This Month in the *Journal*

This month in the *Journal,* van Bokhoven and Brunner (p. 1) discuss p63, a key regulator of limb, epithelial, and craniofacial development. Mutations in *TP63,* the gene encoding p63, are involved in a variety of malformation syndromes, including limb-mammary syndrome, acrodermato-ungual-lacrimal-tooth syndrome, ectrodactyly–ectodermal dysplasia–clefting syndrome, ankyloblepharon–ectodermal dysplasia–clefting syndrome, and nonsyndromic split-hand/split-foot malformation. Along with an outline of what is known about p63 activity and its role in mammalian embryonic development, the authors cover genotype-phenotype correlations and give insight into how one gene can lead to a spectrum of disorders.

Elastin Deficiency and Cell Proliferation, *by Urbán et al. (p. 30)*

Patients with supravalvular aortic stenosis and Williams-Beuren syndrome have occluded arteries as a result of either point mutations in or deletions of the elastin gene. Regions of the aorta in these patients have an abnormally thick wall diameter, because of an increase in the smooth-muscle cell layers in these areas. Urbán et al. uncover a connection between the genetic and physical abnormalities in these patients. They find that defects in the elastin gene result in lower elastin mRNA levels and in decreased deposition of insoluble elastin from cells of patients. These properties are associated with increased proliferation, in culture, of confluent smooth-muscle cells and fibroblasts. Supplementation of the cells with insoluble elastin decreases their proliferation rate, so it seems that elastin itself has an antiproliferative effect. Excessive cell proliferation in the walls of the aorta could lead to the increased number of cell layers and disorganized architecture that are seen on histological examination of aortas from affected individuals.

AE Is Due to Effects in a Novel Zinc Transporter, *by K. Wang et al. (p. 66)*

Acrodermatitis enteropathica (AE) is a zinc-absorption deficiency that manifests with a variety of symptoms, including alopecia, immune-system dysfunction, failure to thrive, dermatitis, and diarrhea. It has been hypothesized that affected individuals are deficient for a binding factor that transports dietary zinc to epithelial cells, and Wang et al. believe that they have determined the identity of this factor. This protein, hZIP4, is a novel transmembrane protein related to a family of protein sequences, some of which transport zinc. hZIP4 is expressed abundantly in the small intestine, stomach, colon, and kidney and is localized to the apical surface of enterocytes in mouse colon. Missense mutations, a splice-site mutation, and an upstream deletion were found in the encoding gene in individuals with AE. Because dietary zinc supplementation is an effective therapy for AE, the authors speculate that either (1) the mutant hZIP4 has only a partial loss of function that can be overcome by excess zinc or (2) another zinc transporter can supplement the activity of hZIP4, to compensate for the defect.

Large Deletions in Kindreds with Autism, *by Yu et al. (p. 100)*

In the course of searching for autism-susceptibility genes, Yu et al. discovered four interstitial deletions, ranging in size from 5 kb to >260 kb, in 12 families with autistic siblings. One of the deletions, a 192-kb deletion on chromosome 8, appears to be a polymorphism, because it is found in a variety of control populations. In fact, the deletion allele is more common in control subjects than in autistic individuals. The other three deletions are restricted to families with autism, but they are not identical in each family and they do not segregate perfectly with the disease. The authors propose a couple of scenarios that could explain the association between these deletions and autism. One scenario is that the deletions are autism-susceptibility alleles. Unfortunately, no gene of known function is disrupted by the deletions. An alternative hypothesis is that alleles at autism-susceptibility loci cause deletions and rearrangements, possibly because of increased meiotic error. In this case, the deletions would be not the cause but, rather, a consequence of autism-susceptibility alleles located elsewhere.

Microcephalin: Mutated in MCPH1 Microcephaly, *by Jackson et al. (p. 136)*

Jackson et al. have uncovered the first gene for primary microcephaly, a disorder in which affected individuals have a small head circumference, resulting from a smaller-than-normal brain. A nonsense mutation was identified in two affected families, and it is predicted to severely truncate the encoded protein. This previously undescribed protein, dubbed "microcephalin" by the authors, contains three BRCA1 C-terminal (BRCT) domains, which are known to interact with each other, with other proteins, and with DNA at double-strand breaks. In situ hybridizations to detect the mouse ortholog in fetal mouse brain indicates that microcephalin is ex-

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pressed at high levels in the developing forebrain, particularly in the lateral ventricles, where neurons that will form the cerebral cortex are produced. Because proteins with BRCT domains are known to be involved in cell-cycle regulation and in DNA repair, the authors speculate on mechanisms by which a defect in these activities may be involved in microcephaly, should microcephalin itself be found to have these functions.

Parent-of-Origin Effect in Retinoblastoma (Report), *by Klutz et al. (p. 174)*

Klutz et al. present two interesting families with parent-of-origin–dependent penetrance of an *RB1* mutation, a phenomenon that has not been reported previously for retinoblastoma. These unrelated families possess the same splice-site mutation, but on different haplotype backgrounds. Individuals who inherit the mutation from their fathers are much more likely to have retinoblastoma than are individuals with a maternally inherited mutation. The mutation alters a splice site and causes exon 6 to be skipped, leading to a frameshift and premature truncation of the encoded protein. Analysis of RNA from individuals with a maternally inherited mutation indicates that they have approximately equal amounts of wild-type and mutant *RB1* transcript. In contrast, those with paternally inherited mutations have much less mutant transcript, relative to wild-type transcript. The correlation between a reduced level of mutant transcript and disease suggests that the shorter transcript may have residual function, although a truncated protein was not detected by western blot. Increased relative abundance of the mutant transcript after treatment with an inhibitor of nonsense-mediated decay indicates that this process may play a role in the reduction of the mutant-transcript levels, but the full explanation behind the parent-of-origin–dependent penetrance in these families is not yet clear.

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