This Month in the *Journal*

MC4-R *Mutations and Autosomal Dominant Obesity,* *by Sina et al.* (*pp. 1501–1507*)

The melanocortin 4 receptor (MC4-R) is a G-protein–coupled receptor, expressed in the hypothalamus, that appears to mediate the hunger-suppressing effects of α-melanocyte–stimulating hormone. Haploinsufficiency for *MCR4* has been seen in human families with extreme obesity, a phenotype that is also found in heterozygous animals carrying a targeted deletion of the mouse *Mc4r.* Sina et al. have searched for mutations in this gene in a group of 492 obese German children, and they report here that 4 of their index patients, representing three distinct families, harbor deletions or nonsense mutations in this gene. The most extreme form of obesity is seen primarily in women in these families, and, interestingly, the knockout mice follow a similar pattern of penetrance. Since assortative mating for weight is well known, it is not surprising that these families include unrelated spouses who are themselves obese; as Sina et al. note, this circumstance complicates efforts to estimate the quantitative effect of *MCR4* defects in these families. The authors find that these families are relatively free of diseases, such as diabetes and hypertension, that are typically associated with a high body-mass index. Although the number of individuals in this group remains small, this observation raises the possibility that this genetic subtype of extreme obesity is relatively benign with respect to co-morbid conditions.

Estimate of Hemophilia B Mutation Rates, *by Green et al.* (*pp. 1572–1579*)*; and* ***Sporadic and Detrimental Mutation Rates,*** *by Giannelli et al.* (*p. 1580–1587*)

In this pair of papers, Giannelli and colleagues attempt to estimate the rate of spontaneous mutations that occur per human generation. First, they turn their attention to the appearance of inactivating mutations in the factor IX (*FIX*) gene, an X-linked locus that underlies the common bleeding disorder hemophilia B. For this work, the authors take advantage of a nearly comprehensive collection of British individuals and families with this disease, and they follow the emergence of all unique mutations in the sample. In addition, they use family histories and haplotype analysis to identify mutations that arise independently within their group but that are identical by state. These data allow them to estimate the frequency of *FIX* mutations and to show that such mutations arise more than eight times as often in the male germline than in the female germline. Their estimate of the overall mutation rate in this gene agrees with previous estimates from smaller samples. However, contrary to some earlier work that showed that males are particularly prone to mutations that involve a C→T transition at CpG dinucleotides, Gianelli et al. indicate that different classes of mutations occur with the same relative frequency in the male and female germlines. In the second paper, the authors pursue this theme of sex-specific mutation rates by examining the accumulated mutations at several X- and Y-linked sites in a human male versus those in a male chimpanzee. Despite the fact that the X-linked loci had existed for two-thirds of their evolutionary history in the female germline—whereas the Y chromosome had been transmitted exclusively from male to male—there was no evidence that these loci had different patterns of mutations. Giannelli et al. estimate that, on average, an individual carries >100 novel mutations, of which perhaps 1 may be expected to be deleterious.

Telomeres of the Inactive X Chromosome, *by Surrallés et al.* (*pp. 1617–1622*)

The inactive X chromosome in a normal female cell can be distinguished from its homologue by its later replication, its condensed, heterochromatic state, and its failure to stain with antibodies to acetylated histone. To this list, Surrallés and coworkers now add the instability of its telomeres. Using a fluorescent probe specific to telomeric sequences, these authors performed quantitative analysis on FISH images of metaphase cells taken from females of different ages. When cells from newborns were compared with those from women in their 30s or their 60s, the overall telomeric fluorescence signal decreased in intensity, as a function of age—as would be expected, given the steady shortening of telomeres at each division in somatic cells. However, although telomeres on the active X chromosomes decreased in brightness at a rate similar to what was seen in those on autosomes, telomere fluorescence on the inactive X chromosome declined significantly more rapidly. The basis of this difference is unknown, but Surrallés et al. suggest that it accounts for the prevalence of X-monosomic cells that have been found in the tissues of older women.

Chromosomal Linkage of Duane Retraction Syndrome, *by Appukuttan et al.* (*pp. 1639–1646*)

Orientation of the gaze by the extraocular muscles is significantly disrupted in Duane retraction syndrome

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(DRS), which owes its name to the tendency of the eye to retract into its socket when an affected person attempts to move the eye toward the medial position. On the basis of both neuroanatomical evidence and recent functional neuroimaging data, it appears that this defect results from the absence of cranial nerve VI, the abducens nerve motor nucleus, which innervates the lateral rectus muscle of the eye. Appukuttan et al. have identified a locus on 2q that is linked to a highly penetrant dominant form of DRS. Working with an extended four-generation family with this disorder, Appukuttan et al. show that the underlying gene maps near an array of homeobox genes, the HOXD cluster. These genes are intriguing candidates for this condition, because they encode transcription factors that regulate morphogenesis and that are expressed in the brain. One other HOX gene has been shown in knockout-mouse experiments to affect one of the motor-neuron nuclei specifically. However, Appukuttan and coworkers found no mutations in the coding regions of the HOXD genes in their study's family with DRS.

Genetics of Ovarian Cancer in Women of Age <30 Years, *by Stratton et al.* **(***pp. 1725–1732***)**

Families with high incidence of breast cancer or hereditary nonpolyposis colorectal cancer are often found to be subject to other cancers, including ovarian cancer. On the basis of studies on such families, it has been proposed that mutations in the *BRCA1* and *BRCA2* genes and in two DNA-repair genes, *hMSH2* and *hMLH1,* predispose to early-onset ovarian cancer. Stratton and colleagues observe that there is a dearth of information about the risk of ovarian cancer for women in the general population, but now they have analyzed DNA from a large group of women who were diagnosed with early-onset ovarian cancer. Crucially, these subjects, who had been diagnosed over a period of 10 years in the United Kingdom, were ascertained without regard to a family history of disease. None of the ~100 individuals examined carried identifiable mutations in *BRCA1, BRCA2,* or *hMSH2,* although two carried mutations in *hMLH1*. Moreover, no cases of early-onset ovarian cancer were found among their first or second-degree relatives, and no obvious familial clustering of ovarian cancer was identified at any age. The lifetime risk for ovarian cancer—as well as for cancer overall—appears to be somewhat increased among relatives of these individuals, but this modest increase in risk is in sharp contrast to that calculated for close relatives of women with early-onset breast cancer.

Heterogeneous Mitochondrial Point Mutations in Deaf Families* (*letter to the editor*),** *by Pandya et al.* **(pp. 1803–1806***)**

Following up on their earlier finding of mitochondrial mutations in Mongolian families with matrilineal deafness, Pandya et al. have screened a group of 480 deaf people for two known sequence changes in their mtDNA. Initial work with restriction enzymes identified 37 individuals with an *Alw*26I polymorphism, which predicted that the well-known mutation 1555A→G was involved in the condition, as well as 9 with an *Xba*I polymorphism that has been seen in several families of different ethnic backgrounds. This latter polymorphism was expected to correspond to the previously identified 7445A→G substitution at the 3′ end of the cytochrome oxidase I (*COI*) gene, but, in all 9 cases, the loss of the *Xba*I site resulted from novel point mutations, 7443A→G, 7444A→G, or 7445A→C. The remarkable concentration of distinct deafness mutations affecting this short sequence probably does not identify a critical region of the COI protein sequence, because 7445A→G is a silent mutation that changes one stop codon to another. Pandya et al. speculate that the nucleotide sequence that includes the *Xba*I site is required for normal processing of the polycistronic RNA transcribed from the L strand of the mtDNA.

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