The candidate gene approach in asthma: what happens with the neighbours?

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In the last few decades, multiple genes important in asthma and atopy development have been identified. A successful approach has been to investigate candidate genes, that is, genes with a biologically plausible function.[1] This approach has also been applied by Zhu *et al*[2] in a previous issue of this journal. They analysed *IL18R1*, an interesting candidate gene for asthma and atopy, and provided replicated evidence in three European populations that SNPs located in *IL18R1* were associated with asthma.[2] Specifically, SNP rs1420099, rs1362348, and rs1974657 were associated with asthma in these three populations.

IL-18 receptor is a key immunoregulator; the gene product of *IL18R1* forms the alpha chain of the IL-18 receptor.[3] Binding of IL-18 to the IL-18 receptor can stimulate Th1 as well as Th2 cytokine release.[4] These findings may indeed point towards a role of IL18R1 in the pathophysiology of asthma.[2] *IL18R1* is localized in the IL1 receptor cluster on chromosome 2q12. In its close vicinity reside *IL1R2*, *IL1RL*, *IL1RL2*, *IL1RL1*, and *IL18RAP*. We have recently undertaken a candidate gene approach analysing genes located in a region of strong linkage disequilibrium (LD) in this gene cluster, that is, *IL18R1*, as well as *IL1RL1* and *IL18RAP*, in two Dutch asthma and one Dutch rhinitis cohort.[5] We reported replicated evidence for association of SNPs in this gene cluster with asthma phenotypes in our two Dutch asthma populations. For *IL18R1*, four SNPs were associated with asthma and bronchial hyperresponsiveness in a combined analysis of the two asthma cohorts ($P<0.05$); these SNPs, that is, rs12999364, rs1558627, rs2270297, and rs1035130, were not genotyped by Zhu *et al*. Furthermore, we found significant associations with SNPs in *IL1RL1* and *IL18RAP*. A haplotype from SNPs in *IL1RL1* and *IL18R1* was significantly associated with bronchial hyperresponsiveness. Strong LD was detected between SNPs in the three genes in this region.

IL1RL1 encodes the receptor for IL-33, which is located on mast cells, Th2 cells, regulatory T cells, and macrophages, and is also present in serum in a soluble form.[6–8] IL1RL1 is a member of the Toll-like receptor superfamily and can either stimulate or inhibit Th2 responses by influencing TLR pathway signalling.[9–12] There is increasing evidence that this gene is important in atopic diseases such as eczema and asthma; interestingly, a recent large genome-wide association study also indicated *IL1RL1* to be important in asthma, and thus *IL1RL1* is also a plausible candidate gene for asthma.[5,13,14]

In their paper, Zhu *et al* mentioned the limitation of not analysing SNPs located in *IL18R2* (also known as *IL18RAP*). SNPs in *IL1RL1* and *IL18RAP*, next to *IL18R1*, may also contribute to the genetic association signal on chromosome 2q12. We suggest that genetic association studies in regions with strong LD may not be conclusive as to which gene or genes are causal in disease development. It would therefore be of interest to investigate also *IL1RL1* and *IL18RAP* in the populations described by Zhu *et al*. Moreover, we suggest the investigation of this region in populations with different LD characteristics and to perform functional studies. Our observations imply that, once positive genetic associations are identified, it is worthwhile to take a look at the neighbouring genes.

Naomi E Reijmerink[1,2], Dirkje S Postma[1] and Gerard H Koppelman[3]
[1]*Department of Pulmonology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;*
[2]*Department of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;*
[3]*Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
E-mail: g.h.koppelman@bkk.umcg.nl

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Reply to Reijmerink *et al*

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We appreciate the comments from Reijmerink *et al* on our IL18R1 genetic association results published in the *European Journal of Human Genetics*.[1] As we had pointed out in the paper, ours was a