Genetic risk factors in atopic diseases

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ABSTRACT

Asthma, rhinitis and atopic dermatitis are closely related phenotypes that are often seen with hypersensitivity. They show strong familial and intra-individual clustering, suggesting overlapping disease aetiology.

Family and twin studies have shown that genetic predisposition is a very substantial risk factor for developing asthma and atopy. But the genes and mode of inheritance behind these complex diseases are still largely unknown.

The purpose of the present study was to identify genes involved in asthma, rhinitis and atopic dermatitis in a Danish population using non-parametric linkage analysis and association analysis.

We fine-scale mapped 11 candidate regions in 136 asthmatic sib pair families using 100 microsatellite markers and were able to replicate three regions. The regions were prior suggested by genome-wide scans on an independent Danish sample by A. Haagerup et al.

The strongest evidence for linkage was detected for chromosome 3q (MLS 3.1) to rhinitis. Combining data with the full sample from Haagerup et al resulted in significant evidence for linkage (MLS 4.95) for rhinitis and suggestive evidence for a positive RAST test (MLS 3.46). Our results suggest that a risk gene for rhinitis or atopy map to the region on 3q. This is the first study to show significant evidence for linkage to rhinitis.

Furthermore, we obtained significant evidence for linkage to asthma to chromosome 12q24 (MLS 3.27) when analysing the replication study combined with original sample (p=0.018). We tested three genes in the region. Suggestive evidence for linkage to asthma was also found on chromosome Xp in the replication study (MLS 2.92).

There is little doubt that development of atopic diseases is due to interactions between multiple genes and various environmental exposures. Three glutathione-S-transferase genes (GST) involved in protecting the cells from oxidative stress were furthermore tested for association to atopic asthma in our study. We found significant association between atopic asthma and deletions of GSTM1 (p≤0.00005) and GSTT1 (p≤0.013) whereas GSTP1 did not show association. The results indicate that deletions of GSTM1 and GSTT1 could be risk factors for asthma and that the genes might have a protective role in the development of atopic asthma.

Future studies will concentrate on identifying the underlying genes in the regions showing evidence for linkage. This could potentially lead to increased knowledge of the aetiological factors underlying atopic diseases and possible new curative therapies.