Zinc-Finger Protein ERIS and Wolfram Syndrome 2, by Amr et al. (*p. 673*)

Wolfram syndrome (WFS) is a recessive disorder characterized by juvenile-onset diabetes mellitus, optic atrophy, and, often, hearing loss. Although most WFS cases have been attributed to mutations in *WFS1,* some patients remain in whom no mutation has yet been identified. Three such families were previously used in linkage analysis, and a new locus for WFS2 was identified on 4q22-25. Amr et al. screened 42 candidate genes in this region and found a single founder missense mutation in *ZCD2,* a gene encoding a zinc-finger protein, called "ERIS." The residue altered is highly conserved, but the authors showed that the effect of the mutation is to abolish a splice site that leads to the skipping of exon 2. Localization studies demonstrated that, like the protein product of *WFS1,* that of *ZCD2* is also found in the endoplasmic reticulum, but the two proteins do not interact with each other. Additional functional work predicted that ERIS may play a role in calcium homeostasis.

Detecting Deletions in Genotype Data, by Kohler et al. (*p. 684*)

There is increasing evidence that copy-number variation (CNV) is an important contributing factor in disease and normal genetic variation. Traditional methodology to identify CNV is expensive and/or the resolution is too low to pick up small microdeletions or microduplications. The decreasing costs of SNP genotyping have opened up a new means of searching for CNV in a large number of samples, but algorithms need to be developed to analyze the data and to correctly differentiate real results from genotyping errors. Kohler et al. developed their tool, *microdel,* which is not only able to detect deletions with use of SNP genotyping data but also able to incorporate frequency and transmission information, to test for association between deletions and a phenotype. Through simulations, the authors demonstrated their ability to detect deletions with reasonable false-detection rate and power. As expected, larger and more-common deletions were identified more reliably, but smaller deletions were also found. *Microdel* was then used to screen 90 CEU individuals (i.e., of European ancestry sampled in Utah) and 90 YRI individuals (i.e., of Yoruba ancestry sampled in Ibadan, Nigeria), and a large number of deletions were discovered in the samples.

Clinical and Molecular Phenotype of AGS, by Rice et al. (*p. 713*)

Several of the clinical features of Aicardi-Goutières syndrome (AGS), which include encephalopathy with intracranial calcification and cerebrospinal-fluid lymphocytosis, can be confused with signs of congenital infection. AGS is also phenotypically and genetically heterogeneous, which makes diagnosis even more difficult. To date, mutations in four different genes have been identified that cause AGS: *TREX1, RNASEH2A, RNASEH2B,* and *RNASEH2C*. Rice et al. collected genotype and phenotype data from 127 AGS-affected pedigrees, in an effort to elucidate the characteristics of AGS and to simplify diagnosis and counseling of patients. The authors discovered that the majority of patients with *TREX1* mutations had a more severe form of the disease and were often affected at birth. In contrast, those with mutations in *RNASEH2B* developed AGS later, with a less severe disease and lower mortality. The authors also noted that the majority of the mutations in their patients would be identified by screening only *TREX1,* three exons of *RNASEH2B,* and a recurrent *RNASEH2C* mutation in Pakistani patients. Additionally, because 22 families were analyzed in which no mutation was found, it was predicted that at least one more AGS gene remains to be elucidated.

PTEN *Promoter Mutations Inhibit Translation,* by Teresi et al. (*p. 756*)

Although mutations in *PTEN* are thought to be the only cause of Cowden syndrome (CS), a portion of patients exist in whom no mutations have been identified. Previously, a screen of putative transcription-factor binding sites within the *PTEN* promoter region revealed new mutations that affected gene expression, but not all cases were explained by these variants. Teresi et al. examined five patients with CS who carried sequence changes in the *PTEN* 5′ UTR that were not predicted to affect transcription. Here, the authors demonstrated that, although the variants inhibit activity when evaluated in a luciferase assay, they do not actually lead to a decrease in luciferase mRNA. This led to the prediction that the variants were affecting expression at the translational level. *In silico* analysis of the variants predicted that they would alter the secondary structure of the mRNA. Concordant with the amount of perturbation predicted at the mRNA level, a measurement of protein levels confirmed that translation was, in fact, affected. The authors suggest that the changes in secondary structure interfere with normal translation.

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This Month on the Cover

Genomic imprinting is the phenomenon in which the copy of a gene from one parent is expressed and the copy from the other parent is not expressed. This dependence on allele origin can lead to unexpected inheritance patterns of diseases caused by defects in imprinted genomic regions. The fact that parental effects may play a role in the expression of some genes was first demonstrated in the 1980s, when Solter and Surani performed nuclear-transplant experiments and showed that both the paternal and the maternal genomic contributions were necessary for normal embryonic development (J Exp Zool 228:355–362; Science 222:1034–1036; Nature 308:548–550; Cell 37: 179–183; Cell 45:127–136). Later, in 1991, DeChiara et al. first identified an imprinted gene, with the discovery that mutations in *Igf2* caused a growth defect in mice only if the mutated allele was inherited from the male parent (Cell 64:849–859). When the maternal copy was mutated, the offspring were not affected. On the cover is the figure containing the pedigree information from the work of DeChiara et al. Note the characteristic inheritance pattern of the growth-defect phenotype. Reprinted, with permission from Elsevier, from DeChiara TM, Robertson EJ, Efstratiadis A (1991) Parental imprinting of the mouse insulin-like growth factor II gene. Cell 64:849–859.

Robin E. Williamson
Deputy Editor