Schizophrenia as a Human Leukocyte Antigen-Associated Disease Revisited

The major histocompatibility complex (MHC) on chromosome 6p represents a unique region of the genome, containing genes encoding human leukocyte antigens (HLA) and many others involved in immune functioning (1). In this issue of the *Journal*, Walters et al. (2) provide the latest intriguing twist in the long-running tale regarding the relationship between the MHC and schizophrenia. HLA loci were among the first genetic markers to be studied in relation to schizophrenia, and more than 30 years ago one of us performed a meta-analysis of the first few HLA association studies and concluded that the results were promising (3). Such early studies were very modest in scale, and a meta-analysis 22 years later, by which time more data had accumulated, produced largely negative results (4). However, the HLA/schizophrenia story never really died, and in a subsequent meta-analysis of linkage studies, the region of chromosome 6p containing the MHC was one of the "hits" (5). More recently, the tale was fully revived with several independent genome-wide association studies (GWAS), followed by a combined analysis by the Psychiatric Genomics Consortium, showing associations between single-nucleotide polymorphisms (SNPs) in the MHC region and schizophrenia (6–11).

The MHC is arguably one of the most complicated and trap-laden regions of the genome.

However, this finding generates a number of questions. Variants in the MHC region have been associated with numerous immunological disorders, but there is no compelling evidence of an auto-immune basis for schizophrenia. Until now, there has been only one other well-established HLA-associated disorder, hemochromatosis, which does not have an immune basis (12). There are also the unique genetic features of the MHC region that make associations difficult to pin down and increase the likelihood of false positive associations.

One of these is linkage disequilibrium (LD), the phenomenon whereby stretches of genome remain in "blocks" despite many generations of meiotic crossing over. The strong LD in the MHC (13), particularly around HLA genes, makes it difficult to identify the causal variants from markers that are merely "tags" in LD. This can be seen in disorders such as rheumatoid arthritis where the initial HLA association was established relatively easily, but it took a surprisingly long time to isolate the causal variants (14). There is also evidence for negative assortative mating affecting the region. That is, individuals tend to select mates who are dissimilar to themselves with respect to MHC genes (15), leading to greater heterogeneity at these loci in their children. Additionally, as one of the MHC's major roles is in protecting against pathogens by recognizing "non-self," there is almost certainly strong selection pressure that increases diversity in the region. Indeed, the HLA loci are the most polymorphic (that is, they have the largest number of common alleles) of any in the genome. Since it is highly polymorphic, the MHC region is highly sensitive to population stratification. This is the phenomenon whereby admixtures of populations

that have differing marker gene frequencies can result in apparent but spurious marker-disease associations. This means careful ethnic matching of case and control subjects is needed to overcome the problem of hidden population structure when it comes to the MHC.

Despite these caveats, there is good reason for optimism that the association with schizophrenia is real. First, the statistical support is becoming more compelling in that increasing GWAS sample sizes have been associated with ever decreasing p values that make the probability of a type I error vanishingly small. Furthermore, a new Irish sample independent of the most recent Psychiatric Genomics Consortium meta-analysis supported the MHC association and, by imputation, found that the most significant result was with a classic HLA-C marker, a class I MHC molecule (16). Second, several strands of research suggest that the MHC plays an important role in neuronal function, with expression levels affecting synaptic plasticity and potentially the formation of new memories (17). Specifically, there is now evidence that class I MHC proteins regulate synaptic responses mediated by *N*-methyl-D-aspartic acid (NMDA) type glutamate receptors (NMDARs) in the mammalian CNS. The mechanism appears to work via tonic inhibition of NMDAR function, which in turn affects downstream NMDAR-induced AMPA receptor trafficking (18). Recent data also indicate that not only are MHC class I proteins required for normal postnatal brain development and plasticity, but they are also widely expressed in the mammalian brain prenatally during the earliest stages of neuronal differentiation (19), consistent with a possible role in neurodevelopmental disorders. Finally, the study by Walters et al. in this issue (2), which looks at structural MRI and cognitive measures in patients with schizophrenia and healthy comparison subjects, found significant associations between a SNP in the MHC, previously identified by schizophrenia GWAS, and both delayed episodic memory and decreased hippocampal volume.

In conclusion, exploring the possible role of the MHC region in schizophrenia has been a long saga. The MHC is arguably one of the most complicated and trap-laden regions of the genome, but it now seems highly probable that it contains one or more genes that confer increased susceptibility to schizophrenia. While this might warrant a reappraisal of whether immune mechanisms play a role in schizophrenia and related disorders, there is increasing evidence that the MHC plays a role in synaptic plasticity and brain development through nonimmune functions. The tale is not yet over, but perhaps we have the beginnings of the denouement.

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PETER McGUFFIN, PH.D., F.R.C.P.
ROBERT A. POWER, M.SC.

From the Medical Research Council (MRC) Social, Genetic, and Developmental Psychiatry Center, King's College London. Address correspondence to Dr. McGuffin (peter.mcguffin@kcl.ac.uk). *Editorial accepted for publication March 2013 (doi: 10.1176/appi.ajp.2013.13030336).*

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