This Month in the *Journal*

This month in the *Journal*, Mona Shahbazian and Huda Zoghbi review the current state of knowledge on Rett syndrome. This disorder of arrested neurological development is caused by mutations in *MECP2,* which encodes a protein that binds preferentially to methylated DNA and is thought to silence transcription of downstream genes through recruitment of co-repressor complexes. Beyond covering basic clinical and neurological features of the syndrome, the review also discusses current ideas on the function of MeCP2 and how it might be involved in this syndrome.

Factor H Dysfunction in Atypical HUS, *by Sánchez-Corral et al.* (*p. 1285*)

HF1 encodes factor H, a plasma protein that controls the function of the alternative complement pathway. Mutations in *HF1* have been found in individuals with atypical hemolytic uremic syndrome (aHUS), a disorder characterized by acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. Although several *HF1* mutations have been found in people with aHUS, many of these individuals have normal complement profiles and factor H plasma levels, so it has been speculated that the protein has altered function. Missense mutations in *HF1* cluster in a region involved in the binding of factor H to C3b deposited on cellular surfaces. To determine how these mutations lead to aHUS, Sánchez-Corral et al. assessed the function of three mutant forms of purified factor H. Although the ability of the three mutants to control activation of complement was normal, they all exhibited a reduction in their ability to interact with surface-bound C3b. This finding is in accordance with the hypothesis that patients with aHUS have a dysfunction in their ability to protect cellular surfaces from complement activation, which can result in tissue damage if complement is activated. This dysfunction is not the full story, however, because there are unaffected carriers of at least one of these mutations. Other factors, such as the level of *HF1* expression, may also play a role in the development of disease. The implications of these findings in terms of treatment of aHUS are discussed.

RHD Incompatibility and Schizophrenia, *by Palmer et al.* (*p. 1312*)

In several studies, Rh incompatibility has been implicated as a risk factor for schizophrenia. However, these earlier studies were not designed in such a way that it was possible to tease apart whether this effect is actually due to maternal-fetal genotype incompatibility. It could be that the risk of schizophrenia associated with this region is really due to effects of the maternal genotype alone or to linkage and association with a susceptibility allele at or near the *RHD* locus. To unravel this association, Palmer et al. adapt a case-parent–trio log-linear–modeling approach that can distinguish maternal-fetal genotype incompatibility from other effects. Their results do, in fact, suggest that the *RHD* locus increases the risk of schizophrenia through a maternal-fetal genotype incompatibility mechanism, which they postulate may act through hypoxia or an increase in unconjugated bilirubin, which is neurotoxic.

Male Mouse Autosomal Recombination Maps, *by Froenicke et al.* (*p. 1353*)

Although recombination appears not to be randomly distributed throughout the genome, the mechanisms governing its distribution are unclear. In order to examine these mechanisms, Froenicke et al. determined the recombination map for each autosome of the male mouse. In combination with FISH, which was used to identify individual chromosomes, antibodies to MLH1 (a mismatch repair protein essential for crossover in mice) were used to determine the positions of crossovers on these chromosomes. Going further, the authors hybridized genetically mapped BACs to the chromosomes. This procedure allows Froenicke et al. to begin to integrate genetic, physical, and cytological maps, in order to study the relationships between them. Among other things, their results suggest that synaptonemal-complex length is correlated with crossover frequency. Additional factors, such as interference and the temporal order of synapsis, may also influence recombination distribution.

Haplotype Blocks in Association Studies, *by Zhang et al.* (*p. 1386*)

It has recently been proposed that the human genome can be partitioned into blocks of limited haplotype diversity and that a limited number of SNPs can capture most of the genetic diversity in these haplotype blocks. But how does use of these so-called "tag" SNPs affect the power of association studies? Zhang et al. address this question through simulations of case-control and family-trio samples, and they compare three kinds of data: all of the SNPs in a region and their corresponding haplotypes, the tag SNPs and their haplotypes, or a set

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of randomly chosen SNPs (equal in number to that of the tag SNPs) and their haplotypes. The results indicate that tag SNPs are more powerful than randomly chosen SNPs and that use of tag SNPs significantly reduces genotyping efforts without significant reductions in study power. Although these numbers are affected by certain parameters used in the simulations, Zhang et al. find that, on average, the use of tag SNPs enables the reduction of the genotyping effort by 75% while reducing the power of a study by only 4%.

***A Founder Mutation in* MSH2,** *by Foulkes et al.* (*p. 1395*)

The identification of population-specific founder mutations can facilitate genetic testing, because it allows one to look first for the most likely mutations before entire gene sequences need to be screened. Foulkes et al. have identified an *MSH2* founder mutation in the Ashkenazi Jewish population that may prove to be an important cause of hereditary nonpolyposis colon cancer (HNPCC) in this group. In large hospital-based and population-based samples, they found several unrelated families who carry this missense mutation, *MSH2*1906G→C*. Although *MSH2*1906G→C* is probably a rare cause of colorectal cancer, it appears that, among Ashkenazi Jews with HNPCC that fulfills the Amsterdam criteria, a significant fraction of cases are due to this mutation. Thus, as the identification of founder mutations in *BRCA1/2* has made it easier to perform genetic testing in breast and ovarian cancer patients from this population, the 1906G→C mutation may be useful for genetic testing for HNPCC in Ashkenazi Jews.

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