

Publication

A large-scale, consortium-based genomewide association study of asthma

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BACKGROUND: Susceptibility to asthma is influenced by genes and environment; implicated genes may indicate pathways for therapeutic intervention. Genetic risk factors may be useful in identifying subtypes of asthma and determining whether intermediate phenotypes, such as elevation of the total serum IgE level, are causally linked to disease. METHODS: We carried out a genomewide association study by genotyping 10,365 persons with physician-diagnosed asthma and 16,110 unaffected persons, all of whom were matched for ancestry. We used random-effects pooled analysis to test for association in the overall study population and in subgroups of subjects with childhood-onset asthma (defined as asthma developing before 16 years of age), later-onset asthma, severe asthma, and occupational asthma. RESULTS: We observed associations of genomewide significance between asthma and the following single-nucleotide polymorphisms: rs3771166 on chromosome 2, implicating IL1RL1/IL18R1 ($P=3 \times 10^{-9}$); rs9273349 on chromosome 6, implicating HLA-DQ ($P=7 \times 10^{-14}$); rs1342326 on chromosome 9, flanking IL33 ($P=9 \times 10^{-10}$); rs744910 on chromosome 15 in SMAD3 ($P=4 \times 10^{-9}$); and rs2284033 on chromosome 22 in IL2RB ($P=1.1 \times 10^{-8}$). Association with the ORMDL3/GSDMB locus on chromosome 17q21 was specific to childhood-onset disease (rs2305480, $P=6 \times 10^{-23}$). Only HLA-DR showed a significant genomewide association with the total serum IgE concentration, and loci strongly associated with IgE levels were not associated with asthma. CONCLUSIONS: Asthma is genetically heterogeneous. A few common alleles are associated with disease risk at all ages. Implicated genes suggest a role for communication of epithelial damage to the adaptive immune system and activation of airway inflammation. Variants at the ORMDL3/GSDMB locus are associated only with childhood-onset disease. Elevation of total serum IgE levels has a minor role in the development of asthma. (Funded by the European Commission and others.)

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