This Month in the *Journal*

Perhaps the oldest—and still the most emotionally charged—disputes in human genetics concern the heritability of cognitive traits. This issue, we feature three articles on recent approaches to the genetics of behavior and cognition. Watkins et al. (p. 1215) describe neuroimaging techniques that are now available to supplement psychometric approaches to behavioral abnormalities. Some of these methods are safe and noninvasive and so should permit longitudinal genetic studies. Using these techniques, Watkins et al. have refined their phenotypic analysis of an extended family with a distinctive speech and language disorder, and they have mapped an autosomal dominant locus, SPCH1, which cosegregates with this defect. Mervis et al. (p. 1222) discuss the heritability of visuospatial constructive cognition, one of several recognized dimensions of measured intelligence. Visuospatial construction is specifically impaired in the contiguous gene–deletion syndrome, Williams syndrome, and Mervis et al. discuss the evidence that haploinsufficiency for one of the genes in the deleted region, *LIMK1,* is responsible for this cognitive phenotype. Finally, Plomin (p. 1476) reviews a book by Nicholas Mackintosh, *IQ and Human Intelligence,* a survey of the recent and historical thinking about the topic. Mackintosh addresses the old controversies in a noninflammatory way, and Plomin explains his hope that this book and the research that it covers will help rehabilitate the notion of general intelligence.

Also in this issue, Shadel (p. 1230) reviews the basis of DNA replication in the mitochondrion and the use of yeast genetics to study this process. Yeast has proved invaluable in the molecular analysis of conserved interactions in this pathway, but Shadel cautions that quirks of yeast cells, particularly their high rate of spontaneous mtDNA deletions, make it dangerous to generalize between yeast mitochondrial phenotypes and normal or pathological events in mammalian cells.

Spectrum of Mutations in WFS1, *by Hardy et al.* **(***p. 1279***)**

Wolfram syndrome is a poorly understood multisystem disorder that presents with diabetes and neurodegenerative symptoms, including optic atrophy, deafness, and, in some cases, severe psychiatric illness. Although the gene that is mutated in this disorder, *WFS1,* has been characterized, the role of the WFS1 protein, in nervous tissue or elsewhere, is unknown. Hardy et al. have ascertained 19 British families in which this condition is linked to the WFS1 locus, and they have screened affected family members for mutations in *WFS1*. Mutations map throughout the gene and include missense and nonsense mutations as well as small deletions and insertions. Of the 24 mutations found, all but 1 were novel, more than doubling the total number of disease alleles known for this gene. Most affected individuals are compound heterozygotes, and the high degree of sequence variation among these individuals makes screening more difficult. Wolfram syndrome overlaps clinically with several disorders linked to mitochondrial mutations, and much of the phenotype could be explained by mitochondrial dysfunction. In some—but not all—earlier studies, individuals with WS are found to contain a high level of mtDNA deletions, but Hardy and coworkers find no evidence for mtDNA instability in their cohort, raising the possibility that this effect is secondary to other stresses on the mitochondrion in the cells of affected people. For more on mtDNA instability, see the article by Shadel (p. 1230).

Hypomethylated Fragile X Full Mutation, *by Burman et al.* **(***p. 1375***)**

Fragile X–associated mental retardation occurs in most cases because of transcriptional silencing of the *FMR1* gene, rather than because of a deletion or point mutation at that locus. This epigenetic effect follows when an unstable CGG trinucleotide repeat in the 5′ UTR of the gene reaches a critical size of >220 repeats and becomes heavily methylated. Such expanded alleles are considered to be full mutations, whereas premutations of 55–220 repeats, which remain unmethylated, predispose to expansion but are otherwise benign. On the basis of studies using methylation-sensitive restriction endonucleases, it appears that the effect on transcription depends on methylation, rather than on the length of the CGG-repeat tract per se, since occasional individuals are found who lack the expected high level of methylation and are of normal intelligence. Burman et al. have studied one such person, using a novel analytical method that is sensitive to methylation throughout the region, not just at rare sites recognized by the standard restriction enzymes. They confirm that this subject's CGG tract, which varies in length from 60 to 700 repeats in blood cells, is free of methylation. Nevertheless, other sites on his X chromosome are normally methylated, and Burman et al. argue that he has no general defect either in de novo or maintenance methylation. Instead, they suggest, methylation of full-mutation alleles may occur only at an early developmental period, and the subject may have

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escaped this DNA modification. Although this fortunate event may be mere chance, it is interesting that, of the subjects' two cousins who carry full mutations, one seems to be unaffected and to lack CGG methylation in this region.

Pseudoautosomal Linkage, *by Horwitz and Wiernik* **(***p. 1413***)**

The pseudoautosomal regions (PAR) of the sex chromosomes, Horwitz andWiernik note, are not represented in standard panels of genetic markers, so genomewide scans for disease genes may systematically avoid these two small regions. Nevertheless, at least three disease genes have been mapped to the short-arm PAR, including the *SHOX* gene, which underlies a rare skeletal abnormality, Leri-Weill dyschondrosteosis (LWD). Horwitz and Wiernik now argue that a gene predisposing to familial Hodgkin disease (HD) also maps to this region. Linkage between *SHOX* and the HD locus was originally proposed because LWD and HD cosegregate in at least one family, as would be expected if a contiguous-gene deletion affected two adjacent loci. Although pseudoautosomal genes are in many respects similar to autosomal genes, genes in the PAR are like sex-linked genes in one critical but seldom noted respect: they are transmitted preferentially from a father to either his daughters or his sons, depending on which chromosome carries the mutation. For this reason, sibs of the same sex are expected to be concordant for disease state if a mutation lies in the paternal PAR. The excess of sex-concordant affected sibs—which has indeed been observed in families with HD—declines with distance from the centromeric end of the PAR, providing a means to map disease genes within the PAR. This approach allows the authors to map the LWD locus to the telomeric end of the PAR, where *SHOX* is known to reside. The same approach suggests a PAR linkage for the HD gene, somewhat more centromeric than *SHOX*.

Human Variation in Mitotic Recombination, *by Holt et al.* **(***p. 1423***)**

Mitotic recombination (MR) becomes a medical concern because of loss of heterozygosity (LOH) in tumor-suppressor genes, but it may be far more widespread, leading to increasing genetic chimerism in tissues as people age. Holt and colleagues have cultured somatic cells from 105 healthy individuals and have applied a selection against the expression of a specific HLA allele, to quantify the rate at which these cells lose expression of a gene. Loss of gene expression due to MR, they find, varies over a remarkably wide range, with 10%–20% of the subjects showing essentially no MR. This work lays the basis for a genetic analysis of MR, which might provide valuable insights into individual differences in aging. Holt et al. note that MR occurs significantly more frequently in cells from women than in those from men, and they speculate that a reduced level of MR in premeiotic male germ cells may be advantageous because of risk of LOH and the large number of mitotic divisions in these cells during a male's life span. If meiotic recombination rates vary in parallel with MR rates, selection at this level could account for the differences that are seen in linkage maps that use male and female recombination data separately to calculate genetic distances.

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