Clinically relevant neurology news and information.

Athena Insight: Stable Scoring Over Time Effectively Communicates Risk in a Changing Gene Landscape

March 10, 2014   04:16pm EDT   ,

Among the greatest challenges in modern genetic testing is that the pace of discovery of new gene variants outpaces the full understanding of their impact. And yet an assessment of the pathogenicity of such new variants is needed to provide the physician with actionable information to fully counsel the patient about their test results.

The Athena Insight program has been meeting this challenge since 2010, providing physicians with real-time assessment of Variants of Unknown Significance (VUS). At the 2013 meeting of the American College of Medical Genetics (ACMG), Izabela Karbassi, PhD, presented an overview of the scoring system used to assign pathogenicity to a VUS, and showed that the scoring system has remained stable over time, a critical feature for effectively communicating risk to physicians.

Dr. Karbassi noted that the Insight program currently assesses variants for 235 genes involved in neurological, endocrine, and nephrotic genetic disorders, a number which has been growing every year. Since inception, the program has made 11,771 pathogenicity assessments on 8,813 unique variants. With such an enormous number of variants, it was essential from the beginning of the program to have a standardized pathogenicity assessment/scoring process. "Standardization drives consistency," Dr. Karbassi said.

The Insight scoring process segregates variants into seven categories on a 7-point pathogenicity scale, based on evaluation of multiple independent types of evidence. Known pathogenic variants are assigned a score of 7, known normal variants are assigned a score of 1, and variants of unknown significance with no apparent tendency toward benign or pathogenic are assigned a value of 4. "Between these points, variants lacking enough data for classification are assigned different scores associated with different degrees of 'probable' pathogenicity," she said.

Dr. Izabela Karbasi
Manager, Variant Science

The scoring system uses a decision-tree approach, which begins with assessment of the variant with the two major variant analysis programs, called SIFT and PolyPhen. Further weighting includes analysis of the domain of the protein affected, the frequency of the variant in the normal population, functional studies where they have been performed, and co-segregation of the variant with the disease within the family. The

system is consistent with guidelines from the ACMG that require multiple independent lines of evidence to classify a variant as benign or pathogenic, to avoid errors from publication bias and other sources.

"This scoring system creates consistency between investigators, and it reflects measurable differences in the confidence of a pathogenicity assessment based on accumulated evidence in the medical literature," Dr. Karbassi said. "Multiple lines of evidence increase the confidence in the assigned pathogenicity score, and also create stability in the assessment over time."

To test the level of stability, Dr. Karbassi and colleagues assessed how often the initial score for a variant changed over time, as new information accumulated. She found that variants scored as a 5 were later downgraded in 33 of 279 cases (11.8%) while variants scored as a 6 were downgraded in 6 of 117 cases (5.1%). Similarly, on the benign end of the scale, she found, variants scoring as 2 were more stable than those scoring as 3. Overall, very few variants initially judged likely benign were later reclassified with a more pathogenic score. Variants initially judged likely pathogenic, which were then rescored, were also more likely to be judged more pathogenic, rather than more benign.

"This stability pattern establishes confidence in the scoring categories, supports their inclusion in result reports, and provides evidence that continuous review of variants is needed to assure the quality of the risk interpretation," Dr. Karbassi said. "We conclude that Athena Insight is a stable scoring system that conveys confident pathogenicity assessments, effectively communicates risk, and provides useful diagnostic information."

Thank you for your response.

The Athena Insight Variant Investigation Team