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FCER1A gene exon 1A polymorphisms in Japanese and Polish subjects – a comparative analysis of haplotypes

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Key words: (genetic) linkage; (genetic) polymorphism; *FCER1A*; haplotype.

Polymorphisms of the gene encoding α-subunit of the high-affinity IgE receptor (*FCER1A*) were suggested to be involved in the pathogenesis of allergic disorders (1–5). *FCER1A*, which was previously thought to consist in five exons preceded by one regulatory region, recently turned out to have two additional untranslated exons (Ex1A and Ex2A) and a distal regulatory region localized upstream (6). Finding of these additional gene regions was the rationale for mutation screening in search for functional variants (3, 4). The distal promoter turned out to have a conserved sequence in Koreans (3) and Poles (4), whereas two frequent polymorphisms, −18674–18675AAins > del (rs10557633) and −18483A > C (rs2494262), were discovered in Ex1A in Polish subjects (4, 5). Although it is still matter of controversies, recent studies on *FCER1A* proximal promoter variants suggested significant differences in their distribution and linkage between caucasians and Asians (2–4). Therefore, we investigated allelic frequencies, haplotypes and genetic linkage measures of the novel Ex1A polymorphisms in Japanese and compared them with those recalculated in Poles (4).

Comparison of *FCER1A* exon 1A polymorphisms between Asians and Caucasians can help in revealing their functional role.

The presence of −18674–18675AAins > del and −18483A > C polymorphisms in Japanese was confirmed by direct sequencing of 32 subjects (Applied Biosystems, Foster City, CA, USA). In brief, 5′-ACAGCAAGACAAGCATGAAGAAAT-3′ and 5′-TGCAGTATTAGTTTCTACACTCCAACA-3′ primers were used to amplify Ex1A region. Then, a bidirectional sequencing was conducted using 5′-CCAATCAAATACTGAACCATACAGG-3′ or 5′-TGAAAACATCTCCTTCATCAGC-3′ primers. Genotypes of −18674–18675AAins > del and −18483A > C polymorphisms were ascertained using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods described previously (4). The only difference was, that *Nsp*I isoschizomer (New England Biolabs, Ipswich, MA, USA) was used instead of *Xce*I restrictase for −18483A > C polymorphism genotyping in studied Japanese subjects. Measures of linkage between the two polymorphisms were estimated using HAPLOVIEW_4.0 (http://www.broad.mit.edu/mpg/haploview/download.php; accessed 21 February 2008), while haplotype analysis was performed with THESIAS_3.1 (http://genecanvas.ecgene.net/uploads/Thesias_Java_interface/; accessed 21 February 2008). Calculation of linkage measures and haplotype prediction were performed in 234 Japanese and 368 Poles, whereas population allelic and haplotype frequencies were estimated in 142 Tokyo Metropolis inhabitants and 154 city of Cracow citizens, representative for Japanese and Polish populations. All Japanese subjects were previously genotyped for −344C > T polymorphism (rs2427827), whereas 308 Poles were previously genotyped for all three polymorphisms (2, 4) and additional 60 Poles for −344C > T variant only.

Frequencies of minor −18674–18675AAdel, −18483C and −344T alleles in Japanese population were 0.095, 0.306 and 0.225 being considerably lower than previously reported in Polish population (0.169, 0.425 and 0.412) (4). Even more strikingly, substantial inter-population differences were observed in genetic linkage analysis of haplotypes (Table 1). A weaker linkage between −18483A > C and −344C > T in Japanese, as evidenced by lower Lewontin's diversity index value (D'), probably resulted from a higher number of recombination events in the past because the fraction of recombinant −18483A|−344T haplotype was elevated. Moreover, the concordance between those two polymorphisms was also lower in Japanese, with a decreased pseudo-correlation r^2 coefficient reflecting not only a higher recombination rate but also a greater difference between −18483C and −344T frequencies in that population. All these corresponded to much higher ratio of −18483C|−344C haplotypes in Japanese as compared with Poles. In the consequence, frequency of subjects carrying −18483C allele but not −344T one was higher in Asians. It could be expected, that a clinical study aiming dissection functional effects of −344C > T and −18483A > C polymorphisms would be much easier in Asians, but not feasible in caucasians because of substantial genetic linkage and concordance between the two variants (4, 5). Also

Table 1. Exon 1A common polymorphisms of *FCER1A* gene (−18674–18675AA ins > del, −18483A > C), and their relation to the functional −344 C > T variant of the proximal promoter among Japanese and Polish subjects

A

Haplotype −18674–18675AA | −18483 | −344*	Japanese population (%), (n = 142)†	Polish population (%), (n = 154)†‡
ins | A | C	0.662	0.565
ins | A | T	0.032	0.010
ins | C | C	0.018	0.019
ins | C | T	0.193	0.237
del | C | C	0.095	0.004
del | C | T	0.000	0.165
del | A | C	0.000	0.000
del | A | T	0.000	0.000
Total	1.000	1.000

B

	Japanese subjects, (n = 234)*		Polish subjects, (n = 368)*	
Pairwise linkage*	D'	r^2	D'	r^2
−18674–18675 AA ins > del | −18483 A > C	1.0	0.263	1.0	0.228
−18674–18675 AA ins > del | −344 C > T	1.0	0.025	0.958	0.221
−18483 A > C | −344 C > T	0.786	0.403	0.959	0.87

Predicted haplotypes and their frequencies are in panel A, pairwise genetic linkage and concordance measurements are in panel B.
D', Lewontin's index of diversity; r^2, pseudo-correlation coefficient.
*Haplotypes prediction and pairwise linkage measures (D', r^2) were estimated in 234 Japanese and 368 Polish subjects.
†Frequencies of predicted haplotypes were assessed in 142 Tokyo Metropolis citizens (representative Japanese population) and in 154 city of Cracow inhabitants (representative for Polish population).
‡The population frequencies in Poles were recalculated form those reported previously (4).

−18674–18675AAins > del polymorphism demonstrated ethnic-dependent differences between Japanese and Poles. Linkage measurements between the two distal promoter polymorphisms, and between each of them and the proximal −344C > T were very high in both population. It seems peculiar, however, that paired haplotypes of these polymorphisms are totally different between Japanese and Poles because −18674–18675AAdel allele is almost always linked to −344T in Poles but never in Japanese.

It can be expected that association studies on Asians should be much easier to show the actual role of −18674–18675AAins > del and −18483A > C polymorphisms because of altered haplotype structure within this population. However, functional studies will be necessary to eventually elucidate the role of Ex1A polymorphisms.

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