This Month in the *Journal*

Spastin-Gene Mutations, *by Svenson et al.* (*p. 1077*)

Autosomal dominant pure hereditary spastic paraplegia (SPG), a neurodegenerative disorder characterized by gait difficulties, leg weakness and spasticity, and hyperreflexia, is most often caused by mutations in *SPG4,* the gene encoding spastin. This protein is a member of the AAA family of ATPases, which are thought to act as molecular chaperones in a variety of cellular processes. Almost all of the mutations that have been identified in the spastin gene affect, either directly or indirectly, the spastin AAA motif, which serves as the active domain for the protein. In this study by Svenson et al., 15 families with autosomal dominant pure SPG were screened for mutations in *SPG4*. Mutations were identified in 11 of the families, and all of these mutations are predicted to affect the AAA motif. One splice-site mutation in this cohort, IVS9+4a→g, results in the deletion of exon 9 from some of the encoded transcripts. However, normal, full-length transcript is also produced from the mutant allele. Attempts to recreate the leaky expression of this mutation in a minigene construct were not successful until flanking exon and intron sequences were included in the construct. The authors propose two main implications of these results: first, difficulty in the reconstruction of leaky expression of the splice-site mutation in vitro suggests that splicing experiments using minigene constructs should be interpreted with caution; second, although a model of haploinsufficiency for autosomal dominant SPG can be invoked, the production of some normal transcript from the IVS9+4a→g mutation in an affected individual suggests that smaller (<50%) reductions in spastin can also cause disease. Thus, the variability of expression of some *SPG4* mutations may explain the variability in symptom severity and progression that is seen with SPG.

Transaldolase Deficiency, *by Verhoeven et al.* (*p. 1086*)

Verhoeven et al. describe a relatively new category of inborn errors of metabolism, errors in polyol metabolism. They present a girl with mild bleeding problems, an enlarged clitoris, aortic coarctation, and liver cirrhosis. She had elevated concentrations of polyols—including arabitol, ribitol, and erythritol—in her urine. In a transaldolase-activity assay, cultured lymphoblasts and erythrocytes from the patient exhibited a buildup of the substrate and a lack of the product of the transaldolase reaction, indicating a transaldolase deficiency. Sequencing of the *TALDO1* gene for transaldolase revealed a homozygous deletion of 3 bp in the patient, which results in the loss of serine 171 in the protein. Transaldolase, along with transketolase, links the pentose phosphate pathway with glycolysis. The authors propose that the transaldolase deficiency leads to polyol accumulation following the inadequate conversion of sugar phosphate intermediates in this metabolic pathway.

Origin of* MECP2 *Mutations in RTT, *by Trappe et al.* (*p. 1093*)

The scarcity of males with Rett syndrome (RTT) has led many people to propose that it is an embryonic lethal disease in males. Carriers of mutations in *MECP2,* the gene for RTT, are affected and are unlikely to reproduce and pass *MECP2* mutations to children. Therefore, RTT is almost always a result of de novo mutations. This led George Thomas to propose that a high male:female germline mutation rate could explain the difference in the number of males and females affected by RTT (see Trappe et al.'s citation of Thomas [1996]). Because *MECP2* is on the X chromosome, fathers cannot pass *MECP2* mutations to their sons. If more de novo mutations arise in males, and if they can pass these mutations only to their daughters, then most affected individuals will be girls. Subsequently, most of the affected girls will inherit a *MECP2* mutation from their fathers, rather than from their mothers. Trappe et al. test this hypothesis through an examination of the parent of origin of the *MECP2* mutations in 27 females affected with RTT. Through use of polymorphisms in *MECP2,* they were able to determine which parent passed the mutated copy of *MECP2* to each affected girl. In 26 of 27 cases, the mutation came from the father. These data provide a likely explanation for the high female:male sex ratio in RTT, and they suggest that, in fact, RTT may not be male lethal.

WNT-4 and Dosage-Sensitive Sex Reversal, *by Jordan et al.* (*p. 1102*)

Wnt-4 is known to be involved in sex determination in mice. Deletion of this gene leads to masculinization of XX mice. This observation, along with the persistence of *Wnt-4* expression in the developing ovary but not in the developing male gonad, suggests that *Wnt-4* plays an important role in ovarian development. To determine whether human *WNT4* also plays a role in sex determination, Jordan et al. first cloned the human homolog

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of *Wnt-4* and localized it to chromosome 1p35. An XY–sex-reversed patient was identified who carried a duplication of the chromosome 1p31-p35 region, and this duplication included *WNT4*. *WNT4* is expressed in fibroblasts from the sex-reversed patient but not in those from normal males, suggesting that *WNT-4* may have played a role in the sex reversal. To determine the consequences of *WNT-4* overexpression, the authors transfected *Wnt-4* cDNA into mouse Leydig and Sertoli cells. *WNT-4* overexpression results in strong up-regulation of *Dax1*, a transcription factor known to play a role in sex determination. Because *Dax1* and *Wnt-4* also exhibit similar expression patterns in embryos and can, when they are in excess, feminize XY mouse embryos, both genes may play a role in the same dosage-sensitive sex-determination pathway.

Disruption of the Imprinting Center, *by Buiting et al.* (*p. 1290*)

Imprinting defects at chromosome 15q11-q13 can lead to either Prader-Willi syndrome (PWS) or Angelman syndrome (AS), depending on the exact sequences involved. An imprinting center has been localized to the *SNURF-SNRPN* locus in this region. The shortest region of deletion overlap for each disease has been used to define two critical regions within this locus: the AS-SRO (AS shortest region of overlap) is 35 kb upstream of exon 1 of *SNRPN*, and the PWS-SRO (PWS shortest region of overlap) includes exon 1. Deletions in PWS-SRO are important for the establishment or maintenance of the paternal imprint. The AS-SRO and PWS-SRO regions are believed to interact to establish the maternal imprint in this region, although a demonstration of this interaction has not been made in humans. Buiting et al. identified two siblings who are affected by AS and who have a rearrangement in the imprinting center of chromosome 15q. The rearrangement is a 1–1.5-Mb inversion that disrupts the imprinting center, moving the AS-SRO away from the PWS-SRO and putting it in an inverted orientation. The mother and the maternal grandfather also carry the inversion, although neither is affected. These results suggest that transmission of the inversion through the maternal, but not the paternal, germline leads to AS. Because the mother shows normal methylation and expression of the *MKRN3* gene in this region, the region can be paternally imprinted, regardless of the inversion. The association between maternal transmission of the imprinting-center inversion and Angelman syndrome suggests that, to establish the maternal imprint, the PWS-SRO and AS-SRO need to be in close proximity or in a particular orientation.

Congenital Blindness and RPGRIP1, *by Dryja et al.* (*p. 1295*)

Many cases of X-linked retinitis pigmentosa are caused by mutations in *RPGR*. Dryja et al. decided to see whether mutations in the gene for the recently identified RGPR-interacting protein, RPGRIP1, are also associated with retinal degeneration. After the complete human *RPGRIP1* sequence was determined, on the basis of homology with the murine sequence, patients with Leber congenital amaurosis, an autosomal recessive retinal dystrophy, were screened for mutations in this gene. Of the 57 patients, 3 had mutations that created premature stop codons in *RPGRIP1*. Three rare missense variants were also discovered in other patients, but their pathogenicity was not clear. Although the number of *RPGRIP1* mutations is small, the discovery of four null mutations in three patients with Leber congenital amaurosis suggests that the mutations are responsible for their retinal disease.

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