This Month in the *Journal*

Glucosidase I Deficiency, *by De Praeter et al.* (*p. 1744*)

De Praeter et al. present a neonate with a novel metabolic disorder that is characterized by generalized hypotonia, hypomotility, dysmorphic features, and a fatal outcome. On the basis of the accumulation of the N-glycan fragment Glc(α1-2)Glc(α1-3)Glc(α1-3)Man of glycoproteins in the patient's urine, the authors postulate a defect in glucosidase I activity, which removes the distal (α1-2)–linked glucose residue from N-linked $Glc_3Man_9GlcNAc_2$. Assays of glucosidase I in liver tissue and skin fibroblasts from the patient confirmed this reduction in activity, whereas sequencing of the glucosidase I locus identified the patient as a compound heterozygote, possessing an R486T mutation on one allele and an F562L mutation on the other. Along with the accumulation of Glc(α1-2)Glc(α1-3)Glc(α1-3), loss of glucosidase I–cleavage activity leads to a deficiency in the complex type N-linked glycans. Subsequently, there is development of dilatation and fibrosis of the bile ducts, demyelinating polyneuropathy, and multilamellar inclusions in the cytoplasm of parenchymal cells, in bile canaliculi, and in the bile-duct lumina. This work highlights the fact that, despite the century of work since Sir Archibald Garrod recognized inborn errors of metabolism, not all of these disorders have yet been recognized.

Origin and Phenotype of Triploidy, *by Zaragova et al.* (*p. 1807*)

Triploidy is a relatively common cause of spontaneous abortions, but the relationship between triploidy origin and phenotype has thus far been unclear. Cytogenetic studies indicate that most cases of triploidy have a paternal origin and that most of these paternally derived cases are partial hydatidiform moles. Molecular studies have come to a different conclusion—that is, that most cases of triploidy are from a maternal origin. To resolve these discrepancies, Zaragova et al. have used a combination of molecular and histological techniques to study the origins of triploidy and have found that the disparate conclusions largely result from differences in ascertainment criteria, since the origin of triploidy affects phenotype. Although maternally derived triploids either abort as young embryos (at <8.5 wk gestation) or survive to form well-developed fetuses and then abort, paternally derived cases of triploidy generally abort at an intermediate time, at 10–20 wk gestation, and sometimes are associated with the formation of partial hydatidiform moles. Since previous studies included samples of different gestational age and phenotype, it seems, on the basis of the samples chosen, that there was inadvertent selection for a particular triploidy origin.

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Search for Type 2 Diabetes Genes, *by Ehm et al.* (*p. 1871*)

In this multicenter, collaborative study, a sample of 1,783 individuals from four ethnic groups was examined for evidence of linkage to type 2 diabetes. A full-genome scan from the first phase of this study provided significant evidence for type 2 diabetes loci on chromosomes 3 and 12, as well as suggestive evidence for loci on chromosomes 5, 10, and X. Although some of these loci had been implicated in other studies of type 2 diabetes, the results generally were not replicated in the second phase of this study. This lack of replication, even in such a large and careful study, emphasizes the difficult nature of linkage studies of complex disorders, in which mutations in several genes may lead to the same clinical phenotype and in which the involved genes may vary between ethnic groups. As linkage analysis for complex disorders becomes increasingly prevalent, the question is raised as to how future studies can be better designed, to increase their effectiveness.

Genomic Differentiation of Neanderthals and Humans, *by Scholz et al.* (*p. 1927*)

Through a Southern hybridization method that assesses cross-hybridization of fossil DNA, Scholz et al. were able to distinguish two well-defined Neanderthal fossils from that of a modern human. For this assay to measure hybridization variation between the samples, significant differences in their genomes—most likely, within repetitive sequences—must be present. The results may be used to argue that Neanderthals and modern humans arose from separate lineages, but the rough nature of the assay prevents conclusive results concerning phylogenetic relationships. Although this method does not allow researchers to study specific sequences, it may allow classification of fossils for which morphology studies could not provide definitive results. Although the classification of these fossils is technically challenging, these data are sure to be provocative.

***Report* (*Histone Acetylation in PWS*),** *by Saitoh and Wada* (*p. 1958*)

The *SNURF-SNRPN* locus on chromosome 15q colocalizes with an imprinted region that is important in Prader-Willi syndrome (PWS), a neurogenetic disorder characterized by obesity, mental retardation, and hypogonadism. *SNRPN* encodes the small nuclear ribonucleoprotein N, which is expressed predominantly in the brain and central neurons and which is believed to be involved in mRNA processing. Normally, only the paternal *SNRPN* allele is expressed, and the maternal allele is methylated and inactive. In individuals with PWS, the paternal allele is either missing or defective, and expression of this gene is therefore not detected. Saitoh and Wada have examined the *SNRPN* locus to understand the basis of imprinting, specifically the role of acetylation in this process. They have found that, on the inactive, maternal alleles of the *SNRPN* locus, the CpG island is hypoacetylated. Increased acetylation and expression of the maternal allele were induced through demethylation of the DNA by 5-aza-dC. These results indicate that methylation, acetylation, and gene expression are intertwined in the process of genomic imprinting. Furthermore, these data suggest that demethylating agents could be used to reactivate the maternal alleles of this imprinted region.

***Report* (*BRCA1 Founder Mutations in Poland*),** *by Górski et al.* (*p. 1963*)

This study of Polish families affected by breast and ovarian cancer has identified recurrent BRCA1 mutations in this population, suggesting the presence of founder mutations. Three recurrent mutations, 5382insC, C61G, and 4153delA, constitute 82% of the BRCA1 mutations recognized in this study. The identification of recurrent mutations in specific populations allows for more cost-effective and rapid screening of individuals for BRCA1 mutations. This information is valuable not only for families in Poland but also for families of Polish descent, a substantial number of whom reside in North America.

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