# This Month in the *Journal*

This month in the *Journal,* Elson et al. (p. 145) have addressed the currently controversial topic of recombination in mtDNA. Obviously, this topic is extremely important, since many studies, particularly studies of mtDNA evolution, are based on the assumption that mtDNA lineages are clonal. In this article, the authors use the same tests as those applied by Eyre-Walker and colleagues, the researchers who first found evidence for recombination in mtDNA. These tests were applied to the complete mtDNA sequences of 64 Europeans and 2 Africans, and, contrary to the results found by Eyre-Walker et al., they yielded no evidence for evolutionarily significant levels of intermolecular mtDNA recombination in humans.

***Palindromes Mediate the Constitutional t(11;22) Translocation,*** *by Edelmann et al. (p. 1)*

Recent work on the origin of the recurrent t(11;22) translocation has provided conflicting results. Hill et al. (see citation in Edelmann et al.) found that the breakpoints on chromosomes 11 and 22 occurred in *Alu* elements and suggested that *Alu*-mediated recombination gives rise to the t(11;22) translocation. Just after the Hill et al. article was published, Kurahashi et al. (see citation in Edelmann et al.) proposed that the formation of a hairpin in palindromic AT-rich sequences flanking both the chromosome 11 and the chromosome 22 breakpoints could generate the translocation. In their model, small regions of mismatch in the hairpin stem are susceptible to nucleases that generate double-strand breaks in the DNA. Illegitimate reciprocal exchange between the affected chromosomes could then lead to the translocation event. In this issue of the *Journal*, the generation of t(11;22) has been revisited by Edelmann et al. These authors have used a PCR strategy that enabled them to amplify across the junction fragments of the translocation, making it possible to more accurately map the breakpoint. The results from these experiments agree with those of Kurahashi et al.; they suggest that the chromosomal breakpoints occur within palindromic AT-rich regions on both chromosomes 11 and 22. Although both Kurahashi et al. and Edelmann et al. had suggested that hairpin structures are crucial for the chromosomal breaks that lead to the translocation, Edelmann et al. were able to get more sequence information in the region of the breakpoints and to use this information to map the breakpoints several base pairs away from those proposed by Kurahashi et al. This puts the breakpoints in the center of symmetry of the palindrome sequences, at the tip of the hairpin. Different carriers of the translocation possess small, overlapping, staggered deletions in this region.


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***Enzyme Replacement in Fabry Mice,*** *by Ioannou et al. (p. 14)*

Individuals with the X-linked disorder Fabry disease are deficient in α-galactosidase A (α-Gal A), and this leads to the accumulation of a glycosphingolipid called globotriaosylceramide (GL-3). Although infusions of purified enzyme into affected patients have indicated that enzyme-replacement therapy for Fabry disease is feasible, sufficient amounts of α-Gal A have not been available for use as a therapy. Therefore, current treatment for this disorder consists of symptom management for extreme pain and for complications of the cardiac, renal, and cerebrovascular systems. In this article, Ioannou et al. describe successful enzyme-replacement therapy in α-Gal A–knockout mice. Sufficient quantities of α-Gal A were produced through the isolation of the human α-Gal A cDNA and its expression in Chinese-hamster-ovary cells. The α-Gal A treatment reduced accumulations of GL-3 in the heart and spleen to undetectable levels and reduced it to 40% of the untreated level in the kidneys. Marked reductions in lysosomal glycolipid storage were also observed in several tissues after treatment. The α-Gal A knockout-mouse model has proved invaluable for providing pharmacokinetic data on this therapy, and it has led to the start of clinical trials for α-Gal A–replacement therapy, which are now underway.

***USH1D and DFNB12 Caused by* CDH23,** *by Bork et al. (p. 26)*

On chromosome 10q21-q22, the critical regions for the recessive nonsyndromic deafness locus, *DFNB12,* and that for Usher syndrome type 1D (USH1D) overlap. Since sensorineural hearing loss is a characteristic of Usher syndrome, Bork et al. speculate that these disorders might share a genetic foundation. The sequences of several genes in the critical region reveal mutations in a novel cadherin-like gene, *CDH23,* with missense mutations in families affected by DFNB12 and with nonsense mutations in families with USH1D. The protein encoded by *CDH23* is predicted to be involved in adhesion, because of its homology to the cadherin family of proteins. It is not the first adhesion protein to be associated with Usher syndrome; a protein with homology to laminin is encoded by the *USH2A* gene. How-

ever, the significance of these findings cannot be fully appreciated until the exact functions of the proteins are uncovered.

***A C7orf2 Mutation Causes Acheiropodia,*** *by Ianakiev et al.* (*p. 38*)

Except for two cases in Puerto Rico, all reported cases of acheiropodia, the so-called handless and footless families, have occurred in Brazil, and it has been suggested that all cases are due to a single common ancestral mutation. Ianakiev et al. have used this fact to their advantage and have been able to narrow the critical region for acheiropodia to 1.3 cM on 7q36, on the basis of identity by descent in five affected Brazilian families. This critical region partially overlaps the critical region for preaxial polydactyly, another disorder that presents as a spectrum of limb anomalies. One of the transcripts identified in this region, *C7orf2,* is the human orthologue of the mouse *Lmbr1* gene, which exhibits altered expression in the limbs of certain mice with preaxial polydactyly. Mutation analysis of *C7orf2* in affected individuals revealed a consistent deletion of exon 4, thereby confirming the prediction of a common ancestral mutation in these families. The authors have been able to estimate that the age of this mutation is ~30 generations, on the basis of the length of the critical region shared through identity by descent in the affected families. Further studies of *C7orf2* are sure to increase our understanding of pattern formation during embryogenesis.

***Genetics of ERP to Semantic Priming,*** *by Almasy et al.* (*p. 128*)

The dissection of the genetic factors that are involved in psychiatric disorders is complicated by difficulties with diagnosis. Almasy et al. have attempted to circumvent this problem through the use of a quantitative trait that has been correlated with psychiatric disease—namely, even-related brain potentials (ERPs). The ERPs of the subjects in their study, participants in the Collaborative Study on the Genetics of Alcoholism, were measured during a decision task for word recognition. Significant heritabilities were measured for the N4 and P3 amplitudes of the ERPs, components that are known to be altered in alcoholics and, in the case of P3, their families. Genetic correlations between N4 and P3 suggest that these ERP components share a substantial genetic basis. This work opens the door to the treatment of psychiatric disorders as quantitative traits in genetic analysis.

***Lactase Haplotype Diversity,*** *by Hollox et al.* (*p. 160*)

The domestication of mammals, ~9,000 years ago, was a highly significant event in human evolution. It is thought to have provided a selective force for lactase persistence, whereby high levels of intestinal lactase activity persist into adulthood. The frequency of lactase persistence varies between populations, and, in this issue of the *Journal,* Hollox et al. examine the lactase-gene haplotypes in several populations and construct a haplotype network, using chimpanzee sequence to deduce the root haplotype. They find that, whereas sub-Saharan African populations have high levels of haplotype diversity at this locus, non-African populations show lower—and generally similar—levels of haplotype diversity. The similar levels of diversity in the non-Africans suggests that much of the diversity at the lactase locus was determined before these populations spread across the Old World and before the domestication of mammals. The reduced diversity in the non-Africans compared with the Africans can also be interpreted as evidence for the "Out of Africa" model for the peopling of the non-African continents. As populations spread out of Africa, where lactase haplotype diversity is high, some of the diversity was lost, because of genetic drift. This is not the only factor influencing haplotype diversity, however. In northern Europeans, there is an unusually high frequency of the A haplotype, and, in this study, this is the only population with a high frequency of lactase persistence. This skewed haplotype frequency suggests that, because of the history of fresh-milk drinking in this population, selection for lactase persistence has been exerted via an allele that is linked to the A haplotype.

KATHRYN BEAUREGARD
Deputy Editor