



Actionable Mutations in ACMG 56 Genes Linked to Increased Disease Risk in General Population

Nov 09, 2016 | [Andrea Anderson](#)

NEW YORK (GenomeWeb) – Individuals from unselected populations who have pathogenic variants in genes for rare Mendelian conditions are indeed more likely to have clinical features of those conditions, according to a [study](#) out today in *Science Translational Medicine*.

A Boston-led team followed thousands of exome-sequenced and clinically-phenotyped European Americans or African Americans profiled for the Framingham Heart Study or the Jackson Heart Study. They looked at how the prevalence of pathogenic variants in 56 genes [earmarked for return of results](#) by the American College of Medical Genetics and Genomics lined up with clinical features in related conditions in an unselected population.

"There's been a big, behind-the-scenes debate about whether these mutations actually have very much impact when you see them outside of a family history," co-senior author Robert Green, a genetics researcher affiliated with Harvard Medical School, the Broad Institute, and Brigham and Women's Hospital, told GenomeWeb. "Almost all of what we know about these rare mutations happens because there's a family that has [mutations in these genes] running in the family."

In their new analysis, he and his colleagues found that around 1 percent of participants in each of the community-based epidemiological studies carried pathogenic variants in the ACMG56 genes. And the individuals with those pathogenic variants were more likely to display clinical features corresponding to the two-dozen inherited conditions linked to the genes previously.

"As a group, the people who carry these mutations are more likely than expected to develop clinical features of the underlying diseases in those mutations," Green said, noting that the results start to provide information on the effect sizes and the degree of risk such mutations confer.

"The results are very helpful data in support of the ACMG secondary findings recommendations as they demonstrate with significance that the variants predict phenotype," Leslie Biesecker, head of the National Human Genome Research Institute's clinical genomics section, told GenomeWeb in an email. Biesecker was not involved in the study.

Though it may seem intuitive that pathogenic changes to genes with documented disease roles can increase the risk of those diseases, Green explained, there has been debate about the extent to which that holds true in the general population.

Some individuals may worry that carrying a risky mutation in a disease-associated gene from the ACMG56 set guarantees that they will get the disease, for example. But at the other end of the spectrum, some experts see the wide range of suspicious-looking mutations in healthy individuals as evidence against widespread roles for these type of mutations in disease.

"The challenge, of course, is to understand how rare events might manifest themselves over many years," Green said, noting that such analyses require large groups of individuals followed for long periods of time.

With that in mind, he and his colleagues took advantage of two large cohorts of sequenced and phenotyped individuals: the Framingham Heart Study, a longitudinal study that has been underway for decades, and the Jackson Heart Study, which has enrolled many African American individuals. They focused their analyses on pathogenic and likely pathogenic variants in the ACMG56 gene set, which is generally considered to have some clinical actionability.

Because these alterations in the ACMG56 genes are rare, even the large sample sizes available are considered relatively small for the type of study the researchers had in mind, Green noted. Nevertheless, they were able to uncover pathogenic variants in ACMG56 genes in around 1 percent of individuals in each population-based group.

Across the 642 variants identified in 462 European Americans profiled by exome sequencing for the Framingham Heart Study, the team found five individuals with pathogenic mutations and two more with likely pathogenic mutations. Across the 3,223 African American participants in the Jackson Heart Study, it identified 4,429 variants, including pathogenic mutations in 19 participants and likely pathogenic mutations in four individuals.

To classify the variants, the researchers used a rigorous variant classification pipeline developed with help from co-author Heidi Rehm, a researcher affiliated with Harvard and the director of the molecular medicine lab at Partners Healthcare Personalized Medicine. They also spent a great deal of time doing manual curation before calling pathogenic variants, likely pathogenic variants, or variants of uncertain significance.

The team then folded in as much information as it could on related clinical features for the Framingham and Jackson Heart Study participants. While the cancer classification was relatively straightforward — either individuals had had cancer or they hadn't — the group took a much more nuanced look at clinical features that might portend cardiovascular disease using information collected systematically for the studies.

In the interest of bringing together the suite of clinical features associated with the pathogenic and likely pathogenic variants across the full set of genes of interest, the researchers then came up with an analytical notion that they dubbed "aggregate penetrance."

"Instead of thinking about penetrance in the conventional way, when you think about it for a single gene and a certain variant," Green explained, the team looked at what happened when they statistically lump group of genes and variants from a given category together.

Biesecker called the method "an important and useful shortcut to develop evidence to test the hypothesis that secondary findings identify individuals with and at risk for serious diseases."

When it scrutinized observed versus expected rates of clinical features related to the 24 conditions associated with the ACMG56 genes, the team found that related clinical features were between 4.7 and 6.4 times more common in pathogenic variant mutation carriers.

The effect was more pronounced in the Framingham Heart Study participants, Green explained, perhaps because that cohort has been followed for a longer period of time, making it possible to pick up disease onset in a larger number of vulnerable individuals.

This suggests that, as a group, pathogenic mutation carriers are at higher risk of such conditions than those in the general population, though the risk is not dramatically higher for any one individual, Green added.

The approach used in the study does not directly address the penetrance of particular pathogenic variants in specific genes. Even so, NHGRI's Biesecker said it "provides to interpreting clinicians relative risks of

phenotypes that are important to identify because for many of these gene variants, there are preventive measures that can be implemented to reduce morbidity and mortality."

The findings still don't prove that there is a clinical benefit to sequencing the ACMG56 genes, Green emphasized, since researchers have yet to demonstrate that having this risk information leads to better outcomes for those with worrisome mutations in the genes.

The size of the populations studied so far is too small to begin parsing out potential genetic modifiers for disease risk. Based on their findings so far, the researchers are collaborating with investigators at the Broad Institute to come up with strategies for looking at the correlation between genotype and phenotype in larger populations.

"Part of the challenge is going to be how to scale some of the processes that we did in this paper if [we] were going to do it with larger populations," Green said. "Since the Broad is so good at finding ways to scale these things, we are working with them."

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