Island Southeast Asian mtDNA, *by Hill et al.* **(*p. 29*)**

Conflicting data have been obtained regarding the history of the people of Island Southeast Asia (ISEA). Whereas linguistic analysis of the Austronesian languages suggests that there was a single dispersal out of Taiwan, there is also archaeological and archaeobotanic evidence that contradicts the hypothesis of just one wave of expansion. Genetic studies of mtDNA and Y chromosomes of the ISEA populations have also been inconclusive because of poor sampling and resolution. Here, the authors addressed the "Out of Taiwan" question by extensive sequencing of the mtDNA from 1,000 individuals from all over ISEA. They identified several potential lineages that are currently found in patterns that support dispersal Out of Taiwan in the mid-Holocene epoch, but these lineages accounted for only ~20% of the modern inhabitants of ISEA. This suggested that, if there was a single dispersion, it was not a major event in the maternal ancestry of the ISEA populations. Analysis of other haplogroups yielded an even more complex picture of the demographic history of the region, since the age of many of the identified lineages suggested that there were various postglacial redispersals.

Family-Based Test of Association for the X Chromosome, *by Chung et al.* **(*p. 59*)**

Methods for family-based association tests have not been well developed for markers on the X chromosome. Current algorithms may have increased type I error in the presence of linkage or may lack power if parental genotypes are missing. To overcome these problems, Chung et al. extended the association in the presence of linkage (APL) test to perform single-locus or haplotype-association tests using X-chromosome markers. Comparisons of all the methods under a variety of disease models and family structures demonstrate how well the new method, APL-X, maintains type I error near nominal levels and outperforms the others in most situations. Additionally, important observations were made regarding the performance of the other methods tested. An important addition to APL-X was the modification for performing haplotype analysis. At this time, there are no other methods that allow for such analysis of markers on the X chromosome, so comparisons were not possible, but results of simulations to estimate the power of the new method were reasonable.

CCM2 Deletions, *by Liquori et al.* **(*p. 69*)**

Cerebral cavernous malformations (CCMs)—enlarged blood vessels that often result in neurological phenotypes such as strokes, seizures, or headaches—are known to be caused by mutations in genes at three loci: CCM1, CCM2, and CCM3. But, in previous mutation screens, as many as 30% of patients with CCM did not have a mutation in any of the genes. Although mutations in a fourth gene may be responsible for the malformations in these patients, linkage data from CCM-affected families suggested that mutations at the known loci should be more prevalent than was observed. Liquori et al. suspected that at least some of the missing mutations could be explained by large genomic rearrangements, so they searched for deletions or duplications at CCM1, CCM2, or CCM3 in 25 mutation-negative unrelated probands with CCM. The authors identified one deletion at CCM1 and 14 at CCM2. Sequence analysis of the CCM2 deletions revealed that eight of them were identical and deleted the same 77.6 kb flanked by *Alu* repeats. To establish whether these eight deletions shared a common founder, microsatellites in the region were typed, and haplotype analysis suggested that the deletion had occurred at least twice independently. The finding of these deletions significantly increased the expected prevalence of CCM due to mutations at the CCM2 locus and underscored the importance of deletion screening in these patients.

Copy-Number Variations in the Human Genome, *by Wong et al.* **(*p.91*)**

There is increasing evidence that large segmental copy-number variations (CNVs) can be associated with disease. To best study the relationship between CNVs and disease, it is important to establish the CNV patterns in unaffected individuals, to serve as a baseline for comparison with affected patients. Several recent studies have demonstrated the prevalence of CNVs, but those analyses focused mainly on deletions or were limited to specific genomic regions. To assess the normal variation of large gains and losses throughout the genome, Wong et al. used a whole-genome tiling BAC array comparative genomic hybridization approach. They observed an average of 155 CNVs per individual. Eight hundred loci were affected at least three times, and it was predicted that the 1,500 genes in these regions were very likely to be commonly associated with CNVs. A closer look at these genes revealed a number that had been previously linked with disease and a large group that was involved with the senses.

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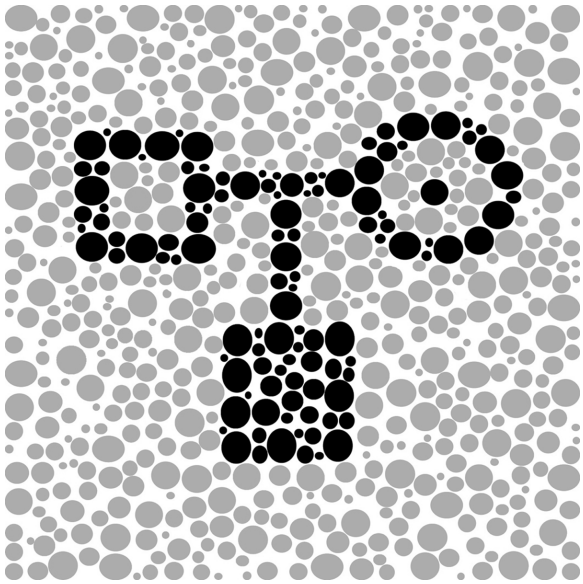
An NF1 Genotype-Phenotype Correlation, *by Upadhyaya et al.* **(*p. 140*)**

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder caused by mutations in the *NF1* gene. The disease is characterized by café-au-lait spots, skinfold freckling, and neurofibromas and may also present with a number of other features. The severity and combination of these clinical features are often quite variable, even within a single family, and very little correlation has been found between *NF1* mutations and the resulting phenotype. One consistent finding is that most patients with NF1 develop cutaneous neurofibromas by age 20 years. Here, Upadhyaya et al. report their mutational analysis of several NF1-affected probands and families who were unusual because none of them had developed cutaneous neurofibromas. An initial screening of *NF1* in three of these unique NF1-affected families revealed that all affected individuals had the same inframe 3-bp deletion. The authors then expanded their search and identified 18 additional unrelated probands without cutaneous neurofibromas who also possessed the 3-bp deletion. This is the first example of a genotype-phenotype relationship between the features involved in NF1 and a small *NF1* mutation.

This Month on the Cover

In 1937, Julia Bell and John Burdon Sanderson Haldane studied six kindreds with the X-linked diseases hemophilia and color blindness to measure the genetic distance between the causative genes for the two disorders (Proc R Soc of Lond B 123:119–150). At the time, linkage studies were being done in other organisms, but this was the first example of genetic linkage in humans. Bell and Haldane determined that the hemophilia gene was very close to the color-blindness gene, and they observed only one questionable cross-over event in the pedigrees studied. In the "Discussion" section of the publication, the authors discussed how useful it would be to map the X chromosome by linking other genes with the color-blindness locus through the study of new kindreds with color-blind members as well as those affected by another X-linked disorder. The image on the cover, created by Robin E. Williamson, is a modified "genetic" version of the traditional Ishihara test used to test for color blindness. The pedigree in the image (more clearly shown here in black and white) depicts a carrier female and an unaffected male with an affected son.



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