This Month in the *Journal*

Proteins rarely function in isolation. To carry out their physiological roles, most proteins must reach a specific intracellular address and interact with multiple structural and regulatory molecules, including specialized "scaffold" or "adaptor" proteins. Three reviews in this issue discuss genetic and other evidence for the importance of such interactions, particularly in the regulation of signal transduction pathways. Bianchi and Beltrame (p. 1573) focus on the macromolecular interactions that cause DNA bending and that bring distant DNA-binding proteins into contact with one another. Loss of this DNA-bending effect in the human *SRY* gene causes male sex determination to fail. Engelman et al. (p. 1578) describe the multiple roles of caveolins in human cellular function. Caveolins organize caveolae, the specialized cell-surface organelles in which the various members of certain signaling pathways are concentrated; heritable defects in one caveolin gene underlie a form of limb-girdle muscular dystrophy and probably several other human diseases as well. Finally, Semb and Christofori (p. 1588) show that cadherin complexes, which participate in cell-cell adhesion, directly suppress carcinoma development, both in human families and in a mouse model system developed to follow tumor progression.

RSK2 Mutations in Coffin-Lowry Syndrome, *by Jacquot et al. (p. 1631)*

Coffin-Lowry syndrome (CLS) arises from mutations in the X-linked I gene, the product of which is a serine-threonine–type kinase expressed in multiple cell types. Jacquot and coworkers describe the exon structure of the gene and identify 23 novel mutations from a set of 37 individuals, ascertained worldwide, with mental retardation and the skeletal and facial features of CLS. All the mutations are point lesions, including missense, nonsense, and frameshift mutations, as well as splice-site changes, and they are distributed evenly throughout the gene. In more than two-thirds of the cases for which maternal DNA was available, the mutations appear to be de novo. The presence of affected female probands whose fathers are unaffected may suggest dominant X-linked transmission, but biased X inactivation might prove to be a more satisfying explanation.

LKB1 Mutations in PJS, *by Mehenni et al. (p. 1641)*

Peutz-Jeghers syndrome (PJS) is unusual among hereditary tumor syndromes in that its underlying gene encodes a tumor-suppressing protein kinase. As with other tumor suppressors, heritable mutations of the *LKB1* gene cause tumor growth—in this case, generally polyps in the stomach and small intestine, as well as gonadal and oral carcinomas—only when a second, somatic mutation occurs. Mehenni et al. have scanned a set of nine PJS families for mutations in *LKB1;* they report that they found novel mutations in seven families. Although no exogenous substrates are known for either LKB1 or its *Xenopus* homologue, Xeek1, these proteins are known to phosphorylate themselves. Mehenni et al. confirm that the four identified *LKB1* missense mutations greatly reduce autophosphorylation activity, suggesting that the mutant alleles encode inactive kinases. The authors' failure to find mutations in two of the families is consistent with evidence for at least one additional PJS locus.

Missense Mutations in ATP7B, *by Forbes and Cox (p. 1663)*

Yeast has proved to be a reliable system for the study of mechanisms of metal-ion homeostasis that are similar to those in human cells. Forbes and Cox have used yeast to follow the consequences of point mutations in the copper-transporter protein ATP7B, which is defective in Wilson disease. Yeast cells lacking the homologous copper transporter, Ccc2p, are deficient in intracellular copper, and their copper-dependent proteins, including the iron transporter Fet3p, are inactive. These cells fail to grow unless supplemented with high levels of extracellular iron, but several groups have found that they can restore the missing function by using the human *ATP7B* gene. Forbes and Cox show that *ATP7B* expressed in yeast activates apo-Fet3p, both in vivo and in vitro, and permits cell growth on iron-restricted media. When missense alleles from Wilson disease families are tested with this assay, eight of nine appear to retain some activity, but one allele with a conservative amino acid substitution emerges, surprisingly, as a null allele completely incapable of complementing the *ccc2* deficiency.

Vitamin D 1α-Hydroxylase Deficiency, *by Wang et al. (p. 1694)*

Wang et al. report the mutations in the vitamin D 1α-hydroxylase gene in a set of individuals with an inborn error of metabolism whose symptoms mimic those of diet-induced rickets. These researchers had already implicated the 1α-hydroxylase gene in this disorder, and now they have explored the haplotypes and disease alleles in 19 patients. The authors employed long-range

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PCR and direct sequencing to identify disease mutations, and they identified all patients in their group as homozygotes or compound heterozygotes, for various exonic mutations. Three tightly linked polymorphic markers allowed them to define disease allele–associated haplotypes in some cases. The authors have also created and expressed all seven of their missense mutant cDNA in cultured cells, and they show that the gene products were indeed inactive, as expected on the basis of known three-dimensional models of P450 enzymes that are related to 1α-hydroxylase.

Xp Turner Syndrome Locus, *by Zinn et al. (p. 1757)*

Haploinsufficiency for multiple X-linked genes might be expected to cause diverse phenotypes, and X-monosomic (Turner syndrome) females are, indeed, subject to numerous developmental abnormalities, such as ovarian failure and short stature. In the hope of mapping common deleted regions that correlate with specific characteristics of Turner syndrome, Zinn et al. have ascertained a set of 28 nonmosaic females lacking some or all of Xp. They report that deletion of a single large region of this chromosomal arm is associated with at least three of the cardinal Turner symptoms, namely, short stature, ovarian failure, and a high arched palate. Because X-chromosomal genes that are subject to inactivation are monoallelically expressed at most points in development in both XO and XX females, Zinn et al. suggest that one or more genes in this interval that escape X inactivation are likely to underlie these three phenotypes.

Automated Detection of Fetal Cells, *by Oosterwijk et al. (p. 1783)*

Genotyping of fetal cells in maternal circulation represents an attractive, minimally invasive alternative to amniocentesis or chorionic villus sampling. The high background of maternal cells represents an obvious impediment to the study of fetus-derived cells, such as nucleated red blood cells (NRBCs), but Oosterwijk and coworkers suggest a histochemical technique that may avoid the need for clean separation of maternal and fetal blood cells. Immunostaining for fetal hemoglobin provides a strong signal that causes NRBCs to stand out from a large excess of maternal RBCs, and this technique is compatible with other staining methods, such as X- and Y-chromosome–specific FISH analysis. Particularly when this approach is automated, FISH of rare NRBCs can reliably indicate fetal sex.

Y-Chromosome Haplotypes of New World Populations, *by Bianchi et al. (p. 1862)*

The timing and number of waves of immigrants across the Bering Strait have been controversial, with various mtDNA studies favoring single immigrations, multiple immigrations, or even continuous immigration. Bianchi et al. now enter this discussion with new data on Y-chromosome haplotypes taken from populations throughout the Americas. The authors focus solely on Y chromosomes that bear the DYS199T allele, which is absent from most populations but which is common among New World populations and some indigenous Siberian groups related to present-day Native Americans. Bianchi et al. have found that the haplotype diversity among Y chromosomes with this marker is dramatically lower than that among Caucasian men and that there is no evidence that the DYS199T variant has arisen more than once. They also deduce that the now-common 0A haplotype was probably carried by a founder male whose descendants spread throughout North and South America. On the basis of the degree of divergence among DYS199T-bearing chromosomes and of an estimate of mutation frequency, the authors suggest that the founder of the lineage lived >800 generations ago.

Genome Screens Using LD Testing, *by Chapman and Wijsman (p. 1872)*

Despite its great success in refining gene localization, linkage disequilibrium (LD) analysis of the whole genome has not yet yielded any disease genes, probably because polymorphic markers are still scattered too thinly across the genome. There is considerable enthusiasm for DNA chip-based methods as an alternative genotyping tool that might make complex genetic diseases tractable for whole-genome LD studies. However, because these chips are—at least to date—best applied to binary determinations (the presence or absence of specific polymorphic alleles), they are apt to lose information, compared with the use of multiallelic markers. Chapman and Wijsman argue that, even for single-gene diseases, the power of such LD screens will be greatly reduced by the reliance on diallelic markers. The authors suggest that, unless dense maps of highly informative multiallelic markers can be included, LD screens may only be appropriate for the most straightforward applications, such as the identification of recent mutations that cause simple recessive disorders.

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