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It takes a village to interpret multigene panels

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The use of multiple information sources and expert reviewers can greatly reduce the uncertainty involved in interpretation of multigene panels, according to a new study. A clinical team from the University of Washington evaluated nearly 1,500 consecutive patients referred for multigene panels that assess breast or colorectal cancer risk. More than 80% of the study subjects had a personal history of cancer. Following International Agency for Research on Cancer (IARC) guidelines, the research team used evolutionary conservation, known and predicted variant consequences, and personal and family cancer history to classify each variant. Among breast and colorectal cancer patients, 13% had variants considered actionable, as did 4% of cancer-free subjects. In contrast to previously reported results of multigene testing that included rates of variables of unknown significance (VUS) up to 88%, this study reduced that number to 7.5%. Investigators attribute the low rate of VUS to a two-step process in which multiple experts first independently evaluated primary calls for all variants, flagging any that were potentially pathogenic. In the second step, reviewers met to discuss all flagged variants and developed a consensus classification for each one. The results indicate that multigene testing need not be overwhelmed by reports of VUS. The authors conclude that for the foreseeable future, medical judgment by experts will be necessary to minimize the number of VUS reported to patients and caregivers.
—Karyn Hede, News Editor

Diving into evolutionary relationships to improve mutation prediction

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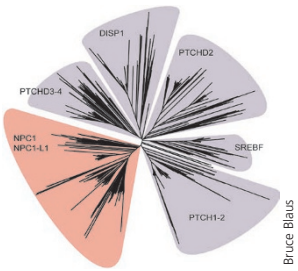

Bruce Blaus

The sifting process of evolution can help predict the effect of a given mutation, but only if used judiciously. Not all families of related genes help predict deleterious effects. In this issue, Adebali *et al.* show that, by carefully analyzing the evolutionary history of genes involved in Niemann-Pick disease type C (NP-C), they could improve the predictive ability of algorithms that categorize single amino acid substitutions. The proof-of-concept study used a computational approach to analyze the evolutionary history of the *NPC1* gene and pinpoint evolutionary events that most likely affected its function. An algorithm built on the evolutionary understanding of the gene was then able to more accurately distinguish between potentially damaging versus probably benign single amino acid substitutions. The key, according to the researchers, was limiting their analysis to genes in other species whose function remains similar to *NPC1*, that is, orthologous genes. Genes that resulted from an evolutionary duplication event and then diverged in their function (paralogous genes) were not helpful in predicting effects of mutations. Yet the current tools that use evolutionary conservation information do not discriminate between orthologous and paralogous proteins. The investigators suggest that eliminating paralogous genes from analyses would improve predictive capabilities. However, they also note that doing so is labor-intensive, involving the manual work of building high-quality data sets, alignments, and trees and defining orthologs and paralogs. They suggest that trying their approach on other well-defined Mendelian diseases could lead to better predictive methods applicable in clinical practice.
—Karyn Hede, News Editor

NEWS BRIEFS

Tracing the genetic origins of the earliest farmers

Early farming practices developed in parallel among at least two groups, and the techniques of farming spread more quickly than the farmers themselves, according to two new analyses of ancient DNA. The discoveries lend credence to the idea that farming spread from multiple groups rather than a single population, as some have suggested. The studies—of early farmers in what is modern-day Turkey and of farmers found across the Fertile Crescent—agree that early farming communities remained genetically isolated for millennia before waves of migration led to genetic mixing of the groups. The studies applied improved methods for extracting and analyzing DNA from skeletons of the Near and Middle East, where the hot climate degrades genetic material. The larger of the studies, published in *Nature*, compared 44 ancient human DNA samples from what is modern-

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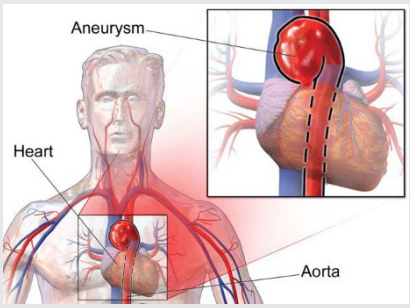
NEWS BRIEFS *(continued)*

day Iran and the region encompassing Israel and Jordan to a DNA database of contemporary individuals from the region. The investigators found that early farming occurred between 10,000–9,000 BC in at least two separate populations in the Middle and Near East, suggesting that groups began practicing agriculture independently. A second study of samples from nine individuals, appearing in *Current Biology*, revealed that early farmers in Anatolia (Turkey) remained relatively genetically isolated during the Neolithic period, from around 9500–6000 BC. The international research team from Turkey and Sweden proposes that early farming populations maintained a relatively stable population structure during the transition to agriculture. Once established, farming techniques spread faster than the farmers, the researchers speculated. The two research teams independently concluded that early farmers descended from local hunter–gatherers and did not mix extensively with other groups until around the Bronze Age, when waves of migration led to genetic mixing among farmers and rapid expansion into western Europe, Asia, and Africa. —*Karyn Hede, News Editor*

New gene associated with risk of aortic rupture identified

Mutation of a protein known to help maintain the integrity of vascular connective tissue has now been shown to cause an inherited form of thoracic aortic aneurysms and dissections (TAAD). The finding adds to a growing list of genes that can underlie familial forms of TAAD, although a pathogenic mutation in this gene has been found in only one family to date. The study, led by researchers at Washington University



School of Medicine in St. Louis, in collaboration with Brigham and Women's Hospital in Boston, identified an autosomal dominant missense mutation in the lysyl oxidase (*LOX*) gene and generated a mouse model that confirmed that *LOX* underlies the disease. The LOX protein, which normally helps cross-link networks of elastic and collagen fibers that line blood vessels, leads to a weakened aorta when mutated. Several individuals in the family studied had a history of aortic aneurysm and other physical features that suggested Marfan syndrome, but tested negative for that disease. The study was published 18 July in the *Proceedings of the National Academy of Sciences*. Using CRISPR genome engineering tools, the research team introduced the human mutation into mice, which developed a condition that mimicked the human form of the disease. Mutation carriers have weakened vessel walls that may predispose them to TAAD. The researchers suggest that clinical sequencing for *LOX* mutations may help provide diagnoses to families that currently have unexplained familial TAAD. —*Karyn Hede, News Editor*