This Month in *The Journal*

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Genetic Interaction and Stratification

Bhattacharjee et al., page 331

A large number of loci have been identified to be associated with complex disease via single-SNP analyses, but a large proportion of the heritability of these diseases remains to be elucidated. The expectation is that variants in multiple genes are involved in contributing to a risk effect and that the effects of these variants alone may be not be strong enough to be considered significant on their own. In this issue, Bhattacharjee and colleagues present their approach to exploring gene-gene interactions in both case-only and case-control study designs. In particular, the authors incorporate principal component analysis into their methods not only to remove the bias introduced by potential population stratification but also as a means of increasing efficiency. Because they are able to assume that an observed correlation between markers in two different genes is not due to shared ethnic substructure in the homogeneous samples they establish, they can exploit this gene-gene independence to gain power. These principles form the basis of a number of proposed algorithms that can be utilized in different scenarios and study designs. The authors demonstrate the advantages of their methods in analyses based on data from a breast cancer study and discuss the situations in which to use each method.

Female-to-Male Breeding Ratio in Modern Humans

Labuda et al., page 353

A variety of analyses have been done to evaluate the breeding patterns of humans through the ages, but results have been conflicting. The favored theory of anthropologists and paleontologists is that our species tends to be monogamous but has instances of polygyny, which means that some males produce more offspring than others, usually as a result of breeding with more than one female. Some genetic studies have supported this idea, but others have suggested that there was actually a historical tendency for some females to breed with more than one male. These different conclusions were attributed to a number of study-design factors that led to potential biases in the analyses. In this issue, Labuda and colleagues examine the issues associated with the previously employed methods and propose a new technique that is robust to the identified pitfalls. The authors evaluate HapMap data and provide evidence that a low level of polygyny did occur in the history of the populations studied, thus supporting the anthropological hypothesis of a general adherence to monogamy sprinkled with some polygyny. This polygyny is not necessarily the result of males breeding with multiple females at the same time; it may be affected by the fact that more males than females remarry and have children after divorce or death of a spouse.

4qter and 10qter Haplotype Distribution

Lemmers et al., page 364

Just proximal to the telomeres on chromosomes are chunks of duplicated DNA called subtelomeres. The sequence homology between the subtelomeres on different chromosomes is very high, but the large variation of the number and orientation of the repeats in these regions contributes to phenotypic diversity. Variation within subtelomeres can also cause disease; the contraction of the macrosatellite repeat D4Z4 within the subtelomere on 4q leads to facioscapulohumeral muscular dystrophy (FSHD). Of particular note, previous work has found that the 4q D4Z4 contraction only leads to FSHD if it is on a specific haplotypic background. In addition, the subtelomere region on 10q contains D4Z4 repeats that are 99% homologous to those on 4q, and yet contraction of the 10q repeats on any haploytpic background does not cause FSHD. Lemmers and colleagues study the 4q and 10q subtelomeric regions in a data set of populations from around the world to learn more about the evolutionary relationship between them. The authors hoped to determine whether the various haplotypes of the 4q and 10q subtelomere regions are due to abundant recurrent chromosomal exchange between the two chromosomes or whether it is more likely that a limited number of translocations occurred early on and have since undergone chromosome-specific evolution. The authors ultimately conclude that it is in fact the intrachromosomal rearrangement of just four ancient transfers that is responsible for the different haplotypes observed in the region. The lack of exchange between the two chromosomes may explain how the disease-causing effect of the D4Z4 contraction remains isolated to a particular 4q haplotype.

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HSP47 in Osteogenesis Imperfecta

Christiansen et al., page 389

Osteogenesis imperfecta (OI) is also known as brittle bone disease. This is because OI is characterized by bones that break easily, sometimes just from a person being hugged. In addition to the tremendous physical impediments for OI patients and their loved ones, OI imparts psychological burdens. OI children are sometimes removed from homes because of suspicion of abuse and can grow up fearful of trying new things, constantly afraid of breaking a bone. Although different types of OI exist and range in severity, all cases of OI are thought to be caused by a lack of functional type I collagen. For many years, mutations in only *COL1A1* and *COL1A2* (the genes encoding type I collagen) have been known to cause OI. Although attempts have been made, genotype-phenotype correlation with these collagen mutations has been challenging. More recently, mutations in genes involved in collagen assembly and modification have been implicated in OI; most of them lead to overmodification of the collagen chains. The relationship between the now more-numerous associated proteins and OI pathology provides hope for identifying a link between mutation type and disease severity. Here, Christiansen and colleagues add another gene to the growing list. They analyze *COL1A1*, *COL1A2*, *CRTAP*, and *LEPRE1* in OI patients lacking overmodified collagen. After finding no mutations in these genes, the authors identify a causative mutation in *SERPINH1* encoding a collagen chaperone protein (HSP47). They find that the mutation leads to the accumulation of type I collagen in the Golgi and that the collagen triple helix formed is hypersensitive to proteasomal degradation. This work sheds further light on the molecular pathogenesis of OI.

Duplication Types and Mechanisms in PTLS

Zhang et al., page 411

Genomic rearrangements include deletions, translocations, duplications, and gene conversions. Rearrangements can involve one, two, or several chromosomes and may occur during meiosis or double-stranded DNA repair. Sometimes genomic rearrangements cause no discernable phenotype. However, chromosomal rearrangements may also cause syndromes that often include intellectual disability. Some rearrangements are more common than others, providing researchers with a starting place for identifying the mechanism of such genomic alterations. One common rearrangement is the 17p11.2 deletion observed in association with Smith-Magenis syndrome (SMS). Recent analyses have identified a reciprocal common duplication in this chromosomal region associated with Potocki-Lupski syndrome (PTLS) and have identified nonallelic homologous recombination (NAHR) as the responsible mechanism mediating these genomic alterations. NAHR is likely to occur at sites of long repeated sequences having high similarity, such as segmental duplications and low-copy repeats. Such is the case on the short arm of human chromosome 17. In fact, in addition to the common 17p11.2 deletion, a less common but recurrent deletion has been identified in the same region. This deletion has been shown to be mediated by a separate set of low-copy repeats. Here, Zhang and colleagues identify a reciprocal PTLS duplication to this uncommon recurrent SMS deletion. They further show NAHR to be the responsible mechanism and identify the presence of homologous recombination hot spots responsible for the duplication. A percentage of these duplications appear to occur through de novo rearrangement in sperm, highlighting the complexity of such genetic alterations.