This Month in the *Journal*

Failure to Confirm DUP25 by FISH in the U.K., *by Tabiner et al.* (*p. 535*)

An unusual interstitial duplication (DUP25) on chromosome 15q24–q26 has previously been reported in individuals with anxiety disorders (by Gratacòs et al., in *Cell* 106:367–379 [cited by Tabiner et al.]). DUP25 occurred in three forms and was found in a mosaic state in 97% of a sample of Spanish panic disorder/agoraphobia sufferers and 7% of control individuals. Tabiner et al. attempt to replicate this finding in case and control individuals from the United Kingdom. Using almost identical probes to those used by Gratacòs et al., they found no evidence of DUP25 in 16 patient and 40 control samples. To verify their experimental procedure, three CEPH cell lines that scored positive for DUP25 in the Gratacòs et al. study were used as positive controls in this study, and, again, no evidence of DUP25 was found. However, suspensions of these cell lines were sent back to the authors of the original paper for testing, and anywhere from 15%–45% of the cells in each line were scored as DUP25-positive by that lab. Perhaps the procedural differences that led to these opposite findings can be determined so that the existence of DUP25 can be definitively confirmed or refuted.

Mitochondrial DNA Mutations and HIV Therapy, *by Martin et al.* (*p. 549*)

The mtDNA polymerase-γ is inhibited by nucleoside analog reverse transcriptase inhibitors (NRTI) because, unlike the nuclear DNA polymerases, it can't effectively discriminate NRTIs from endogenous nucleosides. NRTI therapy has been associated with mtDNA depletion, and Martin et al. decided to assess its effects on mtDNA sequences. To do this, they collected peripheral blood samples from HIV-infected individuals prior to and following several months of NRTI therapy, and they compared mtDNA SSCP and sequence data between these samples. A control group of HIV-infected individuals who did not receive NRTI therapy was used for comparison. Different SSCP patterns were observed between the before- and after-treatment samples in 5 of the 16 patients receiving NRTI therapy. This difference corresponded with an increase in the number of heteroplasmic mtDNA populations following treatment, as well as a decrease in the levels of mtDNA in blood. It seems, therefore, that several months of NRTI therapy may promote the development of mtDNA mutations in peripheral blood. Further work will be required before the effects of these mutations can be determined, although preliminary evidence in this study indicates that NRTI-associated lipoatrophy may be one.

EVC2 ***Mutated in EvC Syndrome,*** *by Ruiz-Perez et al.* (*p. 728*)

A large percentage of individuals with Ellis-van Creveld (EvC) syndrome, an autosomal recessive chondrodysplasia, do not appear to have mutations in *EVC,* which is the only gene known to be responsible for this syndrome. This includes some pedigrees with EvC who show evidence of genetic localization to the *EVC* region. Ruiz-Perez et al. collected seven such families to examine other genes in this region and to see if they could find a second EvC gene. The orthologue of a novel gene in the region was recently found to be mutated in bovine chondrodysplastic dwarfism, which has some phenotypic similarity to EvC, so the authors focused on this gene. Five truncating and one missense mutation were found, and the gene was thus dubbed "*EVC2*." It is interesting that *EVC2* is arranged in a head-to-head configuration with *EVC* and their transcription start sites are separated by only ~2,600 bp. Although no obvious similarities exist between these genes, and their functions are as yet unknown, it could be that they are regulated in a coordinated fashion through their shared promoter region. These findings are supported by a recent publication that also identified two potential *EVC2* mutations in an individual with EvC and that suggested a shared promoter region between *EVC* and *EVC2* (see Galdzicka et al. [2002] *Mol Gen Metab* 77:291–295).

L1 Evolution in Great Apes, *by Mathews et al.* (*p. 739*)

Long interspersed elements (LINEs) have been an important driving force for genomic evolution and are estimated to have been involved in the creation of a large portion of the human genome. Mathews et al. investigate this evolution through a study of L1 retrotransposons, the youngest LINEs in mammalian genomes. Through a PCR procedure, they generate unbiased libraries of recent L1s in human, chimpanzee, and bonobo. Comparisons of the L1 clone sequences allow them to identify species-specific L1 insertions. On the basis of the numbers of species-specific insertions, they calculate that L1s have accumulated in the *Pan* lineages at rates 2.3–3-fold faster than in the *Homo* lineage, since their divergence. Extrapolating from their results, the chimpanzee and

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bonobo genomes may have as many as 760–1,140 full-length L1 insertions that are absent from humans. This type of genomic change may have played a role in the differentiation of humans from our closest relatives.

Novel Missense Mutations in* LRP5 *Gene, *by Van Wesenbeeck et al.* **(***p. 763***)**

The low-density lipoprotein receptor-related protein 5 (LRP5) is a Wnt coreceptor that is expressed in osteoblasts and is required for optimal Wnt signaling in these cells. Inactivating mutations in *LRP5* have been found in patients with osteoporosis pseudoglioma syndrome, a syndrome that includes very low bone mass, whereas a putative gain of function mutation has been found in two families with high bone density. Additional evidence supports the role of this protein in the regulation of bone mass in vertebrates. To examine further the range of clinical phenotypes associated with *LRP5* mutations, Van Wesenbeeck et al. gather a cohort of individuals and families with phenotypes associated with increased bone density, including endosteal hyperostosis, Van Buchem disease, autosomal dominant osteosclerosis, and autosomal dominant osteopetrosis type I. Missense mutations of *LRP5* were identified in 10 families. It appears, therefore, that *LRP5* should be suspect in a range of conditions marked by increased bone density.

KATHRYN GARBER
Deputy Editor