Atopic Asthma and Interleukin-4

Bernadette deGuzman, William Duck, Angela Myrick, Suzanne Proctor, Nupur Sashti, and Mary Beth Weber (Emory University School of Public Health, Dept. of Epidemiology)

Published June 2001

IL-4 Gene

The gene for Interleukin-4 (IL-4) is located on chromosome 5 at position q31. IL-4 is a cytokine secreted by TH-2 cells that stimulates the production of IgE and induces eosinophil-mediated attacks against helminthic infections and allergens.

Gene Variants

Of the five variants in the promoter region, four are rare. No association with atopy or asthma has been found for two of the four rare variants. The most common variant, C590T, has been associated with higher IgE levels in Japanese and U.S. populations. The prevalence varies in populations, with the T allele as common as 79% in Asian populations and as low as 18% in U.S. Caucasians. Overall, little is known about the prevalence of gene variants within various populations.

Disease Burden

Polymorphisms in the promoter and the intron 2 regions of the IL-4 gene have been associated with a variety of allergic conditions, including atopy, eczema, rhinitis and asthma (both atopic and nonatopic). Although published research addressing the role of IL-4 allelic variants in the former three conditions is substantial, fewer than ten epidemiologic studies have examined the link between IL-4 and asthma.

Promoter. A population-based case-control study of Japanese school children found that children with asthma were 2.5 times more likely as their nonasthmatic siblings and twice as likely as nonasthmatic population controls to carry at least one copy of the T allele. A Kuwait hospital-based study reported similar findings. A subsequent case-control study of Canadian infants at high risk for asthma found infants that were diagnosed with "probable asthma" at 12 months were 4.1 times more likely than their peer controls to carry the T promoter allele. Another Canadian study showed a significant link of the IL-4 590T allele to asthma severity. Notably, the source populations differed in this study, with cases selected from Australia, New Zealand, and Vancouver. Controls were drawn exclusively from study participants in Vancouver. One U.S. study significantly linked the TT genotype to reduced FEV1 in whites.

Intron 2. A case-control study in Tunisia reported a significant increase in prevalence of the A1/A3 genotype in people with asthma and further linked the A1 allele to a moderate to severe phenotype.

Gene-Gene Interactions

Because IL-4 carries out its biological effects through binding to the IL-4 receptor complex, interactions between IL-4 and IL-4R polymorphisms were investigated. Of the five receptor-site polymorphisms that have been linked to an altered gene product, only a few have been studied extensively. One study looking at the effect of IL-4, IL-4Rα, and FCERIB genes on asthma severity did not detect a significant interaction between IL-4*C590T and IL-4Rα*Q576R polymorphisms when looking at asthma severity. Future studies may include genes encoding cytokines or cytokine promoters (IL-4, IL-5, IL-13), genes encoding T cells, IgE, and cytokine receptors (IL-4R, JCR, and FcεRI1) and genes that influence bronchial responsiveness (B-AR, lipoxygenase gene).

Gene-Environment Interactions

Few studies have looked directly at interactions between genes and environment; however, the basic mechanism underlying the development of atopic asthma is similar for all environmental exposures. Factors that led to a polarization towards a TH-2 phenotype in young children include dietary factors such as drinking cow or soy milk rather than breast milk, maternal smoking, birth during high pollen counts, and lack of exposure to microbial and viral infections. Infants with many older siblings are theoretically exposed to more infections, which polarize their immune systems toward a TH-1 phenotype and thus protects them against developing allergies, including asthma, later in life. Exposure to dust mite and cockroach allergens mount a humeral response, which can result in asthma attack. Other environmental factors such as smog, caused by such factors as diesel and sulfur dioxide particles, are also linked to the increased incidence of asthma attacks. These particles bind to airway mucosa and act on aryl hydrolase receptors, thereby increasing IL-4 levels and mounting an IgE-specific response. Additionally, some researchers have studied the interaction between antibiotics and IL-4 expression. In one study, B-lactamsms and cepholasporins increases IL-4 production. Other studies have shown antibiotics to suppress levels of IL-4. Further research is needed to clarify the possible mechanisms between antibiotics and IL-4 levels.

Laboratory Tests

Clinically, IL-4 allelic variants can be identified using polymerase chain reaction; however, no laboratory tests are available to the general public for diagnostic purposes.

Population Testing

No population-based testing exists for any genetic polymorphisms related to asthma. The public use of such a test is not practical because: 1) asthma is a polygenic condition, and the gene-disease relation is still poorly understood; 2) no preventive intervention exists. Tests could be effective measures for assessing the efficiency of treatment options as they relate to various asthma gene polymorphisms.

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National Asthma Campaign: http://www.asthma.org.uk

American Lung Association: http://www.lungusa.org

Asthma Gene Database: http://cooke.gsf.de/asthmagen/main.cfm