This Month in the *Journal*

This month in the *Journal,* Dominic Kwiatkowski discusses one of the strongest selective forces that has acted on the human genome in recent times: malaria. One of the striking things about this selection is that it has resulted in several different resistance alleles that vary by location, so that a common malaria-resistance allele in Africa is rarely found in Southeast Asia, and vice versa. Not only do genetic studies of malaria resistance tell us something about humans, they also tell us about the life cycle of the malarial parasites, and they have led to novel approaches to malaria prevention.

Sotos Genotype-Phenotype Analyses, *by Tatton-Brown et al.* (*p. 193*)

Mutations in *NSD1*—and chromosome 5q35 microdeletions that include *NSD1*—cause Sotos syndrome, which is typically known as an overgrowth syndrome. It has been speculated that the phenotypes of individuals with mutations localized to *NSD1* would differ from those with microdeletions, but, since the phenotypic range for these mutations hasn't been defined, this speculation has not yet been thoroughly examined. Tatton-Brown et al. analyzed 530 individuals with a range of phenotypes and found 266 cases that had defects at *NSD1*. The mutation-positive cases were almost completely restricted to those individuals given a clinical diagnosis of typical or possible Sotos syndrome. This contrasts with previous reports that suggested some cases of Weaver and Beckwith-Wiedemann syndromes result from defects in *NSD1*. Also in contrast to previous reports is the fact that Tatton-Brown et al. ascribe the clinical features of 5q35 microdeletions to *NSD1* haploinsufficiency and not to other genes in the deleted interval. This large collection of affected individuals allowed Tatton-Brown et al. to better designate the cardinal features of Sotos syndrome, which are facial dysmorphism, learning disabilities, and childhood overgrowth. Although each is present in >90% of cases, the severity varies quite widely among individuals. Perhaps surprisingly for what has been defined an overgrowth syndrome, 10% of mutation-positive cases had growth within the normal range, so overgrowth is not a requirement for the diagnosis of Sotos syndrome.

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Alleles at* SLC6A4*/SERT Confer Risk of Autism, *by Sutcliffe et al.* (*p. 265*)

Linkage of autism near the serotonin transporter locus *SLC6A4* has been found in a few studies, and support for this locus seems to be stronger in families that have only affected males, which is interesting in light of the fact that the affected male:female ratio for autism is ~4:1. Although *SLC6A4* is a great candidate gene, the results of association studies of this locus have not been strong enough to explain the linkage signal in this area. Sutcliffe et al. reexamine the role of this locus in autism through studies of rare variation in this gene. In a sample in which they demonstrate highly significant linkage to this region, they report coding substitutions in *SLC6A4* that are associated with increased rigid-compulsive behaviors. In their linked families, the most common of these substitutions, Gly56Ala, is at increased frequency compared with previous reports in a control population. Gly56Ala exhibits transmission distortion, and the encoded protein has an elevated basal activity and insensitivity to certain stimuli. Sutcliffe et al. also found noncoding variations that collectively show transmission disequilibrium. They propose that multiple rare variants, rather than common variants, in *SLC6A4* confer susceptibility to autism-spectrum disorders and contribute substantially to the linkage to this region.

CCD and Growth-Plate Abnormalities, *by Zheng et al.* (*p. 305*)

Cleidocranial dysplasia (CCD) is a result of defective ossification and is characterized by a persistently open skull suture, short stature, dental anomalies, and hypo- or aplastic clavicles. CCD is caused by mutations in *RUNX2,* which encodes an osteoblast-specific transcription factor, and is thought to be due to defects in intramembranous ossification and possibly endochondral ossification. Mouse models expressing various forms and amounts of *Runx2* have provided evidence that this transcription factor is crucial for osteoblast differentiation and subsequent bone-matrix deposition by the differentiated osteoblasts, but mouse models could take researchers only so far because of phenotypic differences between *RUNX2*-deficient humans and mice. Zheng et al. characterized the effects of a *RUNX2* mutation in a rare human sample, a 20-wk fetus with CCD. This single-base insertion results in a 50% decrease in *RUNX2*

mRNA in cartilage. Compared with an age-matched control, growth-plate sections in the affected fetus were disorganized and exhibited decreased chondrocyte hypertrophy as well as altered expression of collagen X. Zheng et al. also measured the expression of *RUNX2* target genes and found reduced expression of genes that are normally highly expressed in differentiated chondrocytes. This study supports the proposal that endochondral ossification defects that are the result of altered regulation of genes expressed in chondrocytes contribute to the CCD phenotype.

***French-Canadian LHON Due to* Fille du Roy**, *by Laberge et al.* (*p. 313*)

In contrast to many other countries, the most prevalent mutation that causes Leber hereditary optic neuropathy (LHON) in the French Canadian population is T14484C. Haplogroup analysis of this mtDNA mutation suggested that its increased prevalence is due to a founder effect, possibly from one woman. Laberge et al. investigated this idea through use of Quebec's genealogical records and found that, of the 12 genealogies they could reconstruct for LHON-affected individuals, 11 were related to the same female founder through their maternal lineage. Compared with simulations based on a sample of individuals who were geographically matched with the cases, this level of maternal relatedness was highly significant. The female founder who was identified was born in France and was sent to Nouvelle-France in the 17th century as a "*fille du roy,*" or daughter of the King. During that time, Louis XIV sent the *filles du roy* to Nouvelle-France to improve the male:female ratio in the colony. These single women, often wards of the state, were supposed to marry in the colony, thereby promoting permanent settlement. Laberge et al. traced the migration of the female descendents of this woman largely to southwest Quebec, a location that corresponds quite well with the current distribution of LHON cases due to T14484C in French Canadians.

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