Journal of NeuroVirology (2000) 6, Suppl 2, S15–S17

www.jneurovirol.com

MS genetics: recent Scandinavian efforts

Jan Hillert*,[1]

[1]*Department of Neurology, Karolinska Institute at Huddinge Hospital, SE-141 86, Huddinge Sjukhus, Sweden*

As a potential founder population of MS, the Scandinavian ethnic group is of special interest in MS genetics. Project in these countries have recently led to several reports, including associations with HLA class I, CTLA-4 and suggestive linkage to several chromosomal candidate loci. The analysis of isolated populations within Scandinavia may also prove to be rewarding. *Journal of NeuroVirology* (2000) **6,** S15–S17.

Keywords: multiple sclerosis; genetic mapping; HLA genes; CTLA-4

Introduction

The hypothesis that the world distribution of MS may be explained by the spread of 'Scandinavian genes' still needs to be supported by evidence from epidemiological and molecular genetic research. Even so, it remains a colourful 'Viking saga' that may serve to increase the interest in MS genetics from an anthropological point of view. Contrary to this, the generally stated impetus for the search for MS genes is an increased understanding of the underlying pathogenic mechanisms. This is, however also slightly spurious since few examples of success by this strategy have been documented for complex, i.e. polygenetic and multifactorial disorders.

There is presently a rapid development of knowledge in MS genetics. Compared with practically all comparable diseases, the genetic epidemiology of MS is extremely well characterised. In addition to a number of twin studies we also have access to well-performed studies of both adoptees, half-siblings and even conjugal families. In addition, after a phase of some confusion following the publications of the first generation of genomic screens (Ebers *et al*, 1996; Haines *et al*, 1996; Sawcer *et al*, 1996), we are now beginning to see a picture of increasing clarity and coherence. In fact, in my mind, we may already have roughly localised a number of the most importance genes to specific chromosomal regions.

Still it is sobering to remember that even though we have known of one 'MS-gene', or at least specific chromosomal region, namely the HLA DR-DQ subregion, for more than two decades, we still have several issues to sort out to fully understand the nature of its role in MS.

*Correspondence: J Hillert

Even if the infamous original Scandinavian contribution in MS genetics as a genetic pool for susceptibility may be questioned, it may be noted that the original reports of association with HLA-A, -B and -D were indeed reported from Denmark (Jersild *et al*, 1972, 1973). Ever since, a large number of HLA-related studies have been performed by various groups in both Denmark, Norway, Finland and Sweden. In this presentation, I will briefly describe recent progress concerning the HLA genes, some relevant candidate genes as well as data on a number of loci that have attracted attention following the publication of genomic MS screens.

HLA

It is well established that the HLA class II genes are of importance for the susceptibility to MS. In the 1980s and 1990s, the association with serological specificities was translated into genomic terminology and defined in detail by genomic typing. The MS-associated HLA-DR-DQ haplotype is now established to be HLA-DRB1*1501,DRB5*0101,DQA1*0102,DQB1*0602 (Fogdell *et al.*, 1995). In addition, both Swedish and Finnish studies have demonstrated significant linkage for HLA-DR and -DQ genes (Tienari *et al*, 1993; Fogdell *et al*, 1997). Still, it is clear that the HLA genes only explain part of the genetic contribution to MS.

Recently, we have identified independent associations in MS with the HLA class I alleles HLA-A2 (negative association) and HLA-A3 (positive). These associations were clearly independent of the HLA-DR15,DQ6 haplotype (Fogdell-Hahn *et al*, 2000). These data are in addition to similar independently collected Norwegian material. This observation may help to explain why, in other populations, it has been so relatively difficult to find evidence for linkage in spite of a well-established and often strong association.

Candidate genes
As others, we have investigated a large (>20) number of non-HLA candidate genes for possible association and linkage in MS. The most promising of these so far is the CTLA-4 gene, where both a Norwegian and a Swedish study have found associations (Harbo *et al*, 1999; Ligers *et al*, 1999), in our study with the G allele of a biallelic polymorphism at position 49 of the first exon. This finding was supported by a significant transmission distortion of this allele in a family study.

Candidate loci
In 1996, three genomic screens in MS failed to identify single genetic factors of great importance in MS (Ebers *et al*, 1996; Haines *et al*, 1996; Sawcer *et al*, 1996). On the other hand, a number of loci of possible importance were found. At first sight, however, the evidence for each of these loci was regarded as much too weak to allow great hope for confirmation. The exception from this was a chromosomal segment on the short arm and centromerically on chromosome 5, which gave indications in all three studies, and in addition in a Finnish study (Kuokkanen *et al*, 1996). Recently, in a joint study of 117 affected sibling pairs, further support was observed for this region (Oturai *et al*, in press). In 1997 an independent Finnish genomic screen (Kuokkanen *et al*, 1997) added support to a locus on 17q first indicated to be of importance in the genomic screen by Sawcer *et al* (1996).

In our Swedish material of 48 multiplex families and large numbers of sporadic MS patients and controls, we have investigated a number of these loci for presence of linkage and/or association. In fact, we have observed suggestive linkage and/or significant association for markers in the following loci: 3p12-13, 5p, 7pter-15, 7q35, 12p12-13, 12q23 and 17q25 (Xu *et al*, 1999; Xu *et al*, unpublished). Further, at least three of these loci are syntenic to loci of importance for experimental autoimmune encephalomyelitis as well as for experimental arthritis. This strengthens the argument that these loci may harbour genes with importance for autoimmunity, and is well in line with the observation of clustering of genes for autoimmune disorders as pointed out recently by Becker *et al* (1998). The bottom line of these observations is that although the various loci did not at first seem very impressive, several of them may still turn out to contain relevant genes for MS. In addition, it may be possible to isolate these genes through the use of animal models.

Analyses of an isolated population
In a localised population from the northernmost part of Sweden, we are investigating 30 individuals, of which 25 belong to an extended pedigree originating from a common ancestral couple in the eighteenth century. The approach is to identify identical chromosomal regions shared by descendants of this affected population. So far, the majority of patients have been shown to share an extended haplotype in an 8 cM region on 17p. This mapping will be completed within the next few months, and may illustrate yet another possible way to identify chromosomal regions of relevance at least in sedentary populations of this type available in the Nordic countries.

Summary
In conclusion, after a long period of time, during which the HLA class II genes have been the only ones with a confirmed importance, we are now rapidly entering into a phase where more genes, and in addition a number of chromosomal regions, are being convincingly tied to the susceptibility to MS. The search for these genes is now accelerating and may prove to be of relevance for other complex autoimmune disorders.

References

Becker KG, Simon RM, Bailey-Wilson JE, Freidlin B, Biddison WE, McFarland HF, Trent JM. (1998). Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune disorders. *Proc Natl Acad Sci (USA)* **95:** 9979–9984.

Ebers GC, Kukay K, Bulman DE, Sadovnick AD, Rice G, Anderson C, Armstrong H, Cousin K, Bell RB, Hader W, Paty DW, Hashimoto S, Oger J, Duquette P, Warren S, Gray T, O'Connor P, Nath A, Auty A, Metz L, Francis G, Paulseth JE, Murray TJ, Pryse-Phillips W, Risch N. (1996). A full genome search in multiple sclerosis. *Nature Genetics* **13:** 472–476.

Fogdell A, Hillert J, Sachs C, Olerup O. (1995). The multiple sclerosis- and narcolepsy-associated HLA class II haplotype includes the DRB5*0101 allele. *Tissues Antigens* **46:** 333–336.

Fogdell A, Olerup O, Fredrikson S, Vrethem M, Hillert J. (1997). Linkage analysis of HLA class II genes in Swedish multiplex families with multiple sclerosis. *Neurology* **48:** 758–762.

Fogdell-Hahn A, Ligers A, Grønning M, Hillert J, Olerup O. (2000). Multiple sclerosis. A modifying influence of HLA class I genes in a class II associated autoimmune disease. *Tissue Antigens* **55:** 140–148.

Haines JL, Ter-Minassian M, Bazyk A, Gusella JF, Kim DJ, Terwedow H, Pericak-Vance MA, Rimmler JB, Haynes CS, Roses AD, Lee A, Shaner B, Menold M, Seboun E, Fitoussi RP, Gartioux C, Reyes C, Ribierre F, Gyapay G, Weissenbach J, Hauser SL, Goodkin DE, Lincoln R, Usuku K, Oksenberg JRA. (1996). A complete genomic screen for multiple sclerosis underscores a role for the major histocompatibility complex. The Multiple Sclerosis Genetics Group. *Nature Genetics* **13:** 469–471.

Harbo HF, Celius EG, Vartdal F, Spurkland A. (1998). CTLA4 promoter and exon 1 dimorphisms in multiple sclerosis. *Tissue Antigens* 52.

Jersild C, Fog T, Hansen GS, Thomsen M, Svejgaard A, Dupont E. (1973). Histocompatibility determinants in multiple sclerosis, with special reference to clinical course. *Lancet* **2:** 1221–1225.

Jersild C, Svejgaard A, Fog T. (1972). HL-A antigens and multiple sclerosis. *Lancet* **1:** 1240–1241.

Kuokkanen S, Sundvall M, Terwilliger JD, Tienari PJ, Wikstrom J, Holmdahl R, Pettersson U, Peltonen L. (1996). A putative vulnerability locus to multiple sclerosis maps to 5p14-p12 in a region syntenic to the murine locus Eae2 [see comments]. *Nature Genetics* **13:** 477–480.

Kuokkanen S, Gschwend M, Rioux JD, Daly MJ, Terwilliger JD, Tienari PJ, Wikstrom J, Palo J, Stein LD, Hudson TJ, Lander ES, Peltonen L. (1997). Genomwide scan of multiple sclerosis in Finnish multiplex families. *Am J Hum Genet* **61:** 1379–1387.

Ligers A, Xu C, Saarinen S, Hillert J, Olerup O. (1999). The CTLA-4 gene is associated with multiple sclerosis. *J Neuroimmunol* **97:** 182–190.

Oturai A, Larsen F, Ryder LP, Madsen HO, Hillert J, Fredrikson S, Sandberg-Wollheim M, Laaksonen M, Koch-Henriksen N, Sawcer S, Fugger L, Sorensen PS, Svejgaard A. (1999). Linkage and association analysis of susceptibility regions on chromosomes 5 and 6 in 106 Scandinavian sibling pair families with multiple sclerosis. *Ann Neurol* **46(4):** 612–616.

Sawcer S, Jones HB, Keakes R, Gray J, Smaldon N, Chataway J, Robertson N, Clayton D, Goodfellow PN, Compston A. (1996). A genome screen in multiple sclerosis reveals susceptibility loci on chromosome 6p21 and 17q22. *Nature Genetics* **13:** 464–468.

Tienari PJ, Wikstrom J, Koskimies S, Partanen J, Palo J, Peltonen L. (1993). Reappraisal of HLA in multiple sclerosis: close linkage in multiplex families. *Eur J Hum Genet* **1:** 257–268.

Xu C, Dai Y, Fredrikson S, Hillert J. (1999). Association and linkage analysis of candidate chromosomal regions in multiple sclerosis: indication of disease genes in 12q23. *Eur J Human Genet* **7:** 110–116.