Zonadhesin Reveals Rapid Adaptive Evolution, *by Gasper et al.* (***p. 820***)

After a sperm enters an egg during fertilization, the first step involves sperm proteins binding to proteins of the egg's zona pellucida. The highly species-specific nature of this interaction is expected to be due to rapid evolution of the gamete proteins. It has not yet been completely elucidated which sperm proteins are involved in the process, but, because the zona pellucida proteins ZP1 and ZP2 show strong signals of positive selection, it has been suggested that the crucial sperm proteins will demonstrate a similar signature. Zonadhesin, encoded by *ZAN,* has been implicated as the sperm protein involved, because it functions as a matrix receptor and contains a number of different types of binding domains. Gasper et al. examined the evolution signature of *ZAN* by comparing the gene sequences from a large set of primate species with those from two human populations. Their analyses reveal that one exon of *ZAN* is evolving much more quickly than is the rest of the gene and may represent the site of gamete interaction. Additionally, there is evidence that, among human sequences, positive selection has increased the prevalence of a *ZAN* variant in which a frameshift mutation has occurred, suggesting that the gene encoding the truncated protein, initially believed to be a pseudogene, retains function.

MCMC Linkage Analysis, *by Wijsman et al.* (***p. 846***)

When linkage analyses are performed, decisions need to be made regarding the most appropriate methods to use, the best type and density of markers to select, and how these relate to the size and completeness of the available pedigrees. Because algorithms to perform exact analyses are not computationally possible for large pedigrees with dense marker coverage, sampling Markov chain–Monte Carlo (MCMC) methods are popular choices. Two of the most commonly used, MORGAN and SimWalk2, have similarities and differences, and Wijsman et al. compare the two to determine for which situations each is more suitable. Using simulated pedigrees of various sizes and with differing amounts of missing data, they evaluate the accuracy and the computation time of the programs for different densities of multiallelic STR markers or SNPs. The authors find that, although SimWalk2 tends to be faster and more accurate when using STRs on larger pedigrees with increased missing data, both algorithms perform comparably for STRs in general. Unexpectedly, they report that MORGAN also performs well for dense SNP data, which is in contrast to the current expectation that traditional methods are not properly equipped to handle dense SNP data.

Mitochondrial Translation Defect, *by Smeitink et al.* (***p. 869***)

Oxidative phosphorylation (OXPHOS) defects occur because of the dysfunction of any of the five mitochondrial OXPHOS complexes. The proper maintenance of these complexes requires the efficient translation of mitochondrial-encoded polypeptides, a process mediated by mitoribosomes. The machinery of mitoribosomes involves the interaction of a variety of nuclear-encoded and mitochondrial-encoded polypeptides—including initiation factors, elongation factors, release factors, recycling factors—as well as mtDNA-encoded tRNAs and rRNAs. Many issues with the translation of mitochondrial-encoded proteins have already been attributed to mutations in mitochondrial genes, but new cases of nuclear-gene defects have been identified. Here, Smeitink et al. screened two OXPHOS-deficient patients and found that both had the same mutation in EFTs, one of the elongation factors that is encoded by the nuclear gene *TSFM*. Immunoblot results indicated that both EFTs and its binding partner, EFTu, were at lower levels in patient cells; however, overexpression of either of the wild-type elongation factors increases the level of both. To demonstrate the importance of these factors in mitochondrial translation, the authors overexpressed EFTs or EFTu in patient cells and showed that this leads to a significant increase in the synthesis of the OXPHOS-complex proteins and restores OXPHOS-complex assembly to normal levels.

HCCS ***Mutations in MLS,*** *by Wimplinger et al.* (***p. 878***)

The critical region for microphthalmia with linear skin defects syndrome (MLS), an X-linked disorder characterized by skin and ocular manifestations in females and by lethality in males, has been narrowed to contain three known genes. Because of the scarcity of MLS-affected families without chromosomal abnormalities, it has been difficult to determine which gene's deficiency is actually responsible for the disease. Wimplinger et al. screened the genes in patients with no obvious chromosomal rearrangements and discovered that *HCCS,* the gene encoding mitochondrial holocytochrome c-type synthase, was disrupted. The authors then set out to establish that the *HCCS* mutations affected protein function. The effect of two of the mutations was first assessed using a yeast system. Yeast deficient for the ortholog of cytochrome c heme lyase cannot grow on a nonfermentable carbon source, but pre-

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vious work has demonstrated that this deficiency can be complemented by human HCCS. The expression of two of the *HCCS* mutants was unable to rescue the mutant yeast phenotype, which supports the hypothesis that these mutations severely affect protein function. The authors also demonstrate that one of the mutations keeps HCCS from localizing to the mitochondria. Additionally, congruent with the prediction that cells expressing the mutant *HCCS* will have inhibited growth, the X inactivation is skewed in the females with MLS who have these mutations.

***Distinct 10q Haplotypes in CS and BRRS,* by *Pezzolesi et al.* (*p. 923*)**

Germline mutations in *PTEN* are associated with a large group of cancer syndromes collectively referred to as "*PTEN* hamartoma tumor syndrome" (PHTS). Included in this group are the distinct clinical entities of Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome, and Proteus-like syndrome. Evidence suggests that at least CS is genetically homogeneous and that *PTEN* is the disease's primary etiologic locus, yet there are many patients with CS in whom no *PTEN* mutation has yet been identified by traditional screening. In an effort to more closely examine the relationship between variation in the region and PHTS, Pezzolesi et al. looked for *PTEN* haplotypes that are associated with the syndrome. Although various significant differences were observed between the frequencies of haplotypes in the groups evaluated, a striking observation was the prevalence of low-frequency haplotypes in patients with PHTS compared with controls. This suggests that these rare haplotypes may play a role in the development of PHTS in these patients and that disease-causing functional variants may be in linkage disequilibrium with the haplotypes. These haplotypes may also help to explain the phenotypic variability observed among patients with PHTS who have the same *PTEN* mutation.

This Month on the Cover

Barbara McClintock's work focused on maize chromosomes and the genetics of corn. Early in her career, she identified the 10 maize chromosomes and could correlate phenotypic characteristics with chromosomal bands. In 1931, with Harriet Creighton, she demonstrated that the "crossing-over" of genetic markers affected the phenotypic presentation of corn (Proc Natl Acad Sci USA 17:492–497). She also showed that radiation affects chromosome structure and that this affects kernel phenotype. But it is for her discovery of transposons that McClintock eventually received the most recognition. She reported that kernel pattern seemed to be controlled by signals that could move intra- or interchromosomally. She called the movement of these signals "transposition" and referred to the moving pieces themselves as "transposons" ("Mutable Loci in Maize," Carnegie Institution of Washington Yearbook 47 [1948], pp. 155–169). In 1951 at Cold Spring Harbor, McClintock presented her work about gene transposition in maize. Few understood or appreciated the importance of her discovery or the relevance it had to human genes. It was a time when it was accepted that the gene was the heritable unit, but everyone believed that the whole genetic structure of the chromosome was static and unmoving. It wasn't until 1983 that McClintock's work was properly recognized and she was awarded the Nobel Prize in Physiology or Medicine for revealing that genetic material can jump around, or transpose. Special thanks to Matthew Feldman, Johns Hopkins University, for the photograph.

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