This Month in the *Journal*

***Mutations in* BRCA2,** *by Edwards et al.* (*p. 1*)

Studies of families with breast cancer have suggested that male carriers of at least some *BRCA2* mutations are at increased risk of prostate cancer at early ages. To further examine the contribution of this gene to prostate cancer, Edwards et al. ascertained a sample of individuals who were diagnosed with prostate cancer when younger than 56 years of age. These men were screened for *BRCA2* mutations; six truncating mutations, as well as 22 variants of unknown significance, were found. Of the six men with truncating mutations, only one had a family history of prostate cancer, whereas two had a family history of breast or ovarian cancer. Thus, there were *BRCA2*-associated prostate cancer cases with no family history of breast or ovarian cancer. These results suggest that *BRCA2* mutations may be responsible for a significant fraction of early-onset prostate cancer, even in families without a history of breast and ovarian cancer.

CRYM *Mutations in Nonsyndromic Deafness,* *by Abe et al.* (*p. 73*)

Congenital deafness is a genetically heterogeneous disorder. Although several genes for deafness have been identified, there are many more deafness loci for which no gene has been cloned. Rather than starting with genetic linkage data to identify additional deafness genes, Abe et al. decided to identify candidate genes using microarrays to identify those that are highly expressed in the inner ear. They looked for transcripts that were highly expressed in cochlear and vestibular tissue, relative to a mix of several other tissues. As a proof of principle, nine genes known to be involved in nonsyndromic deafness were included in the array, and expression in the inner ear was confirmed for seven of these genes in the experiment. In fact, the gene with the highest relative expression in the inner ear was *COCH*, which is involved in autosomal dominant nonsyndromic hearing loss. The authors decided to focus on *CRYM*, the gene with the second highest relative expression in the inner ear. DNA sequence of this gene in 192 patients with nonsyndromic hearing loss identified two individuals with mutations, a missense mutation, and a mutation of the stop codon. Aberrant localization of both variant proteins in transfected cells supports their classification as mutants, but this awaits confirmation in additional families affected with deafness.

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FGF14 *Mutation in Dominant Ataxia,* *by van Swieten et al.* (*p. 191*)

Several different loci are known to be involved in the hereditary spinocerebellar ataxias (SCA). Disease-associated mutations in the SCA genes are almost all tri- or pentanucleotide expansions. Now, van Swieten et al. report a rare point mutation associated with an SCA phenotype. This mutation, a missense change in the gene for fibroblast growth factor 14 (FGF14), was found in a large family with early-onset tremor, dyskinesia, and slowly progressive cerebellar ataxia that was not due to any of the previously known SCA loci. Protein modeling predicts that this mutation would destabilize the encoded protein. Further supporting the involvement of this mutation in the phenotype is the fact that *Fgf14* knockout mice show an ataxic phenotype reminiscent of the one seen in this family. At this point, little is known regarding the function of FGF14, so its role in the development of ataxia is unclear.

MSR1 *Variants and Prostate Cancer Risk,* *by Xu et al.* (*p. 208*)

In a recent issue of *Nature Genetics* (32:321–325), Xu et al. found six rare missense mutations and one nonsense mutation in *MSR1* that showed some association with both hereditary and nonhereditary prostate cancer. *MSR1* encodes the macrophage scavenger receptor 1 protein, which is a macrophage-specific receptor that has been implicated in a number of processes, including inflammation, oxidative stress, and immunity. In a follow-up to this paper, Xu et al. examined five common variants in *MSR1* and found that they, too, are associated with nonhereditary prostate cancer. None of the previously studied rare *MSR1* mutations is found on the risk haplotype containing the common *MSR1* variants, so it seems that their effects are independent. Although the associations between *MSR1* and prostate cancer have been modest so far, the data suggest that common *MSR1* sequence variants may be associated with prostate cancer risk in the general population.

Association of IVF with BWS, *by DeBaun et al.* (*p. 156*) and ***Letter to the Editor,*** *by Orstavik et al.* (*p. 218*)

Over the past year, there has been a smattering of reports suggesting that children conceived through use of assisted reproductive technologies (ART) may be at increased risk of low birth weight and birth defects. In

this issue of the *Journal*, two additional articles add evidence that intracytoplasmic sperm injection (ICSI) may be associated with imprinting defects in children conceived by this method. DeBaun et al. use data gathered through the Beckwith-Wiedemann Syndrome (BWS) registry and estimate that there is a sixfold increase in BWS in children born after ART compared with the general population. All of the case subjects with BWS identified in this study were conceived though ICSI. Imprinting studies on DNA from these individuals indicate that five of six children tested had abnormal imprinting of at least one BWS-associated gene. Orstavik et al. also report a sporadic imprinting defect in an individual who was conceived by ICSI and who has Angelman syndrome. BWS and Angelman syndrome are rare disorders, making it difficult to determine whether the apparently increased rate of these syndromes in the ART sample is significant. However, these data suggest that the risks of ART should be studied further.

KATHRYN GARBER
Deputy Editor