This Month in the *Journal*

When we think of complex traits, we often think of the contribution of multiple genes and environmental factors to the phenotype. This month in the *Journal*, Sriram et al. discuss a factor that may contribute to the complexities of phenotypes associated with single-gene disorders: moonlighting activities. Moonlighting enzymes are metabolic enzymes with more than one unrelated function. One can imagine that, when researchers are blind to one or more functions of a moonlighting enzyme, there may be aspects of a phenotype that are not explained by the main function of the protein. The authors discuss known moonlighting activities as well as methods for identifying additional moonlighting activities. As new functions are identified for some proteins, it is likely that we will resolve some of the mysteries of complex phenotypes related to those proteins, leaving us better able to make genotype-phenotype correlations.

SNPs Responsible for a Linkage Signal, *by Li et al.* **(***p. 934***)**

Many research groups follow a similar procedure in their attempts to identify a genetic locus: start with a genome scan and follow that up with an association study in the regions that showed linkage with the trait. But it can be difficult to determine which associated markers are responsible for the linkage signal. To get around this problem, Li et al. developed a method that uses affected sib pairs and jointly models linkage and association. This allows them to determine whether a candidate SNP accounts for the linkage to a region. Further, they can estimate the amount of linkage disequilibrium between the candidate SNP and the actual disease alleles to get an idea of the degree to which a SNP accounts for the linkage signal. Simulations indicate that their method has good power to detect an association even when the sibling recurrence risk is low.

OTX2 ***Mutations in Ocular Malformations,*** *by Ragge et al.* **(***p. 1008***)**

Ragge et al. report the first *OTX2* mutations associated with ocular malformations. Their results stem from a candidate-gene approach that included *OTX2* because of reports that the murine version of the gene is a key regulator of photoreceptor-cell development and the finding that deletions of the region surrounding *OTX2* are sometimes observed in people with anophthalmia. Of the 333 individuals with ocular malformations who were screened for *OTX2* mutations, 8 had heterozygous sequence changes in the coding region, although the significance of two of these variants is not clear. Ocular phenotypes ranged from borderline microphthalmia to bilateral anophthalmia, and some individuals also had severe learning disabilities and seizures. Reduced penetrance, parental mosaicism, and phenotypic variability appear to be commonly associated with these mutations and may make genetic counseling of affected families less than straightforward. In contrast with the craniofacial malformations reported in heterozygous *Otx2* knockout mice, there was an absence of craniofacial abnormalities in the study individuals, although the authors point out that this could have been due to the sample ascertainment. In conjunction with expression studies, these mutations give greater insight into the role of *OTX2* in ocular development.

FOXP2 Truncation Impairs Speech and Language, *by MacDermot et al.* **(***p. 1074***)**

In 2001, Lai et al. (see references in MacDermot et al.) reported a family with a missense mutation in *FOXP2* and a proband with a translocation disrupting the same gene; both mutations were associated with a severe speech and language disorder. The report of Lai et al. generated a lot of interest in *FOXP2,* and subsequent studies were designed to look for mutations in individuals with such language-related phenotypes as autism, dyslexia, and speech-language impairment. Despite these efforts, the missense mutation in the original family is the only unequivocal *FOXP2* mutation that has been found. MacDermot et al. reasoned that their chances of finding additional *FOXP2* mutations would increase if they focused on individuals with a phenotype similar to the cases in the original report. The hallmark of this phenotype was verbal dyspraxia, which is a deficit in the coordination of the orofacial movements required for speech. They screened *FOXP2* in 49 probands with difficulties in speech articulation but no mental retardation, congenital abnormalities, or hearing problems, and they report a nonsense mutation that segregates with the phenotype and results in functional, if not actual, *FOXP2* haploinsufficiency. Two other coding changes in *FOXP2* were identified but were not present in affected siblings of the probands and are therefore of uncertain significance. A preliminary characterization of the phenotype in the family with the nonsense mutation suggests that the language defects are similar to those reported in the earlier *FOXP2*-associated family. Comparisons of these

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families may yield further insight into the role of FOXP2 in neurological and cognitive development.

SUCLA2 *Mutation in mtDNA Depletion,* *by Elpeleg et al.* (*p. 1081*)

While we're talking about moonlighting proteins (see the review article in this issue), it might be interesting to mention that Elpeleg et al. report a somewhat unexpected mutation associated with encephalomyopathy and mtDNA depletion. It was found in a family with severely retarded psychomotor development, muscle hypotonia, impaired hearing, and seizures. The activities of oxidative phosphorylation complexes containing mtDNA-encoded proteins were decreased in the affected individuals, which was consistent with the 50% reduction in the mtDNA-nuclear ratio in these kids. Homozygosity mapping localized the critical region to chromosome 13, and predictions for mitochondrial localization based on the ORFs in this region were used to prioritize the candidates therein. The affected individuals all had a rearrangement in *SUCLA2*, a gene encoding part of the ADP-forming succinyl-CoA synthetase (SCS-A), which plays a role in the tricarboxylic acid cycle. So what does this have to do with mtDNA levels? It turns out that SCS-A is tightly associated with a nucleoside diphosphate kinase (NDPK) that is critical for maintaining homeostasis of deoxyribonucleotides. Although the significance of this association is not clear, it appears that SCS-A disruption might alter NDPK function and lead to mtDNA depletion. Although a true moonlighting activity for SCS-A hasn't yet been demonstrated, these results point to a secondary and unexpected role for the protein.

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