Analysis of the Ser786Pro IL-4 Receptor Alpha Polymorphism: Structure/Function and Its Relationship to Asthma

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Asthma and other atopic disorders affect a large percentage of the population. While many factors contribute to the phenotype of asthma, there is a strong genetic predisposition. IL-4, a pleiotropic cytokine produced by Th2 cells and mast cells, is a central mediator of allergic inflammation. Along with IL-13, it is the major cytokine responsible for the induction of IgE synthesis. Furthermore, IL-4 acts on Th0 cells and promotes their differentiation into Th2 cells resulting in the production of more IL-4 and IL-13, thereby propagating the allergic cascade. IL-4 exerts its activities by interacting with a specific cell surface receptor comprised of a binding component, IL-4 receptor alpha (IL-4R?). and the common Gamma (?c) chain, which is shared by multiple cytokine receptors. Both IL-4 and IL-13 utilize IL-4R? as a component of their cognate receptor complexes. The central role of IL-4R? in both IL-4 and IL-13 signaling makes it an ideal candidate asthma gene. Six known polymorphisms of the IL-4R? have been described. and two of these polymorphisms have been linked to atopic asthma. The central objective of this study was to elucidate the role of the Ser786Pro polymorphism in asthma, and its impact on IL-4R function. 167 well characterized asthma patients and 45 controls were genotyped at this location. 'We found that Pro786 occurred infrequently in the general population with an allele frequency of 1.7%. The Pro786 allele frequency was 2% in the asthma group and 1.1% in the control group. The asthma group was subdivided into allergic and nonallergic asthma, and the Pro786 allele frequencies were 2.2% and 0.9%. respectively, suggesting an association of Pro786 with allergic asthma. While these values failed to be statistically significant due to the low frequency of Pro786 allele in our population, there was an enrichment of the Pro786 allele in the allergic asthma group. Furthermore. the data suggested linkage disequilibrium between Ser786Pro and the Gln576Arg allele, which is associated with atopy. Large population studies will be needed to determine the potential impact of Ser786Pro when it exists in combination with the other known polymorphisms. In order to study the impact of the polymorphism on receptor signaling function, we transfected a mouse B lymphonia line with the wild type and Pro786 variants of human IL-4R?. The Ser786Pro polymorphism in isolation did not affect IL-4R function. However, the Ser786Pro lymorphism in combination with other polymorphisms such as Gln576Arg may alter receptor function.