This Month in the *Journal*

Case Selection Based on Allele Sharing, *by Fingerlin et al.* (*p. 432*)

Suppose you have a sample of affected families, and you want to look for complex disease associations in a candidate region. Given that funding agencies aren't usually throwing money at all of us, how can you maximize the usefulness of this sample without genotyping everybody? Fingerlin et al. explore case-selection strategies to address this problem in the context of a study design that also uses unaffected, unrelated control individuals. They ask the following question: if you are using only one sibling from each family, is it best to choose one randomly or to use siblings from pairs with the most evidence for allele sharing in the region of interest? The idea here is that selection based on allele sharing might increase the frequency of the disease-associated allele in the case sample, making it easier to find. Second, they wanted to know whether it is better to use siblings from all of the sibships or only those who show linkage to the area of interest. Their results indicate that, in a variety of disease models, selection of affected siblings on the basis of allele sharing is an effective way to increase the power to detect a disease association, compared with randomly chosen siblings. Further, selection of these siblings from families that show linkage to the region of interest allows a decrease in the number of individuals genotyped per marker while maintaining the magnitude of the test statistic, thereby freeing up resources to type more markers in the region. These findings are likely to be useful, for example, in the design of association studies aimed at following up the results of genomewide linkage scans.

XCI in a Mouse Model of Rett, *by Young and Zoghbi* (*p. 511*)

Girls with the classic Rett syndrome (RTT) phenotype, which is caused by *MECP2* mutations, are apparently normal at birth but enter a period of regression after several months, during which motor and language skills are lost. Some individuals have a more severe phenotype that presents shortly after birth, whereas others have a milder phenotype and retain some speech and motor capabilities. To study this phenotypic variability in detail, Young and Zoghbi use a mouse model of RTT, which eliminates variability in environment and genetic background. These mice carry an *Mecp2* mutation that is fully penetrant in male mice and variably penetrant in females heterozygous for the mutation. They directly counted individual cells from the brains of these mice using immunofluorescence and found that the majority of mice exhibit unbalanced X chromosome inactivation (XCI) that is skewed in favor of the wild-type allele. This skewing appears to have relevance for phenotypic variability, because the more the XCI pattern favors expression of the wild-type allele the less likely the mice are to exhibit four Rett-like phenotypes that were evaluated. Neuronal cultures were used to determine why this unbalanced XCI might have occurred. When primary neurons from these heterozygous mice are cultured, the percentage of cells expressing the wild-type allele actually increases by day 3 in culture, suggesting a selective advantage for cells expressing wild-type *Mecp2*. In support of this selective advantage is the fact that a wild-type population of cells will predominate after 7 d in a culture that started with an equal ratio of neurons carrying wild-type *Mecp2* and those carrying the truncating *Mecp2* mutation. These findings are surprising, considering that most girls with classic RTT have balanced XCI. Young and Zoghbi speculate that there may be females with *MECP2* mutations and unbalanced XCI but who do not appear in these RTT studies because they are asymptomatic or misdiagnosed.

Human Male Recombination Maps, *by Sun et al.* (*p. 521*)

Sun et al. present the first complete set of recombination maps for every autosome in a human male. This map was created by staining spermatocytes in two ways: centromere-specific multicolor FISH was used to identify individual autosomes, and immunofluorescence for MLH1 and SCP3 was used to mark recombination foci and synaptonemal complexes (SCs), respectively. This map makes it clear that every autosome bivalent has at least one recombination focus and that the number of foci generally correlates with the size of the chromosome. The positions of these foci are not random but exhibit positive interference, although there are rare instances when foci are very close to each other. In addition, there is repression of recombination near the centromere. Although SC lengths generated using these maps generally correspond to mitotic length estimates, there are some discrepancies; chromosomes with high proportions of G-band staining have shorter SC lengths than would be expected on the basis of their mitotic lengths. Because G-band regions

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generally contain fewer genes, this finding would suggest that recombination occurs preferentially in gene-rich regions.

Genomewide Scan for Menopausal Age, *by van Asselt et al.* (*p. 444*)

Both twin and family studies suggest that variation in age at menopause is controlled, at least in part, by genetic factors. In fact, a strong association has been found between the menopausal ages of mothers and daughters. Although two genes, the factor V Leiden gene and one encoding estrogen receptor 1 α, are associated with variation in age of menopause, their effects are small. To find additional genes affecting this trait, van Asselt et al. collected a sample of sib pairs from the extreme parts of the trait distribution, a strategy that should increase their power to detect a quantitative trait locus. They found suggestive linkage to chromosome 9q21.3 and significant linkage to chromosome Xp21.3. If they separated the families on the basis of whether they exhibited early or late menopause and analyzed these subgroups separately, they found that the peak on chromosome X was almost entirely due to women with early menopause. This peak is located in a region of interest for premature ovarian failure (POF), the cessation of menses at or before 40 years of age. This is not strictly a POF locus, though, because suggestive linkage is still present after exclusion of women who meet the criteria for POF. Perhaps one gene in this region explains not only POF, but also more general variation in age at menopause.

WNT3 ***Mutation Causes Human Limb Agenesis,*** *by Niemann et al.* (*p. 558*)

The congenital absence of all four limbs, or tetra-amelia, is very rare and is associated with other abnormalities, such as craniofacial, urogenital, and pulmonary defects. Because of this phenotype, the gene mutated in tetra-amelia must be a key player not only in early limb development but in the development of other organ systems as well. In an attempt to identify this gene, Neimann et al. studied a consanguineous family with tetra-amelia and other craniofacial and urogenital defects. Homozygosity mapping pointed them toward a locus on chromosome 17. Within the critical region was *WNT3,* a member of the family of *WNT*-signaling molecules that play many roles in development. In mice, *Wnt3* is involved in the establishment of the apical ectodermal ridge and is essential for normal limb development. Sequence of this candidate gene indicated that the affected fetuses were homozygous for a nonsense mutation in *WNT3,* whereas unaffected family members were heterozygous. The mutation would truncate the protein after only 82 amino acids, suggesting it is a loss-of-function mutation. In contrast to the finding in humans that a complete lack of WNT3 signaling prevents proper development of the limbs and other organs, mice homozygous for null *Wnt3* alleles have an earlier developmental defect and fail to gastrulate. This suggests that members of the *Wnt* family may have species-specific roles and that there are other WNT proteins in humans that regulate gastrulation.

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