This Month in *The Journal*

Sarah Ratzel[1] and Sara B. Cullinan[2]

To NMD or Not to NMD: That Is the Question

Coban-Akdemir et al., p. 171

The introduction of premature termination codons (PTCs) typically results in transcripts that undergo nonsense-mediated mRNA decay (NMD). Many disorders—dominant and recessive—can be caused by this class of loss-of-function allele. However, some PTC-containing transcripts escape surveillance by the NMD machinery, generating novel polypeptides that, depending on their nature, can acquire new functions. Although a simple rule of thumb is that PTCs introduced in penultimate and final exons escape NMD, the reality is that the determination of "NMD competence" is not quite that simple. Moreover, the lack of supporting data from mouse knockouts and *in vitro* systems can make it difficult to assess causality when variants likely to escape NMD are found in sequencing studies. In this issue, Coban-Akdemir et al. present two complementary online tools to assist in the investigation and prioritization of variants predicted to escape NMD. The application of these metrics highlighted examples of genes known to harbor pathogenic gain-of-function or dominant-negative alleles and also identified candidates worthy of closer scrutiny. This work reinforces the importance of considering more than one mode of pathogenicity and also suggests that numerous biological insights, including a few surprises, remain to be discovered in the study of rare human diseases.

Epimutation Explains Loss of *BRCA1* Expression

Evans et al., p. 213

BRCA1 and *BRCA2* mutations are commonly identified in individuals with breast and ovarian cancer. Most identified mutations are in the coding sequence and result in either missense amino acid substitutions or loss of function at the protein level. However, even in some families with high risk and early-onset presentations, mutations remain elusive, indicating that alternative approaches to identifying additional variation might be useful. Hypermethylation of tumor-suppressor gene promoters is observed in many cancers, including breast and ovarian cancer; therefore, assessing methylation changes segregating in families affected by breast and ovarian cancer could point to underlying causal DNA variants. In this issue, Evans et al. sought to identify changes in *BRCA1* promoter methylation in association with allelic loss of mRNA expression, which also segregated with cancer occurrence in families. Sequencing of *BRCA1* uncovered a heterozygous single-nucleotide variant linked in *cis* to the hypermethylation. This variant is in exon 1, a non-coding region not typically evaluated during routine genetic tested. Altogether, this work suggests that for individuals with high risk and a familial history of breast cancer, methylation analysis could provide valuable clinical insights when performed in conjunction with more routine sequencing and copy-number-variant analysis.

A New Renal Resource

Gillies et al., p. 232

Nephrotic syndrome (NS), a heterogeneous disorder typified by proteinuria and edema, can progress to chronic kidney disease and end-stage renal disease. A spectrum of rare and common variants is associated with NS pathology, but much of the genetic etiology of this disease remains unknown. Moreover, most analyses of kidney gene expression are limited to disease-free and/or bulk tissue samples, hindering disease-specific discovery efforts. In this issue, Gillies et al. present their analyses of biopsied glomeruli and tubulointerstitium from more than 100 individuals with NS. In addition to cataloging and fine-mapping *cis*-expression quantitative trail loci (eQTLs) for these kidney structures, the authors used single-cell RNA-sequencing data to explore cell-type specificity of these eQTLs. In a further application, the authors integrated their eQTL data with the results of a nephropathy genome-wide association study to identify genes in which changes in expression might be associated with additional kidney pathologies. As researchers continue to explore the genetic underpinnings of diverse pathologies, studies that utilize multiple technologies and datasets are likely to become more common and more comprehensive in nature.

Making Sense of Mutable Amplicons

Teitz et al., p. 261

Compared with other chromosomes in the human genome, the structure of the Y chromosome is unique.

[1]Scientific Editor, *AJHG*; [2]Deputy Editor, *AJHG*
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It doesn't recombine with a homologous chromosome, and it has large regions of amplicons containing genes that are highly expressed in testes. Because amplicons are composed of highly identical segmental duplications, quantifying them is difficult. Clues about amplicon evolution from other species are sparse: ampliconic sequences across mammals are dramatically divergent. In this issue, Teitz et al. develop a tool for accurately determining amplicon copy number in 1000 Genomes Project samples and use this information to evaluate the effects of selection on amplicon evolution. Notably, the amplicon reference number is reliably maintained across Y chromosomes from individuals worldwide even in the oldest Y chromosome linages. However, in about one-sixth of males, a deleted or duplicated amplicon was identified. Phylogenetic analysis and simulations demonstrated that this pattern is consistent with mutation-selection balance. In support of this hypothesis, cases of amplicon rescue could also be identified. This work suggests that although amplicons frequently undergo copy-number changes in individuals, selection acts to maintain the reference copy number across populations and time. As sequencing technology improves and amplicons are better defined across species, future studies could provide improved views of the genomic dynamics of amplicons across time.

The Consequences of an Out-of-Shape ER

Breuss et al., p. 296

Comprising a network of sheets and tubules, as well as a single bilayer that forms the nuclear envelope, the endoplasmic reticulum (ER) is an organelle with a remarkably complex architecture. Recent advances have provided insight into how ER form influences function by identifying proteins required for the formation and stabilization of ER structure. Moreover, studies of rare human disorders have begun to establish a connection between ER shape and neurological function. In this issue, Breuss et al. identify homozygous mutations in lunapark (*LNPK*) in three children with severe developmental delay, hypotonia, epilepsy, and corpus callosum hypoplasia. LNPK is described as an ER-curvature-stabilizing protein, and although its mitotic inactivation enables the dynamic ER-remodeling process, its absence promotes the formation of aberrant structures. Accordingly, Breuss et al. observed abnormal shape and size in the ER of cells from affected individuals. Moreover, in their studies, mouse and human cells demonstrated an expression pattern consistent with a function in neurodevelopment, leading to the hypothesis that LNPK activity is required for corpus callosum development. Future studies in animal and cell-based models should yield additional insights into how ER shape influences brain development.