; for *FPRL1*-1636G>T: forward, 5'-CAG-GAAACAGCTATGACC-3'; reverse, 5'-TGTAACGACGGC-CAGT-3'; and extension, 5'-GGCACGTGCCTGTAATCCAG-3'; and for *FPRL1*-5840G>T: forward, 5'-CAGGAAACAGCTAT-GACC-3'; reverse, 5'-TGTAACGACGGCCAGT-3'; and extension, 5'-AACATTCTGCCTGACAGGACCATG-3'. Differences in genotype frequency between the CU and control groups were assessed using the χ^2 test. Five haplotypes of the *FPRL1* promoter polymorphism were constructed by using Haploview v4.0 (<http://www.broadinstitute.org/mpg/haploview>). The neutrophil chemotaxis assay was performed using peripheral blood from 17 healthy volunteers according to a previously reported method.⁷ *N*-formyl-Met-Leu-Phe (fMLP) (Sigma-Aldrich Corp, St Louis, Missouri) was used as a chemoattractant.

Patients with CU were older than controls (mean age, 39.6 vs 33.5 years; $P<.001$), but the sex distribution was not different between them (46.1% men with CU and 42.9% male controls). Compared with controls, the CU group had a higher rate of atopy (49.38% vs 11.48%, $P<.001$) and a higher mean serum total IgE level (198.95 vs 94.62 IU/mL, $P=.01$). The *FPRL1* promoter polymorphism was significantly associated with the CU phenotype; the homozygous GG genotype of the *FPRL1*-6136G>T polymorphism was significantly lower in the CU group than in the control group ($P=0.008$ in dominant analysis model) (Table 1). Among 5 haplotypes, the frequency of ht4[TGT] was significantly lower in the CU group than in the control group ($P=.01$) (Table 1). Moreover, the 4 patients with ht4[TGT] showed significantly lower neutrophil chemotactic activity (24.4%) after fMLP stimulation compared with that of the 13 patients having other haplotypes (45.8%, $P=.04$) (data not shown).

Mononuclear cells, mast cells, and neutrophils have been found to participate in chronic inflammation at urticaria sites of patients with CU.^{2,3} *FPRL1* regulates leukocyte infiltration into the inflammatory sites. Based on the lower frequency of the ht4[TGT] with lowered neutrophil migration under fMLP stimulation, we suggest that the genetic variability of the *FPRL1* gene may be involved in neutrophil

migration, affecting recruitment and activation of the other inflammatory cells in patients with CU.

These results suggest that the *FPRL1* gene polymorphism may contribute to CU by modulating neutrophil migration into the inflammatory site of the skin. The *FPRL1* might be activated by exogenous and host-derived agonists, and it possibly contributes to some of the autoimmune expression of CU by inducing the release of proinflammatory mediators. Further in vitro and in vivo functional studies are needed to clarify the cellular mechanisms in patients with various kinds of CU.

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Erratum

In the article "Passive and active smoking and exhaled nitric oxide levels according to asthma and atopy in adults" by Nadif et al (*Ann Allergy Asthma Immunol*. *Ann Allergy Asthma*

Immunol. 2010;104:385-393), the values listed as "All" for "No Asthma" and the values listed as "All" for "Asthma" were transposed in Table 2. The corrected table is printed here.