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Additive association between *FCER1A* and *FCER1B* genetic polymorphisms and total serum IgE levels

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Key words: *FCER1A; FCER1B;* genetic polymorphism; IgE; IgE receptor.

FCER1A and _FCER1B_ polymorphisms showed an additive association with total serum IgE in allergic patients.

FCER1A and *FCER1B* are the genes encoding subunits of the high-affinity IgE receptor. Recently, our group (1) and Bae et al. (2) reported on higher total serum IgE levels in allergic patients having genotypes TT or TT/CT of the functional *FCER1A* −344C > T promoter polymorphism. The initial observation was replicated by using an extended group of allergic subjects (3), and additional two frequent *FCER1A* polymorphisms were located in novel untranslated *FCER1A* exon 1A (3, 4). One of them (−18483A > C) tended to be associated with higher serum IgE levels in the nonhomogenous group of allergic subjects, and its CC genotype demonstrated a highly significant association in the subgroup of asthmatics (3). Being located within the same genetic locus, interestingly, −344C > T and −18483A > C had very similar frequencies and were in close but not complete linkage disequilibrium.

Previous reports highlighted *FCER1B* genetic variants (Glu237Gly and −109T > C) to be associated with total serum IgE concentrations in allergic subjects (5, 6). The missense mutation Glu237Gly, however, was found to be rare in Caucasians (5). The association between *FCER1B* gene promoter −109T > C transition and total serum IgE, to the best of our knowledge, has not been studied outside Asia (6).

We completed genotyping of the functional *FCER1B* −109T > C promoter polymorphism in 154 allergic subjects, comprising 88 asthmatics, 50 urticaria patients, five persistent allergic rhinitis patients and 11 subjects with pollinosis (75% atopics) and the same number of age- (mean ± SEM, 40.4 ± 1.1 years *vs* 40.2 ± 1.1 years) and sex-matched (M : F, 48 : 106; both groups) population-based controls, previously genotyped by us for *FCER1A* polymorphisms (1, 3). Total serum IgE levels significantly differed between the groups (median ± IQR, 122 ± 265.5 IU/ml *vs* 30.5 ± 78.2 IU/ml; $P < 0.001$) (3). *FCER1B* −109T > C polymorphism was genotyped using the PCR-RFLP method described by Hizawa et al. (6), using an isoschizomer *Tru*1I (Fermentas, Vilnius, Lithuania) instead of *Tru*9I restrictase.

Table 1. Association between *FCER1A & FCER1B* polymorphisms and total serum IgE levels

	Allergic subjects			Age- and sex-matched controls		
	Log IgE*	SEM	*n*	Log IgE*	SEM	*n*
Genotypes of *FCER1B* −109T > C promoter polymorphism			154			154
TT	2.21†	0.07	57	1.40	0.08	57
TC	1.96	0.07	72	1.62	0.07	70
CC	2.00	0.14	25	1.49	0.12	27
Compound genotype groups of *FCER1A* −344C > T|−18483A > C & *FCER1B* −109T > C polymorphisms			148‡			150‡
−344TT|−18483CC & −109TT	2.45§	0.11	12	1.12	0.13	9
−344CT/CC|−18483AC/AA & −109TT	2.16	0.08	44	1.44	0.09	46
−344TT|−18483CC & −109TC/CC	2.21	0.14	20	1.58	0.12	18
−344CT/CC|−18483AC/AA & −109TC/CC	1.91	0.07	72	1.58	0.07	77

*Log IgE' denotes total serum IgE levels transformed using base 10 logarithm.

†$P = 0.045$ for comparison between −109TT, −109TC and −109CC genotypes (one-way ANOVA); $P = 0.01$ for comparison between −109TT and −109TC/CC genotypes (unpaired Student's *t* test)

‡Due to not complete linkage between −344C > T and −18483A > C polymorphisms (3) a few individuals with other diplotypes of *FCER1A* gene were excluded from analysis.

§$P = 0.005$ for contrasting *FCER1B* −109TT and −109TC/CC genotypes with compound *FCER1A* −344TT|−18483CC and −344CT/CC|−18483AC/AA groups (one-way ANOVA); $P = 0.02$ *post hoc* test of *FCER1B* −109TT & *FCER1A* −344TT|−18483CC *vs FCER1B* −109TC/CC & *FCER1A* −344CT/CC|−18483AC/AA genotype groups (Bonferroni test).

Genotypes of *FCER1B* −109T > C polymorphism were in Hardy–Weinberg equilibrium in both groups and did not differ between patients and controls ($P = 0.95$, χ^2 test) (Table 1). Total serum IgE levels were log-transformed before the comparisons. In allergic patients, one-way ANOVA contrast of IgE levels using −109T > C genotypes (TT, TC and CC) was significant ($P = 0.045$) (Table 1). Difference in IgE levels between variant homozygotes and heterozygotes or wild-type genotypes (−109CC *vs* −109TC/TT) was not significant ($P = 0.57$), whereas under dominant model subjects carrying the variant allele had lower IgE than those with wild type genotype (−109TC/CC *vs* −109TT) ($P = 0.01$) (unpaired Student's *t* test). These results directly replicated findings by Hizawa et al. (6). Thus, similarly to the previous report, we used *FCER1B* −109TT homozygotes (high IgE genotype) as a reference for further analyses. *FCER1A* genotypes were grouped as previously described (1, 3). A further stratification of *FCER1B* −109TT (high IgE) and −109TC/CC (low IgE) genotypes on *FCER1A* compound genotypes (diplotypes) −344TT|−18483CC (high IgE) and −344CT/CC|−18483AC/AA (low IgE) resulted in significant differences ($P = 0.005$; one-way ANOVA) (Table 1). *Post hoc* tests were significant for the contrast of allergic subjects with *FCER1B* −109TT & *FCER1A* −344TT|−18483CC (the highest IgE) *vs* *FCER1B* −109TC/CC & *FCER1A* −344CT/CC|−18483AC/AA genotype group (the lowest IgE) ($P = 0.02$; Bonferroni test) (Table 1). However, factorial ANOVA contrasting *FCER1B* −109TT and −109TC/CC genotypes with *FCER1A* −344TT|−18483CC and −344CT/CC|−18483AC/AA diplotypes revealed no multiplicative genetic interaction ($P = 0.98$). Thus, our results show that *FCER1A* −344C > T|−18483A > C and *FCER1B* −109T > C polymorphisms are related to total serum IgE levels in allergic patients in additive, rather than multiplicative, manner. Similar statistical inferences based on the control group data gave no significant results. However, *FCER1B* −109TT controls tended to have higher serum IgE levels than subjects carrying the variant −109C allele ($P = 0.08$; unpaired Student's *t* test).

The interaction between *FCER1A* and *FCER1B* genes mutations was not studied before. To our knowledge, this is also the first report associating total serum IgE levels with *FCER1B* −109T > C polymorphism in Caucasians.

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Two cases of occupational rhinitis caused by biodiastase in hospital and pharmaceutical workers

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Key words: biodiastase; fungal amylase; occupational rhinitis; specific IgE.

The first report to detect serum-specific IgE-binding components caused by biodiastase.

Biodiastase, composed of fungal α-amylase, has been commonly prescribed as a digestive enzyme in this country; however, *Aspergillus oryzae*-derived α-amylase can induce IgE-mediated occupational asthma in bakery workers or those involved in the pharmaceutical industry (1–3). This is the first investigation of IgE-binding components and the first report of specific serum IgE-binding components as well as serum-specific IgE and IgG4 antibodies to biodiastase in an exposed worker with occupational rhinitis (4).

We studied two workers with occupational rhinitis: one a university hospital nurse who had dispensed biodiastase to admitted patients for 4 years, and the other a pharmaceutical company employee who had been involved in the preparation of biodiastase powder for 11 years. To evaluate their IgE responses, we performed a skin prick test (SPT) in both workers, which generated strongly positive responses to biodiastase (6+ and 3+, ratio of allergen and histamine wheal, respectively). Biodiastase extracts collected from their workplaces and fungal α-amylase (Sigma, St Louis, MO, USA) were prepared in our laboratory according to a previously described method (5) and used to detect serum-