GenomeWeb News

Variability in Autism Diagnostic Gene Panels Sparks Push for Standardization

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SAN FRANCISCO (GenomeWeb) – What originally began as an attempt to provide families and clinicians with advice on where they could obtain molecular diagnostic testing for autism has evolved into an effort to push for standardization of such tests.

Researchers from the Hospital for Sick Children in Toronto analyzed next-generation sequencing gene panels being offered by commercial clinical labs to diagnose autism and found that there is very little overlap between the tests in terms of the genes that are included.

The results were unexpected, to say the least, said Stephen Scherer, director of the Center for Applied Genomics at the SickKids Hospital and a senior author of a commentary describing the findings that was published in *npj Genomic Medicine* last month.

"I was surprised and everyone I've shown these results to was surprised," Scherer said.

The findings have spurred Scherer's team to push for the development of a standardized list of genes that should be included on any NGS panel marketed for autism. To that end, Scherer hosted a two-day workshop with experts in the field with the dual goals of defining the bare minimum gene list that any clinical diagnostic test should have, and of figuring out a process for updating and curating that list.

Scherer said that his team began analyzing commercial autism gene panels a few years ago after interacting with families with children who had autism and their clinicians. Scherer is one of the leaders of the MSSNG study to sequence 10,000 individuals with autism, a research study that also enables the return of some results to participants.

As part of that project, Scherer said that Ny Hoang, a genetic counselor and first author of the recent *npj Genomic Medicine* commentary, would often get questions from families about where and how they could get additional molecular testing. Clinicians would also ask for recommendations for labs where they could order molecular testing.

So, the team began compiling a list of companies that offered testing with the goal of "doing a landscape survey to see what's out there," Scherer said.

Ultimately, they identified 21 different laboratories that offered next-generation sequencing panels for autism. The group evaluated only NGS tests and not microarrays, which are used as first-line tests, and only panels that included three or more genes.

Among the 21 laboratories, the team identified 2,928 unique genes, the vast majority of which were included by fewer than five of the labs. Only one gene was included on every panel, MECP2. That gene is associated with Rett syndrome, which previously was considered to be on the autism spectrum, but no longer is.

There were 178 genes that were included on panels of at least five labs. Yet, of the top 16 most shared genes, the majority are associated with physical and systemic features, not autism specifically, the researchers found.

"I think this is a catastrophe," Catalina Betancur, director of research at the National Institute for Health and Medical Research (INSERM) in France and a lead investigator of the international Autism Sequencing Consortium, said. "Families are being charged to be tested with these panels, which in most cases are very incomplete. In almost all cases [the panels] include genes that are not involved in autism and, most seriously, do not include genes that are known to be involved in autism," she said.

Betancur acknowledged that while the "genetics of autism are very complex," there are nonetheless a number of well-known rare variants for which "there shouldn't be any confusion around."

Scherer said that there were a number of reasons why there was such little overlap between the gene panels. But, the main issue, he said, is that there are no guidelines. "You really have to understand all the research data out there and draw from the best research studies to generate your gene list," he said. "If you don't understand the field, and even if you do, it's complicated."

Compounding the problem is the fact that there is currently no agreed-on set of autism-related genes. In addition, he said, issues arise when panels are developed without having expertise in the specific disease. In other cases, he said, companies likely include genes in order to differentiate their test in the market.

"People are confused about the literature," Betancur added. While many studies indeed do report on rare disease-causing variants, there are also a lot of studies that find correlations between more common variants that turn out not to hold up. Yet in some cases, such variants are being included on clinical tests. "You have to be very cautious when interpreting the literature," she said.

Nancy Spinner, chief of the division of genome diagnostics at Children's Hospital Philadelphia, said that much of the discrepancy between gene panel tests could be due to the fact that there has been so much genomic research in the last several years that disease causing genes are a "moving target." Studies can initially point to what researchers think is a novel disease causing variant but further research sometimes finds that it is in fact benign.

She said that any set, validated gene list would have to also include the ability to be updated. CHOP's genomic diagnostic lab does not currently offer autism gene panels, she said, but it does offer diagnostic NGS panels for other genetic disorders as well as a medical exome test.

In some cases, the discrepancies are related to terminology. For instance, some of the panels marketed as autism panels actually included a gene list that was more broadly associated with intellectual disability, and so while some of the genes may have been related to autism, others were associated with other intellectual disabilities.

The "bonified autism genes are related to intellectual disability," Scherer said, but not all intellectual disability genes are related to autism. That becomes a problem for a family with a child with autism who is seeking a more specific molecular diagnosis. A test marketed as an autism panel may not include all known autism genes and may include many genes that are irrelevant for their child.

Scherer said he hopes the workshop and the commentary will spur discussion and the creation of an initial 15 to 20 gene list that everyone agrees would be the bare minimum of what any NGS diagnostic panel should include. Then, he said, the goal would be to develop guidelines, similar to those that ClinGen has developed for curating disease associated genes, but specific to autism.

Then, "I think a critical thing will be to put the list up and have a mechanism for the community to give feedback," Scherer said.

Betancur agreed that having experts develop a curated gene list, similar to the ClinGen effort, would be an important step. ClinGen already has an intellectual disability focused working group, but both Betancur and Scherer said it would be important to have a more specific autism-focused gene list..

"It would be really helpful for the community, for both clinical labs and researchers" to have a curated gene list of autism-related genes, she said.

Scherer agreed and said that he thought that commercial labs offering such tests would benefit from being able to have a standard reference set of genes that should be included on tests.

Spinner added that while autism may be one of the more complex disorders, the issue of variability among gene panel tests was likely not a problem only for autism. For instance, she noted that for hereditary hearing loss, available gene panel tests can vary from as few as 20 genes to more than 100.

Scherer agreed. "This is broadly an issue," he said. He cited a study published earlier this year in *Circulation* where an international group of researchers investigated genes that are commonly analyzed when testing for Brugada syndrome, a hereditary cardiovascular disorder that causes heart arrhythmia and can lead to sudden death.

The researchers reported that while more than 20 genes have been reported to cause Brugada syndrome and are routinely analyzed, there has been so much variability in the study designs that led to these disease associations that they decided to analyze 21 genes that were routinely tested by diagnostic laboratories to determine whether in fact there was enough evidence to definitively say they were disease causing. Of those 21 genes, the authors ultimately found that only one had sufficient evidence.

"It's not specific to autism," Betancur said.

Ultimately, a validated gene list will be helpful not just for diagnostics, but also for research, Scherer said. Functional biologists studying pathways, gene expression, and the impact of alterations rely on gene lists. "We're only as good as our gene list," he said.