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NEWS AND COMMENTARY

Multiple Sclerosis

Light at the end of the tunnel

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The search for genes that influence susceptibility to multiple sclerosis has a long history, during which considerable effort has been expended for relatively little dividend. However, two papers in a recent edition of *Nature Genetics* suggest that progress is finally being made.

Earlier efforts at whole-genome screening for linkage[1] taught researchers that studies aiming to identify genes for multiple sclerosis would need large cohorts of affected individuals, dense maps of markers, and accurate high throughput genotyping. The recent *Nature Genetics's* papers from Lincoln *et al*.[2] and Reich *et al*.[3] indicate that these prerequisites are now being met, so that a new era of research into this complex disease is starting.

The one secure observation concerning the genetics of multiple sclerosis is that in virtually every population the disease is associated with the DR15 haplotype from the Major Histocompatibility Complex (MHC) on chromosome 6p21.[4] Unfortunately, the high gene density, extreme polymorphism, and extensive patterns of linkage disequilibrium found within the MHC have confounded attempts to resolve this association, evidence for which was first provided more than 30 years ago.[5] The strongest association signal within the MHC is generally seen in the region of the class II Human Leucocyte Antigen (HLA) genes but many researchers suspect that secondary loci conferring independent risk map elsewhere within the MHC or nearby.

Seeking to refine the primary association and localise secondary loci, Lincoln *et al*.[2] identified 1068 single nucleotide polymorphisms (SNPs) from a 13.3 Mb interval including the MHC region (3.6 Mb) and attempted to type these in large cohorts of families from Canada ($n=566$) and Finland ($n=571$), together including more than 4200 individuals. Despite the fact that 40% of their selected SNPs failed to type, the authors were still left with a final map of almost one marker every 10 kb across the MHC. Although this represents less than 1% of the variation within the region, after statistical analysis the authors were able to confirm the pre-eminence of the class II genes, with no evidence to support the existence of a secondary locus. Higher density efforts are sure to follow in the wake of this screen. Indeed, a high density set of haplotype tagging SNPs covering the MHC has already been established,[6] and is ripe for application to multiple sclerosis.

Meanwhile Reich *et al*.[3] have reported the first admixture screen ever performed in an autoimmune disease. This represents the culmination of many years of preparatory work. The propensity for multiple sclerosis to affect Europeans more frequently than Africans suggests that African-Americans with the disease may have a disproportionately greater degree of European ancestry in those regions of the genome encoding susceptibility genes. Identifying susceptibility genes by mapping such distortions of ancestry in affected individuals is the principle underlying admixture mapping. Unfortunately, application of this approach is highly demanding and thus far few groups have succeeded in using the method.

Reich *et al*.[3] have shown remarkable foresight and tenacity in establishing the crucial collection of African-American cases needed to do such a study. Furthermore, they have almost single handedly developed the essential marker resources[7] and novel analytical methods.[8] Typing 1082 ancestrally informative SNPs, markers reliably distinguishing European and African populations, in 484 cases and 1043 controls, Reich *et al*.[3] implicate a novel susceptibility locus on chromosome 1.

They suggest that the absence of linkage in this region among European families[1] indicates that the responsible variant is likely to have a very high background frequency in Europeans. It may therefore be difficult to identify this variant in standard homogeneous European populations. The novelty of admixture mapping limits our ability to appreciate the magnitude of the observed chromosome 1 excess in European ancestry. On the face of it, the 2.4% difference in average European ancestry observed between two large control groups makes it surprising that a local 5.9% difference attracts quite such an extreme lod score. The absence of any admixture signal from the MHC region underlines earlier observations by the authors concerning the similarity in frequency of multiple sclerosis-associated MHC alleles among European and African populations.[9] At loci where risk alleles have a similar frequency in the original populations no distortion of ancestry would be expected. Failure to confirm the chromosome 1 finding in a second cohort (143 cases) is disappointing but this analysis was clearly hampered by the modest size of the replication set. As the authors continue to accumulate cases, we can look forward to further resolution of this exciting finding based on novel methodology.

Altogether, these papers illustrate the need for large sample sizes and novel strategies in identifying genes that increasingly look to be individually of modest effect but collectively are of considerable importance in determining disease susceptibility■

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References

1 International Multiple Sclerosis Genetics Consortium (IMSGC): A high-density screen

for linkage in multiple sclerosis. *Am J Hum Genet* 2005; **77**: 454–467.
2 Lincoln MR, Montpetit A, Cader MZ *et al*: A predominant role for the HLA class II region in the association of the MHC region with multiple sclerosis. *Nat Genet* 2005; **37**: 1108–1112.
3 Reich D, Patterson N, Jager PL *et al*: A whole-genome admixture scan finds a candidate locus for multiple sclerosis susceptibility. *Nat Genet* 2005; **37**: 1113–1118.
4 Rosati G: The prevalence of multiple sclerosis in the world: an update. *Neurol Sci* 2001; **22**: 117–139.
5 Jersild C, Svejgaard A, Fog T: HL-A antigens and multiple sclerosis. *Lancet* 1972; **1**: 1240–1241.
6 Miretti MM, Walsh EC, Ke X *et al*: A high-resolution linkage-disequilibrium map of the human major histocompatibility complex and first generation of tag single-nucleotide polymorphisms. *Am J Hum Genet* 2005; **76**: 634–646.
7 Smith MW, Patterson N, Lautenberger JA *et al*: A high-density admixture map for disease gene discovery in African Americans. *Am J Hum Genet* 2004; **74**: 1001–1013.
8 Patterson N, Hattangadi N, Lane B *et al*: Methods for high-density admixture mapping of disease genes. *Am J Hum Genet* 2004; **74**: 979–1000.
9 Oksenberg JR, Barcellos LF, Cree BA *et al*: Mapping multiple sclerosis susceptibility to the HLA-DR locus in African Americans. *Am J Hum Genet* 2004; **74**: 160–167.