This Month in the *Journal*

Trisomy and XCI, *by Beever et al.* **(***p. 399***)**

Skewed X-chromosome inactivation (XCI) has been found, in some studies, at an increased frequency in samples of women with recurrent spontaneous abortion (RSA). The reasons behind this association are unclear, and Beever et al. decided to delve into it further through analysis of the karyotypes of losses from these women. One theory for the association between skewed XCI and RSA is that the women carry male-lethal X-linked mutations that result in skewed X inactivation in the mothers and a decrease in the number of sons born to them. Beever et al. find no evidence for an excess of male losses in mothers with ⩾90% skewed XCI, so X-linked male-lethal mutations do not appear to be the explanation for the association between skewed XCI and RSA in their cohort. However, an increase in trisomic losses was seen in women with extremely skewed XCI, and this does not seem to be due to an increase in maternal age. Because follicular reserve is known to be associated with the risk of aneuploidy, the authors propose that a reduced follicular reserve in these women is associated both with skewed XCI and with increased risk of RSA due to trisomic losses.

GJA1 ***Mutations in ODDD,*** *by Paznekas et al.* **(***p. 408***)**

Oculodentodigital dysplasia (ODDD) is an autosomal dominant disorder that presents with a wide-ranging phenotype that can include, among other things, craniofacial and limb dysmorphisms, neurodegeneration, conductive deafness, and spastic paraplegia. The gene for connexin 43, *GJA1,* was considered a candidate gene, because it maps to the critical region on chromosome 6q22-q23; it is expressed in a wide range of tissues; and the connexins, of which gap junctions are composed, are involved in many physiologic and developmental processes. Paznekas et al. recruited 17 families with ODDD and found *GJA1* mutations in all of them. These mutations are distributed throughout the gene, and all but one of them is a missense mutation. On the basis of previous studies of mutations in other connexin genes, it seems likely that these mutations are dominant negative mutations that prevent proper formation or function of gap junctions.

0002-9297/2003/7202-0001$15.00

Evaluation of **BBS1** ***Complex Inheritance,*** *by Mykytyn et al.* **(***p. 429***)**

Some evidence suggests that a form of complex inheritance that has been termed "triallelic inheritance" is required for Bardet-Biedl syndrome (BBS). In this form of inheritance, two mutations at one locus and a third mutation at a separate locus all contribute to expression of the phenotype. Mykytyn et al. examined, in a cohort of people with BBS and their relatives, whether the recently identified *BBS1* gene plays a part in this type of inheritance. No affected individuals who possessed at least one *BBS1* mutation were found to have mutations in *BBS2, BBS4,* or *MKKS,* the other known BBS genes. In addition, no unaffected relatives of patients with BBS were found to have two mutant *BBS1* alleles, meaning that there is no evidence for reduced penetrance in individuals with only two mutations. Overall, these results suggest that *BBS1* does not contribute to complex inheritance involving other BBS loci. However, this does not rule out the contribution of other loci that may modify the BBS phenotype in people who do carry two *BBS1* mutations.

Sip1/Zfhx1b ***Knockout Mouse,*** *by Van de Putte et al.* **(***p. 465***)**

Mutations in *ZFHX1B,* encoding Smad-interacting protein-1 (Sip1), are believed to be involved in a syndromic form of Hirschsprung disease that includes mental retardation, facial dysmorphology, and heart disease in its phenotype. Van de Putte et al. generated a strain of mice that is homozygous for a null allele of *Zfhx1b,* which is comparable to the type of mutations found in most individuals with this syndrome. The homozygous mutation is embryonic lethal, and these embryos exhibit an early arrest in cranial neural crest cell migration and a lack of a vagal-level neural crest. In addition, expression of markers in the neural ectoderm and neuroepithelium is misregulated in these mice. Mice heterozygous for the *Zfhx1b* mutation do not have an aganglionic intestine, which is characteristic of Hirschsprung disease in humans. However, the lack of vagal neural crest precursors, which normally give rise to enteric glia, in this knockout mouse model does suggest that Sip1 is involved in innervation of the intestine. The effects of the *Zfhx1b* knockout on cranial neural crest cell migration also suggests an explanation for the facial dysmorphology associated with this syndrome, because the cranial neural crest forms craniofacial cartilage, bone, and connective tissue.

PEX7 *and Refsum Disease,* *by van den Brink et al.* **(***p. 471***)**

Mutations in *PHYH* cause Refsum Disease (RD), because of a deficiency of the encoded peroxisomal enzyme phytanoyl-CoA hydroxylase. PhyH normally catalyzes a step in the degradation of phytanic acid, so this fatty acid accumulates in affected individuals and is associated with retinitis pigmentosa, cerebellar ataxia, absence of a sense of smell, and peripheral neuropathy. Van den Brink et al. study two probands with RD in whom no *PHYH* mutations could be found. Along with a deficiency of PhyH activity, fibroblasts from these individuals also have a defect in import of proteins with peroxisomal targeting signal type 2 (PTS2). The peroxin 7 protein, encoded by *PEX7*, is involved in this process, and the probands with RD were both found to have mutations in *PEX7*. *PEX7* mutations are also involved in rhizomelic chondrodysplasia punctata (RCDP) type 1, a much more severe disorder than RD. It presents at an earlier age; includes growth retardation, profound developmental delay, and ichthyosis; and is fatal early on. Curiously, both probands with RD carry a nonsense mutation that has also been found in people with RCDP type 1. The explanation for the milder phenotype in the probands with RD lies with the second mutation in each, which encodes proteins that appear to have some residual peroxin 7 activity that may prevent development of the more severe RCDP phenotype.

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