

Tim 1: a novel asthma susceptibility gene

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Atopy, which includes asthma, allergic rhinitis, and atopic dermatitis, is a complex trait that arises as a result of environmentally induced immune responses in genetically susceptible individuals. The prevalence of all atopic diseases has dramatically increased in industrialized countries over the past two decades. However, the relevant environmental and genetic factors that confer asthma susceptibility are poorly understood. Asthma susceptibility has been linked to chromosomes 5, 6, 11, 14, and 12. Of these, chromosome 5q23-35 has received the greatest attention, because it contains a large number of candidate genes.

To simplify the analysis of asthma susceptibility genes located at human 5q23-35, we examined congenic mice that differed at the homologous chromosomal segment. We identified a Mendelian trait that confers reduced T_H2 responsiveness and protects against AHR. Thus we defined *T cell and Airway Phenotype Regulator (Tapr)*, a locus genetically distinct from the IL-4 cytokine gene cluster, that controls the development of AHR and T cell production of IL-4 and IL-13. Within the region associated with *Tapr*, we positionally cloned a novel gene family encoding T cell membrane glycoproteins with conserved immunoglobulin variable domain (IgV) and mucin domains. We refer to protein products of these family members, which are expressed on T cells, as T cell, Immunoglobulin domain, and Mucin domain (TIM) proteins because of their predicted structure. The TIM family consists of eight TIM genes on mouse chromosome 11B1.1 and three TIM genes on the syntenic human chromosome 5q33.2. The three members of human TIM genes are most closely related to murine TIMs 1, 3 and 4.

We identified major polymorphisms in TIM-1 and TIM-3 that are strongly associated with T_H1 - T_H2 differentiation and the expression of AHR in our congenic mice. Significantly, the human homologue of TIM-1 is the cellular receptor for hepatitis A virus, HAVcr-1, and, therefore, our findings suggest that $CD4^+$ T cells and TIM-1 may mediate the known protective effect of prior infection with hepatitis A on the development of atopy. Since the prevalence of hepatitis A infection is greatly reduced in industrialized countries, our findings may explain in part the large increase in asthma prevalence over the past two decades in these countries.

References:

- McIntire J, et al. 2001. Identification of *Tapr* (an airway hyperreactivity regulatory locus) and the linked *Tim* gene family. *Nature Imm* 2:1109.
- Umetsu DT, et al. 2002. Asthma: an epidemic of dysregulated immunity. *Nature Imm*. 3:715

