Search for Susceptibility Genes in Alopecia Areata

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Alopecia areata (AA) is a multifactorial disorder, in which genetic and environmental factors combine to result in the phenotype (Green and Sinclair, 2000). The prognosis of AA is unpredictable and there is no definitive treatment. Several lines of evidence support the polygenic inheritance of AA, including the high prevalence of the trait, the Gaussian curve of distribution of the phenotype, and heritability among first-degree relatives (Aita and Christiano, 2001). Genetic studies have been limited to association analyses, which suggest that a permissive HLA status may potentiate the development of AA (Welsh _et al_, 1994).

With the hypothesis that there is a genetic basis underlying the susceptibility to develop AA, we initiated a search for susceptibility genes by performing a genome-wide scan in multiplex AA pedigrees. The genetic dissection of complex traits has traditionally been focused on large collections of small families (affected sib pairs, for example). But it has recently been shown that a small sample of larger pedigrees can potentially derive more robust results, because of a reduced level of genetic heterogeneity ("noise"), enrichment of genetic factors within families, and the availability of the pedigree structure (Terwilliger and Goring, 2000).

The ascertainment and diagnosis of the families studied was undertaken by a dermatologist (Dr Abraham Zlotogorski), and using the diagnostic questionnaire developed by the NIH AA Registry. We collected DNA from a total of 22 multiplex AA pedigrees, comprising 69 unaffected and 78 affected family members. We performed a genome-wide scan using a panel of 324 microsatellite markers, with an average marker spacing of 10 cM in all DNA samples.

Because of the complex nature of traits, it is expected that a number of genetic components will be contributing to the final presentation of the phenotype. For this reason, we subjected the dataset derived from the genome-wide scan to a combination of different statistical tests (Terwilliger and Ott, 1994): (i) the heterogeneity LOD score, maximized over four settings of the penetrance parameters (MAXHLOD); (ii) the mean test for affected sib-pairs, as implemented in the ANALYZE program (ASP); a test of allele sharing that uses all sibs (ALLSIBS); and a likelihood version of the transmission disequilibrium test (TDT-LIKE). This strategy represents a combination of parametric or model-based (MAXHLOD) and non-parametric or model-free (ASP, ALLSIBS, and TDT-LIKE) tests.

We identified several chromosomal regions yielding suggestive LOD scores, including the HLA region on chromosome 6. These intervals could harbor potential susceptibility loci for alopecia areata. In order to exclude those regions that represent spurious positive scores and to confirm and refine the true susceptibility loci, we are currently undertaking a fine-mapping study in a larger group of AA families.

We anticipate that these studies will lead to the identification of AA susceptibility genes, and provide a foundation for understanding the interactions of these gene(s) with each other and with other variables such as the immune system and environmental factors.

References

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