Transcriptional Targets of FOXP2 *in Brain,* by *Spiteri et al.* (*p. 1144*) *Direct Neural Targets Regulated by* FOXP2*,* by *Vernes et al.* (*p. 1232*)

The development and maintenance of speech and language skills is a complex process in which several genes are most likely involved. Disruption of the gene encoding a forkhead-box transcription factor, *FOXP2,* has been associated with language dysfunction in a small number of cases. In concordance with the hypothesis that *FOXP2* is involved in language and speech, strong signals of positive selection have also been found around the human gene. Spiteri et al. and Vernes et al. predicted that identification of the genes whose expression was affected by *FOXP2* would potentially reveal other genes involved in the language pathway. Spiteri et al. performed ChIP-chip analysis on brain tissues to identify such downstream targets of *FOXP2*. Several of these genes were found to also be under positive selection in humans. Similarly, Vernes et al. used ChIP-chip analysis to establish a list of target genes in neuronlike cells. The overlap between the gene lists provides a compelling set of candidates for further investigation.

Rapid Adjustment of Correlated P *Values,* by *Conneely and Boehnke* (*p. 1158*)

As genotyping becomes more efficient and cost-effective, the ability to simultaneously test several markers, phenotypes, and models improves. But with these multiple tests comes the recognized need for correction to avoid false-positive results. Simple correction methods can be too conservative because they do not account for correlation between variables, but permutation, the ideal standard for *P* value calculation, is computationally intensive and can be restrictive for large studies. Various techniques have been proposed to incorporate an effective number of tests or to simulate test statistics, but such methods are not always accurate and/or can be time consuming. Conneely and Boehnke introduce the calculation *P* Values Adjusted or Correlated Tests (P^{ACT}), which corrects *P* values while also accounting for correlation. When P^{ACT} was compared with simulation methods as well as with permutation methods, P^{ACT} achieved comparable accuracy in a fraction of the computational time.

Mitotic NAHR Causes Type 2 NF1 *Deletions,* by *Steinmann et al.* (*p. 1201*)

Neurofibromatosis type 1 (NF1) is frequently caused by deletions on 17q that include the *NF1* gene. Although some of these deletions have breakpoints in random sequences, many of them can be classified into one of two groups: type 1 or type 2. Type 1 deletions have been highly studied and are known to occur by nonallelic homologous recombination (NAHR), with breakpoints that often occur in recombination hotspots. Type 2 deletions have breakpoints in the gene *SUZ12* and the pseudogene *SUZ12P,* but extensive characterization of type 2 breakpoints had not been performed previously, and little was known about the deletion mechanism. Steinmann et al. analyzed the sequences of the breakpoints in all 13 known de novo cases of type 2 deletions and established that, in the same way as type 1 deletions, type 2 deletions occurred via NAHR. But, in contrast to type 1 deletions and many other disease-causing deletions resulting from NAHR, breakpoints of type 2 deletions did not occur at recombination hotspots. The authors also report that all de novo cases of NF1 were somatic mosaics and that, in comparison with NF1-affected patients with type 1 deletions, a significantly higher proportion of patients with type 2 deletions were women.

Common Variation in U.S. Populations, by *Guthery et al.* (*p. 1221*)

In population-based association studies, significant findings are often identified in one ethnic population, and the effect that disease-causing variants will have in other populations is not always clear. Much of this uncertainty is the result of not knowing how much allelic variation is shared among populations. Such a comparison has not been straightforward with previously obtained data, because of a potential bias introduced by the fact that SNPs identified for genotyping in multiple populations were originally chosen from sequencing in small samples. Guthery et al. undertook a large resequencing effort to establish how much of rare and common genetic variation is shared among the populations in the United States. The authors evaluated the allele frequencies of SNPs in almost 4,000 genes in African Americans, Asian Americans, Latino/Hispanic Americans, and European Americans. They reported a positive correlation between the minor-allele frequency of a SNP in one population and the probability that the SNP would be present in another population.

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Effect of Common SNPs on HDL-C, *by Spirin et al.* **(*p. 1298*)**

As the number of variants identified to be putatively associated with a complex disease increases, a subsequent step is to determine how the known variants contribute to an overall risk effect. Spirin et al. chose to evaluate how common SNPs in seven genes involved in high-density lipoprotein (HDL) metabolism contributed to normal variation in HDL cholesterol (HDL-C) levels. The authors used a forward stepwise regression to determine that a combination of four SNPs significantly affected the levels of HDL-C in groups from the Dallas Heart Study, as well as in an independent population sample. Their method allowed them to discard multiple SNPs that were in high linkage disequilibrium with each other unless each of those SNPs was presumed to be functional on its own. This analysis demonstrated that the effects of the variants were additive and that no significant epigenetic interaction among the SNPs was evident.

This Month on the Cover

In 1903, William C. Farabee described a large pedigree in which a "diminution in the number of phalanges" was "inherited in conformity with Mendel's law for five generations" (Farabee WC [1903] Hereditary and sexual influence in meristic variation: a study of malformations in man. PhD thesis, Harvard University, Cambridge, MA). With that report, brachydactyly A became the first phenotype recognized and described to be inherited in an autosomal dominant fashion. On the cover is an x-ray of the right hand of Martha Styer, a descendant of the brachydactyly pedigree originally studied by Farabee. Special thanks to Ms. Styer and Dr. Dennis Bulman, Ottawa Health Research Institute, for the image.

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