This Month in the *Journal*

With the advent of very-high-throughput genotyping techniques, the first genomewide association studies are under way. However, the best approach to the design of these studies is still under debate. This month in the *Journal,* Duncan Thomas, Robert Haile, and David Duggan summarize recent discussions that occurred at a workshop on this topic. Several aspects of genomewide association studies are covered, including marker selection, study power, statistical approaches to the data, and the use of multistage sampling designs. Although a full understanding of this approach awaits the completion of more studies, the participants in the workshop were optimistic that the challenges of genomewide association studies are surmountable, provided there is appropriate planning and use of resources.

Chromosome 10q26 and Age-Related Maculopathy, *by Jakobsdottir et al.* **(***p. 389***)**

Multiple recent reports of the association of complement factor H with age-related maculopathy (ARM) have indicated that the *CFH* gene plays an important role in genetic predisposition to this disorder, which is the leading cause of central blindness in the elderly. Although the *CFH*-containing region on chromosome 1 has been pulled out in multiple linkage studies of ARM, chromosome 10q26 has also been strongly implicated. Jakobsdottir et al. focused on these two regions in a linkage and association study of ARM. They found that variation in *CFH* accounts for the linkage signal to chromosome 1, although Y402H, which is believed to be the major determinant of ARM in this gene, may not be the only important variant. The association to chromosome 10q26 proved more difficult to tease apart. Three tightly linked genes—*PLEKHA1, LOC387715,* and *PRSS11*—and a second locus containing two genes—*GRK5* and *RGS10*—both were implicated in the analyses. Taking their data in total, Jakobsdottir et al. feel that the *PLEKHA1/LOC387715* locus is most likely to be involved in ARM and that it confers an odds ratio for ARM similar to that of *CFH*. Because *LOC387715* is known to be expressed only in placenta, whereas *PLEKHA1* is expressed in retina, *PLEKHA1* is the most likely candidate gene. Its function as an activator of lymphocytes fits with the proposed role of aberrant immune responses in ARM.

Duplication of the* MECP2 *Region in XLMR, *by Van Esch et al.* **(***p. 442***)**

Loss of function of *MECP2* causes Rett syndrome, a disorder in which intellectual, motor, and communication skills are adversely affected and seizures are often present. Van Esch et al. now find that duplications of *MECP2* and the resultant overexpression of this gene might also contribute to a Rett-like phenotype. Their work began with a family with six affected males who had delays in psychomotor development, seizures, absence of speech, microcephaly, increased muscle tone and reflexes, and recurrent respiratory infections. Previous linkage analysis had assigned the disease locus to Xq28-Xqter, a region that contains *MECP2*. However, no mutations were found. Now, Van Esch et al. use an X-chromosome array to look for alterations in gene dosage in this family and report a duplication that includes *MECP2*. When the authors tested 17 additional individuals with a similar phenotype, they found three additional duplications that were associated with a twofold increase in *MECP2* expression. The minimal region of overlap of these duplications extends from *L1CAM* to *MECP2,* and these are the only two genes in the duplication known to be associated with CNS development and function. The duplications are also found in unaffected carrier females, but these women exhibit extreme skewing of X inactivation. Although the role of other genes in the duplication cannot be ruled out, similarities with the phenotype of mice overexpressing *Mecp2* and the lack of resemblance to phenotypes associated with *L1CAM* mutations led the authors argue that the phenotype is due largely to overexpression of *MECP2*. In support of this argument is the recent work by Meins et al. (J Med Genet 42:e12), who reported a duplication in this region that was associated with a similar phenotype. This duplication did not include *L1CAM,* which leaves *MECP2* as the only mental retardation (MR)–related gene in the overlapping duplicated region. It therefore appears as though tight regulation of *MECP2* expression is crucial for proper development. Not only does loss of *MECP2* function cause Rett syndrome, but overexpression of *MECP2* also appears to cause a severe MR syndrome.

0002-9297/2005/7703-0001$15.00

MS Linkage Screen, *by the International Multiple Sclerosis Genetics Consortium* **(***p. 454***)**

Several genome scans for multiple sclerosis (MS) have been performed, and the only region consistently implicated in this disorder has been the major histocompatibility complex (MHC) region on chromosome 6p21. Members of the International Multiple Sclerosis Genetics Consortium (IMSGC) felt that the low information extraction and genotyping success rates in these studies were not optimal, so they did a pilot study showing that use of SNP-based mapping sets could greatly improve these parameters and thus the power of studies using the same samples. Encouraged by this result, the IMSGC has now rescreened available MS-affected families of Northern European descent with the Illumina BeadArray linkage mapping panel. They genotyped >4,500 SNPs in 730 families and were able to achieve an error rate of only 0.002% and a level of information extraction nearly twice that of a recent meta-analysis for MS. In a nonparametric linkage analysis, they achieved a whopping multipoint score of 11.66 for the MHC region, further cementing the role of the MHC in MS. This score is much higher than has been reported in previous studies, thereby illustrating the increase in power that is achieved through use of the SNP-based strategy. In contrast to previous proposals that there may be more than one MS risk locus within the MHC, the data from this study suggest that the MHC-based risk can be attributed solely to the *DRB1*1501* haplotype. When they looked beyond the MHC, they also found suggestive linkage to chromosomes 17q23 and 5q33, whereas an ordered-subset analysis (OSA) suggested that a locus on chromosome 19p13 acts independent of MHC to confer risk of MS. The authors stress that there were no loci outside the MHC region that had sibling recurrence ratios >1.2, so future studies of MS candidate genes must be very powerful to be successful.

Genetics of Cognition in Schizophrenia, *by Hallmayer et al.* **(***p. 468***)**

Schizophrenia is a complex disease believed to be a conglomerate of several disorders. This heterogeneity not only hinders clinical diagnoses but also presents a significant obstacle in the quest for susceptibility genes. The work of Hallmayer et al. highlights the benefits of analyzing a subset of phenotypes within the schizophrenia landscape. By focusing on specific cognitive, behavioral, and personality traits of their subjects, the group is able to identify a distinct subtype of the disease that is characterized by neurocognitive deficit (CD). This classification accounts for 30%–50% of the families studied and provides enough data to reliably link the subtype to 6p24, a locus previously identified as a potential schizophrenia hotspot. This locus was identified after OSA was done on data from a whole-genome scan. Although the LOD scores calculated from the genome scan are not compelling, OSA reveals that the probands with CD have a much higher LOD score at 6p24 than does the overall sample. Of note, when the two groups were then separated for linkage analysis of the region, the CD LOD score increased to 3.32, whereas that of the remaining families was calculated to be −2.12. Further, it is reported that, although a battery of tests was used during the reported study, similar conclusions would have been made if only four select parameters had been analyzed. It is hoped that the availability of such an abridged neurocognitive testing scheme will lead to easier phenotype classification and the identification of more homogeneous subtypes of schizophrenia, which will facilitate genetic analysis.

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