This Month in the *Journal*

This month in the *Journal,* Geoff Woods, Jacquie Bond, and Wolfgang Enard discuss primary microcephaly (MCPH). This neurodevelopmental disorder is characterized by a small but architecturally normal brain and nonprogressive mental retardation. Over the past couple of years, four genes involved in MCPH have been identified. The authors present a model that suggests that mutations in these genes lead to MCPH through effects on neurogenic mitosis. Beyond their clinical implications, research results for MCPH have intrigued people interested in evolution, because the *MCPH* genes may have played a role in the dramatic increase in the ratio of brain to body size that developed during human evolution. Woods et al. also describe attempts to examine the selective forces operating on the *MCPH* genes.

Array-CGH at Single-Exon Resolution, *by Dhami et al.* **(***p. 750***)**

Dhami et al. developed a method for genomewide analysis of copy-number changes at the resolution of single exons. This array–comparative genome hybridization (array-CGH) method allows the detection of copy-number changes of array elements on the order of hundreds of base pairs in length, which is ~2 orders of magnitude smaller than previous array-CGH methods. Their approach to generating the array uses a modified primer to amplify exonic sequences that can then be attached in a single-stranded fashion to glass slides. The use of single-stranded array elements increases their signal:noise ratio by an average of 1.79-fold. The method is illustrated with an exonic array that represents five disease-related genes: *COL4A5, DMD, PLP1, NF2,* and *PMP22*. DNA samples from 31 patients with known copy-number changes in these genes were used to test the five-gene array. All of the changes were detected, including four that involved only a single exon. The authors are already looking forward to the development of an array that can assess copy-number changes for virtually all exons in the genome, and they propose several potential applications of this technique, including chromatin immunoprecipitation analysis, screens for copy-number polymorphisms, and diagnostics.

LD Extent in Rural Communities, *by Vitart et al.* **(***p. 763***)**

I grew up in a small town. Most of the people I grew up with still live there and married other locals. In Atlanta, on the other hand, it's hard to find natives. Vitart et al. wanted to determine whether these rural/urban differences in population stability translate into differences in linkage disequilibrium (LD). They chose Scotland as an example of an outbred European population. Rural, urban, and isolated populations are represented in their sample of >900 people, and inclusion in the study required that all four grandparents came from the same region as the sampled individual. Vitart et al. figured that general differences in population stability between rural and urban populations might translate into differences in LD between the populations. In fact, that holds true; there is greater LD in rural Scottish populations than in urban ones, and isolated island populations have even greater LD. For the design of large sample collections for association studies, the authors think it might be advantageous, in terms of increased study power, to sample within stable rural populations rather than urban populations, as many large-scale studies do.

ABCA12 ***Mutations in Harlequin Ichthyosis,*** *by Kelsell et al.* **(***p. 794***)**

Harlequin ichthyosis is a severe congenital skin disorder that is often fatal very soon after birth. In affected babies, the skin is dried out so much that the limbs are held in rigid semiflexion, and the skin forms hard diamond-shaped plaques with cracks between them. There is abnormal keratin structure, keratinocyte differentiation, and lipid transport in the skin of these individuals, but the underlying genetic cause has been a mystery. Kelsell et al. sought the disease gene through a homozygosity approach, using genotypes from a SNP mapping 10K array. A single region, on chromosome 2q35, had a significant amount of homozygosity in five of the six affected individuals examined. Located within that region is *ABCA12,* which encodes an ATP-binding cassette protein that is believed to transport epidermal lipids. Mutations in *ABCA12,* the majority of them truncating, were found in 11 affected individuals. In contrast, missense *ABCA12* mutations have been reported elsewhere in individuals with the less severe but related phenotypes lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma. In addition to giving insight into this devastating disorder, this work has more practical implications, because it paves the way for prenatal diagnosis for affected families.

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A Novel* STX16 *Deletion Causes PHP-Ib, *by Linglart et al.* (*p. 804*)

GNAS is a complex, imprinted locus associated with pseudohypoparathyroidism (PHP). Through a series of alternative transcripts, it encodes the α-subunit of the stimulatory G protein ($G\alpha_s$), neurosecretory protein 55, the extra large $G\alpha_s$, and some nontranslated RNAs. Some of the transcripts are paternally derived and others are maternal; this is under the control of differentially methylated regions in this locus. Depending on how you look at it, Linglart et al. either simplify or complicate our understanding of this locus with their report of an additional imprinting control element (ICE) associated with *GNAS* that was defined using a family with PHP-Ib. Many families with this disorder carry an identical 3-kb microdeletion, upstream of *GNAS,* that is associated with a methylation defect limited to the *GNAS* exon A/B transcript. The family in this study shares the methylation defect at A/B but did not have the 3-kb deletion. Instead, they have an overlapping 4.4-kb microdeletion within the *STX16* gene. PHP-Ib in this family is not due to loss of *STX16,* because this gene is normally biallelically expressed and therefore not consistent with the maternal inheritance pattern of PHP-Ib. Instead, Linglart et al. propose that the region of overlap of the 3- and 4.4-kb deletions (~1.3 kb) contains a new ICE that is necessary for regulation of methylation at exon A/B.

Exact Tests of Hardy-Weinberg Equilibrium, *by Wigginton et al.* (*p. 887*)

Deviations from Hardy-Weinberg equilibrium (HWE) can indicate several things, including nonrandom mating, genotyping error, population stratification in the sample, and association of an allele with a trait. Most commonly, HWE is tested through a goodness-of-fit χ^2 test. Wigginton et al. show that this test can have inflated type I error rates and can lead to false rejections of HWE. They describe an exact test for HWE and an efficient implementation of this method that is suitable for large-scale data, and they show that it is accurate over many allele frequencies. They test this approach on a set of >18,000 markers from the International HapMap project and find that the exact test—but not the χ^2 test—rejects HWE at the appropriate level. The authors advocate use of the exact test rather than the χ^2 test for tests of HWE.

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