This Month in the *Journal*

Variants in PAF-Acetylhydrolase and Asthma, *by Kruse et al.* (*p. 1522*)

Platelet-activating factor (PAF) is a phospholipid that is involved in inflammation. Loss-of-function mutations in PAF hydrolase (PAFAH), an enzyme that degrades PAF, are associated with severe asthma. In a white population, Kruse et al. have examined the association of PAFAH with asthma and atopy and have found three common variants in PAFAH: Arg92His, Ile198Thr, and Ala379Val. Although the Arg92His variant is not associated with disease, the Ile198Thr and Ala379Val variants are associated with asthmatic and atopic phenotypes in various assays, including a measure of IgE concentrations and a skin-prick test for specific sensitization. To understand how these variants lead to asthma or atopy, functional studies were performed on purified preparations of recombinant PAFAH. The Ile198Thr and Ala379Val variants exhibit an increased K_M, meaning that there is a decreased substrate affinity for the enzyme. The resulting increase in the PAF half-life prolongs signal transduction by this molecule and most likely leads to higher IgE levels. The results of this study indicate that the Ile198Thr and Ala379Val variants of PAFAH are associated with an increased risk of asthma and atopy and that this is probably due to decreased enzyme efficiency.

Variants of* CACNB4 *in Patients with Epilepsy and Ataxia, *by Escayg et al.* (*p. 1531*)

The voltage-gated calcium channels are involved in neurotransmitter release and have been implicated in a mouse model of epilepsy and ataxia. This model, the *lethargic* mouse, has a null mutation in the β4 subunit of these calcium channels, resulting in severe ataxia and absence seizures. Escayg et al. have examined the human orthologue of β4, *CACNB4* on chromosome 2q22-23, to determine whether this protein is involved in human epilepsy and ataxia. Sequence analysis of *CACNB4* in individuals with familial epilepsy and ataxia revealed two mutations: R482X, which shortened the protein by 38 amino acids, and C104F, a missense mutation with incomplete penetrance. To determine the effects of these mutations on channel activity, each was expressed in *Xenopus* oocytes. Both mutations increase slightly the current density of the channels. R482X also alters the kinetics of channel inactivation. The effects of the mutations on channel activity, along with the cosegregation of the mutations with disease, strongly implicate *CACNB4* as the causative mutation in these cases of epilepsy and ataxia.

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Hyperglycerolemia and Glucose Metabolism, *by Gaudet et al.* (*p. 1558*)

Gaudet et al. have studied French Canadian families with hyperglycerolemia, in order to determine the effects of elevated glycerol levels on metabolism. The five families were from a population with a known founder effect; thus, it was possible to identify a common disease haplotype on Xp21.3. This region includes the gene for glycerol kinase (GK), the enzyme that brings glycerol into the metabolic pathways. Sequence analysis of the GK gene identified an N288D missense mutation in exon 10 of all the obligate carriers and affected individuals. In addition to hyperglycerolemia, N288D was associated with impaired glucose tolerance and higher body-fat accumulation, indicating that regulation of glycerol levels has wide-reaching effects on metabolism and that the GK gene plays an important role in this regulation. Additional genes must be involved in this regulation, since normoglycerolemic families, who lack mutations in GK, also showed a correlation between mean glycerol levels and the degree of impaired glucose tolerance. Furthermore, the variance in plasma glycerol levels was six times higher between than within normoglycerolemic families.

Composite QTL Statistics, *by Forrest and Feingold* (*p. 1642*)

Extreme discordant sibling pairs are, in theory, very powerful for the mapping of quantitative-trait loci. In practice, however, it is often difficult to recruit the number of discordant sib pairs that is required for this type of mapping. Forrest and Feingold have attempted to balance these issues by developing a new statistic for the analysis of moderately discordant sib pairs. To increase the power of moderately discordant sib pairs, the authors propose a composite statistic that uses complementary information from both an identity by descent (IBD) statistic and a "trait value given IBD" statistic, such as Haseman-Elston regression or variance-components analysis. This composite statistic increases the power of moderately discordant sib pairs in linkage analysis, it can be calculated by use of existing software, and

it makes sample ascertainment easier than it is for extremely discordant sib pairs.

Selection at the Duffy Locus, *by Hamblin and Di Rienzo* **(***p. 1669***)**

The *FY*O* allele of the Duffy locus is not transcribed in red blood cells, and the lack of this cell-surface receptor gives resistance to *Plasmodium vivax* malaria. *FY*O* has the highest known level of interpopulation differentiation for any allele in humans. It is therefore assumed that positive selection for the *FY*O* allele through an infectious agent has led to the almost complete fixation of this allele in sub-Saharan African populations. Hamblin and Di Rienzo have studied the effects of this selection on sequence variation in the region of the Duffy locus. They have found that directional selection in sub-Saharan African populations has reduced the number of polymorphic sites near the Duffy locus and that this signature of selection extends over several kilobases. In addition, they have found that the *FY*O* allele occurs on two major haplotypes in three of the African populations that they studied, and this suggests that the *FY*O* allele was present in more than one haplotype before selection occurred.

Report* (*Oophorectomy and the Risk for Down Syndrome*),** *by Freeman et al.* **(p. 1680***)**

It is well established that the risk of having a child affected by Down syndrome (trisomy 21) increases with maternal age. However, the biological basis for this risk is not clear. As women age, there is a reduction in the number of oocytes that they possess, and it has been hypothesized that this leads to increased aneuploidy. Fewer oocytes are also found in women who, because of either surgical or congenital means, are missing all or part of an ovary. Freeman et al. have examined the risk of Down syndrome in this population, and this has allowed them to study the effect of reduced ovarian complement, independent of maternal age. They have found that women with a reduced ovarian complement are more likely to give birth to a child with Down syndrome. These women are also known to show physiological signs that are normally associated with advanced maternal age, such as lower estrogen levels and shorter menstrual cycles. These findings suggest that the physiological age of mothers, rather than chronological age, is important in the assessment of the risk of Down syndrome.

KATHRYN BEAUREGARD
Editorial Fellow