provide a link between paramyxoviral infections in infancy with subsequent asthma in later in life.

**Reviewer’s Comments.** This is a very provocative study that strikes at the core of the ongoing debate regarding the specific role of acute viral lower respiratory tract illnesses and the predisposition to chronic asthma. Previous investigations have demonstrated that paramyxoviral infections and asthma may activate a network of epithelial immune-response genes that are part of the innate immune response. The current investigation provides strong evidence to support this concept and provides new insight into how paramyxoviral infections may lead to chronic airway changes in structure and function, which are typical of asthma. Additional studies will be needed to identify the genes responsible for epithelial remodeling and chronic hyperreactivity in response to this type of viral infection. Furthermore, additional investigation will be needed to confirm and further elucidate this type of a viral pathway, which is distinct from an allergen-driven pathway that may lead to chronic airway dysfunction manifested in asthma.

**ASSOCIATION OF THE ADAM33 GENE WITH ASTHMA AND BRONCHIAL HYPERREACTIVENESS**


**Purpose of the Study.** To identify novel genetic polymorphisms associated with bronchial hyperreactiveness (BHR) in asthma.

**Study Population.** Four hundred sixty white affected sib-pair families from the United States and the United Kingdom with current asthma.

**Methods.** A genetic linkage analysis was performed for current asthma and BHR. Case-control, transmission disequilibrium, and haplotype analyses were conducted to identify the gene(s) most commonly associated with asthma. Novel genes of interest were identified by a combination of public data mining, complementary DNA (cDNA) library screening, direct cDNA selection, and reverse transcriptase-polymerase chain reaction (RT-PCR).

**Results.** Positional cloning revealed a novel genomic region of interest on chromosome 20p13. Ultimately, polymorphisms in the ADAM33 gene were linked to asthma and BHR. ADAM 33 is a complex metalloproteinase with numerous diverse functions that is expressed in lung fibroblasts and bronchial smooth muscle, but not bronchial epithelial cells. The alleles in ADAM 33 that were associated with an increased susceptibility to asthma were common, ranging from 20% to 95%.

**Conclusions.** Allelic variation in the ADAM33 gene may underlie lower airways dysfunction in asthma, including BHR and airway remodeling.

**Reviewer’s Comments.** What are the genetic predispositions to asthma? In this study, current asthma and BHR were linked to a new category of molecules. ADAM proteins are a subfamily of matrix metalloproteinases. They have diverse posttranslational cellular functions, capable of regulating myogenic fusion, proteolysis, cell adhesion, and cell signaling. Their proteolytic functions include the shedding of cell-surface cytokine and cytokine receptors that are involved in inflammation, cell proliferation, and cell death. How the linkage of the ADAM33 gene to asthma and BHR and its expression in human lung fibroblasts and bronchial smooth muscle relates to asthma is not clear. It is speculated that ADAM33 expression may be a primary cause of fibroblast proliferation, and their differentiation into myofibroblasts and smooth muscle, leading to subepithelial fibrosis, smooth muscle hyperplasia and increased matrix deposition, underlying BHR, and airway remodeling. For more information on this subject, please see a brief editorial, titled “Inherit the Wheeze” by Drazen and Weiss, that accompanies this article on pages 383–384 of the same issue, and a review article, titled “ADAM33 Surfaces as an Asthma Gene,” by Shapiro and Owen in the *New England Journal of Medicine* (2002;347:936–938).

**SEQUENCE VARIANCE IN THE FcεRI ALPHA CHAIN GENE**


**Purpose of Study.** A known relationship exists between immunoglobulin E (IgE) levels and expression of high-affinity IgE receptors (FcεRI). Sequence variants in the FcεRI-binding alpha chain of FcεRI, which may affect IgE binding, were examined in asthmatic and nonasthmatic subjects to look for a relationship to IgE levels.

**Study Population.** The study subjects were 389 patients with asthma treated only with inhaled albuterol and with an average forced expiratory volume in 1 second (FEV1) of 62.3% of predicted, and 341 patients without a history of asthma or atopy by questionnaire.

**Methods.** DNA was extracted from peripheral blood and screened for mutations in the core promoter and exons of the FcεRI alpha chain gene by single-strand conformational polymorphism using radiolabelled primers. The most common site of polymorphism, the T/C –335 locus, was genotyped by restriction fragment length polymorphism. For stratification analysis, subjects were genotyped at 40 unlinked candidate single nucleotide polymorphisms, selected from a database. IgE levels were measured for each subject. For subjects in the highest and lowest quartile of IgE, stratification analysis was performed to look for genetic polymorphisms occurring at high or low frequency.

**Results.** Three single nucleotide polymorphisms were detected in the 5’ flanking region of the FcεRI alpha chain gene, although no variants were detected in the gene itself. The most common was a T/C translocation at −335 basepairs before the translational start site, whose frequency differed significantly between whites and blacks (P < .0001). In the entire cohort of white asthmatic patients, the T/C translocation was not associated with IgE levels, but a lower proportion of the CC genotype was found in whites in the highest quartile of IgE. In black asthmatics, the same trend was not observed.

**Conclusions.** Homozygosity for the C allele at locus –335 of the IgE-binding alpha chain of FcεRI may lead to lower IgE binding.

**Reviewer’s Comments.** This study population may have been biased toward milder or undertreated asthmatics, because no patients on medications other than inhaled albuterol met the selection criteria. Although this study suggests a possible connection between IgE levels and T/C translocation at the −335 locus of the FcεRI alpha chain promoter region, the overall lack of association between the IgE level and CC genotype at this locus raises additional questions about the relationship of this translocation to IgE binding. Future studies including a more represen-