# This Month in *The Journal*

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## NODAL Signaling in Developmental Defects

**Roessler et al., page 18**
Mutations in a number of genes involved in the patterning of the midline have been linked to holoprosencephaly (HPE), congenital heart defects (CHD), and asymmetric internal organ positioning. Genes in the NODAL signaling pathway are known to be involved in these disorders, but a wide range of clinical malformations is seen in patients with the same mutation, so it is thought that interactions with other genes and the environment are responsible for phenotypic variability. In an effort to learn more about the components interacting to produce these clinical spectra, Roessler et al. examine the sequence of six genes of the NODAL pathway in patients with HPE, laterality, and CHD. A number of variants are detected, and the authors predict that common polymorphisms in one member of the pathway might modify the effects of other pathway genes. The functional consequence of many of the sequence variants is analyzed via a zebrafish assay, and the potential disease contribution of each mutation is assessed. This whole-pathway approach allows the authors to comprehensively examine a number of potential genetic factors that interact to cause these complex disorders.

## Fragile X and Circadian Behavior

**Zhang et al., page 43**
Fragile X patients are affected not only by cognitive impairment, hyperactivity, and autistic behaviors but also by sleep abnormalities. Fragile X syndrome is caused by a triplet expansion mutation in *FMR1*, the gene encoding FMRP. FMRP is a member of a family of RNA-binding proteins that also include FXR1P and FXR2P. Evidence from work in a fly model has suggested that these proteins are involved in circadian behavior, so Zhang et al. examine circadian rhythms in mice deficient for FMRP and FXR2P. The mice are first entrained in a cycle of light and dark and are then kept in complete darkness, and the timing of their activity level is monitored. The knock-out mice demonstrate shorter circadian periods, and double knock-out mice are arrhythmic. Molecular work suggests that the central pacemaker is not affected in these mice but that downstream, peripheral clock mRNA levels are disrupted. These results suggest that some redundancy exists between *FMR1* and *FXR2* and that both are involved in the maintenance of proper circadian behavior.

## RANK Defects Cause Human ARO and Low Igs

**Guerrini et al., page 64**
One type of autosomal-recessive osteopetrosis (ARO) is due to a lack of functional osteoclasts, and mutations in *TNFSF11*, the gene encoding RANKL, were recently identified in patients with this type of ARO. Because RANK is the receptor for RANKL and mice deficient for either of the proteins are affected with severe osteoclast-poor ARO, Guerrini et al. screen a panel of ARO patients for mutations in *TNFS11A*, the gene that encodes RANK. Mutations are identified in eight patients from seven different families, and bone biopsies of three patients confirm an absence of osteoclastic activity. To isolate the point of dysfunction, the authors then culture patient cells with M-CSF and RANKL, which normally induces monocytes to differentiate into osteoclasts, and find that mutant cells do not show an increase of osteoclasts. The authors point out important differences in the potential ways to treat ARO if the causative mutation is identified. RANKL-deficient ARO has been shown not to respond to hematopoietic stem cell transplantation (HSCT) but might be rescued by treatment with exogenous RANKL. In contrast, because RANK is the receptor in the pathway, RANK-deficient ARO will most likely not respond to administration of RANKL, but HSCT might be effective. This is a great example of how genetic diagnosis of disease plays a significant role in determining the best course of treatment.

## Selection and Alternative Splicing

**Ramensky et al., page 94**
Alternative splicing is recognized as a common genomic mechanism that serves to increase the complexity and variety of the proteome. What is less clear is how the process of alternative splicing developed evolutionarily. Are certain exons alternatively spliced as a result of the pressure of positive selection, or are multiple isoforms of proteins the result of the slackening of negative selection? Ramensky et al. explore this question by comparing the signals of selection in constitutive exons to those of alternatively spliced exons. The authors also study the patterns of divergence between humans and chimpanzees in these regions. By combining the data produced by these simultaneous analyses, Ramensky et al. are able not only to observe a relaxation of negative selection in exons that are

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alternatively spliced but also to report a significant increase in positive selection at these sites.

## Genotype-Specific Recurrence Risk

**Slatkin, page 120**

A great deal of work has gone into conducting genome-wide association studies (GWAS) to detect alleles that are associated with disease risk. The overall effect of individual risk alleles is usually quite small, and it is thought that it is the interaction between multiple loci and factors that contribute to disease susceptibility. Additionally, it is difficult to determine how much of an effect each risk variant has in comparison to that of other variants. These complexities make the clinical application of GWAS findings difficult. Here, Slatkin proposes a method that will estimate the genotype-specific recurrence risk to relatives of cases evaluated in GWAS. The increase in risk to the relatives of probands might be significantly higher than the background risk and might reach levels that would be useful in counseling scenarios. These analyses also establish another means of verifying the effect and interaction of the risk alleles identified in the GWAS. The work reminds us of the unique information that can be gained from using family studies to parse out disease-susceptibility variants.