

Letter to the editor

FCER1A genetic variability and serum IgE levels

We read with keen interest a very recent study by Chen et al. (1), which further expands on the recent findings by Weidinger et al. (2) who reported on the results of large genome-wide scan that demonstrated IgE receptor (FcεRI) α-chain (FcεRIα) gene (*FCER1A*) variability to be a major marker of serum IgE levels in population. Chen et al. (1) successfully showed an association between *FCER1A* variants and serum IgE levels present in cord blood/small children to be independent of environmental stimuli, which seems to be an important genetic input on our understanding of multi-factorial etiology of allergic disorders. We would like to congratulate the authors of both the above very analytically powerful studies (1, 2) for scientific and statistical power as well as for elegance and excellence of their work.

The large and powerful trials by Weidinger et al. (2) and Chen et al. (1) demonstrated two common variants *FCER1A* rs2427837 and rs2251746 to be strongly associated with serum IgE levels in general and paediatric populations. While direct evidence for strong functional activity of rs2251746 *FCER1A* proximal promoter polymorphism was previously demon-

strated (3, 4), showing it to be a potent regulator of *FCER1A*/FcεRIα expression in mast cells and/or basophils, no such data were yet provided for rs2427837 variant. Therefore, an association between rs2427837 polymorphism and IgE levels (1, 2) might possibly result from its almost complete linkage disequilibrium (1, 2) with functional (3, 4) rs2251746 variant. One might also cautiously speculate that some more functional *FCER1A* variants could by their haplotypic relationships/interplay with rs2251746 polymorphism, at least in small part, functionally contribute to the association with serum IgE levels observed for rs2251746 variant in population (1, 2). For example, rs2427827 polymorphism, close neighbour of rs2251746 variant in *FCER1A* proximal promoter, was also demonstrated to affect *FCER1A* transcriptional activity/FcεRIα expression in mast cells and/or basophils (4, 5) in an additive manner with rs2251746 polymorphism (4).

While the regulatory mechanism by which (serum) IgE upregulates cell surface FcεRI expression is well known (6), no direct evidence for the causal role of FcεRI(α), *FCER1A* or *FCER1A* genetic variants in regulation of IgE synthesis and/

or levels was yet provided. Therefore, it might be only speculated that any alterations in FcεRI expression, including also those genotype-related, might affect IgE synthesis and/or levels. Thus, previous results showing how *FCER1A* proximal promoter polymorphisms regulate FcεRI(α) expression in mast cells and/or basophils (3–5) might provide only a partial mechanistic background for previously observed *FCER1A* genetic variants-serum IgE levels genotype-phenotype associations (1, 2, 5). Further functional studies focused on the analysis evaluating the putative effects of (genotype-related) alterations in FcεRI expression level on IgE production/levels seem to be required to reveal the underlying mechanism(s).

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