# This Month in the *Journal*

***Portrait of a Founder Event,*** *by Behar et al.* (*p. 487*)

Ashkenazi Jews are often highlighted in genetic studies because of a variety of recessive disorders that are unique to the population. Also, a great deal of controversy surrounds the issue of which mechanisms are responsible for the prevalence of these isolated diseases. Some groups hypothesize that historical conditions favored heterozygotes, and others believe that the cause was rapid population expansion following a founding event. As a result, the maternal history of these people has been the subject of debate. Behar et al. shed some light on the issue by using complete mtDNA sequence analysis to identify the founding lineages of Ashkenazi haplogroups. Their data support the presence of a founding event in the maternal history of Ashkenazi Jews, with 40% of the modern Ashkenazi population sharing one of four lineages. The authors also demonstrate that these four mtDNAs are not observed in European populations, so it is unlikely that the lineages were introduced from Europe. Instead, evidence of these haplogroups in southwestern Asia and North Africa suggests a Near Eastern ancestry.

***Comparison of Phasing Algorithms,*** *by Marchini et al.* (*p. 437*)

With rapid improvements in genotyping technology fueling a growing interest in performing genomewide association studies in large cohorts, it is increasingly necessary to develop methods for efficiently handling a large volume of genotype data. For many disease-mapping endeavors as well as evolutionary genetic studies, it is useful to convert disconnected genotypes into phased haplotypes. Because it is cumbersome and expensive to do this experimentally, a variety of statistical and computational methods have been developed to predict how variant alleles are grouped together. Here, Marchini et al. discuss five leading phasing algorithms by briefly detailing the mathematical basis of each and outlining their differences and similarities. Each approach is then expanded to deal with trio data, since they all previously could be applied only to data from unrelated individuals. Finally, by evaluating error rates and running time, the authors compare the algorithms, using simulated data and real data from the HapMap project. The methods all perform comparably well, with PHASE having the lowest error rates.

**GNPTAB** ***Mutations in MLII and MLIIIA,*** *by Kudo et al.* (*p. 451*)

The UDP-*N*-acetylglucosamine:lysosomal enzyme *N*-acetylglucosamine-1-phosphotransferase (GlcNAc-phosphotransferase) is necessary for proper lysosomal trafficking. A complete loss of GlcNAc-phosphotransferase activity causes mucolipidosis II (MLII), a severe disease in which lysosomal targeting and the secretion of lysosomal enzymes are affected. The more mild disorders mucolipidosis IIIA (MLIIIA) and mucolipidosis IIIC (MLIIIC) are caused by decreased or altered enzyme activity. MLIIIA and MLIIIC are clinically indistinguishable, but a differential diagnosis can be made on the basis of the finding that, whereas MLIIIA is caused by a general loss of GlcNAc-phosphotransferase activity, the decreased normal function of the enzyme in MLIIIC is due not to a lack of enzyme activity but to aberrant substrate recognition. GlcNAc-phosphotransferase is assembled from two subunits, an $\alpha/\beta$ subunit encoded by the gene *GNPTAB* and a $\gamma$ unit encoded by *GNPTG*. A great deal was learned about the functions of these subunits when it was discovered that *GNPTG* mutations cause MLIIIC. The substrate-recognition function of the enzyme was then attributed to the $\gamma$ subunit, and it was hypothesized that the $\alpha/\beta$ subunit was responsible for the catalytic activity. It was then predicted that MLII and MLIIIA are caused by defects in the $\alpha/\beta$ subunit. Kudo et al. screened MLII- and MLIIIA-affected families for mutations in *GNPTAB*. Truncating mutations that render the enzyme completely inactive were found in all patients with MLII. Less severe mutations that retain some activity are found in patients with MLIIIA.

***Telomere QTLs in Healthy Females,*** *by Andrew et al.* (*p. 480*)

Telomeres, the complexes made up of DNA and protein at the ends of eukaryotic chromosomes, are crucial for the maintenance of chromosome architecture and integrity. It is well documented that the length of telomeres decreases with cell division in vitro, and this shortening is a factor in replicative senescence in cultured cells. Studies of donor white blood cells have also demonstrated that telomeres shorten with age in vivo. There is also evidence that there is a great deal of variability in telomere length among a population of people of the same age. Because of the importance of these structures, it is likely that these interindividual differences might be in-

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volved with susceptibility to certain diseases. Andrew et al. analyzed the mean telomere length in a large cohort of unselected, healthy women, to establish the heritability of telomere variation. By using DZ and MZ twins, they were able to account for common environment effects and to calculate a narrow heritability estimate of 36%. They followed up these results with a genomewide scan and identified a locus on 14q23.3 with significant linkage to telomere length. A suggestive locus was found on 10q26.13.

**KRT5** ***Mutations in Dowling-Degos Disease,*** *by Betz et al.* (*p. 510*)

Dowling-Degos disease (DDD), first described in 1938, is an autosomal dominant skin disorder characterized by disfiguring hyperpigmentation of the flexures. To date, the genetic etiology of DDD has been unknown. Betz et al. performed linkage analysis in two German DDD-affected pedigrees and identified a locus on 12q that overlaps with a cluster of keratin genes. Sequencing of these genes revealed a frameshift mutation in *KRT5* that segregates with the disease in the families. The authors then screened eight unrelated patients with DDD and found that five carry the same frameshift mutation and that one has a nonsense mutation. KRT5 is a key component of the intermediate filament cytoskeleton in stratified epithelia. Mutations in *KRT5* have also been found in patients with the more-severe skin disorder epidermolysis bullosa simplex (EBS). In EBS, only missense mutations have been identified, and it has been shown that they act in a dominant negative manner. Here, because of the location of the mutations and the early truncation of the transcripts, it is presumed that DDD is caused by loss-of-function variants. This is supported by western-blot experiments that demonstrate that the frameshift polypeptide does not incorporate into the cytoskeleton network at all and remains completely—and aberrantly—in the soluble fraction. Also, microscopy analyses of skin biopsy samples from patients with the frameshift mutation reveal structures that closely resemble those of the patient with the severely truncating nonsense mutation. The identification of a *KRT5* haploinsufficiency model assists in the development of new hypotheses about the protein function.

## This Month on the Cover

For the first half of the 1900s, there was a great deal of controversy concerning how many chromosomes were in a normal human cell. For many years, it was believed that 48 was the correct number, but, in 1956, Tjio and Levan carefully demonstrated that there are indeed 46. (Image reproduced with permission from Tjio and Levan [1956] Hereditas 42:1–6.) The study of human chromosomes quickly progressed, and, with so many groups working in cytogenetics, it became crucial to standardize the chromosome nomenclature. This task was tackled by the late Theodore T. Puck (see his obituary, pp. 365–366 [in this issue]), who was a driving force behind the Denver Conference (Lancet 1:1063–1065), where the leaders of the field came together to work out a system for organizing and naming the chromosomes.

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