Medical Xpress

# Classifying sequence variants in human disease

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Sequencing an entire human genome is faster and cheaper than ever before, leading to an explosion of studies comparing the genomes of people with and without a given disease. Often clinicians and researchers studying genetic contributions to a certain disease encounter variations that appear to be responsible, only to find other people with the same mutation who don't have the disease or who are affected to a lesser degree.

How do doctors pinpoint the genetic changes that really cause disease? An open-access policy paper to be published Wednesday in *Nature* proposes guidelines for researchers studying the effects of rare genetic variants. The recommendations focus on several key areas, such as study design, gene- and variant-level implication, databases and implications for diagnosis.

Co-author Chris Gunter, PhD, associate director of research at Marcus Autism Center and associate professor of pediatrics at Emory, is one of the organizers of the 2012 workshop of leading genomics researchers, sponsored by the National Human Genome Research Institute, that led to the paper.

"Several of us had noticed that studies were coming out with wrong conclusions about the relationship between a specific sequence and disease, and we were extremely concerned that this would translate into inappropriate clinical decisions," she says.

Potentially, based on flawed results, physicians could order additional testing or treatments that are not truly supported by a link between a genetic variant and disease, and this paper could help prevent such inappropriate decisions, Gunter says.

The group of 27 researchers proposes two steps for claiming that a genetic variation causes disease: detailed statistical analysis followed by an assessment of evidence from all sources supporting a role for the variant in that specific disease or condition. In addition, they highlight priorities for research and infrastructure development, including added incentives for researchers to share genetic and clinical data.

One case cited in the paper relates to autism. Researchers found four independent variations in a gene called TTN when they compared genomes between individuals with and without autism. However, the TTN gene encodes a muscle protein (titin) that is the largest known; variations are simply more likely to be found within its boundaries compared to those of other genes. Without applying the proper statistical corrections, researchers may have falsely concluded that TTN was worthy of further investigation in autism studies.

The authors note that many DNA variants "may suggest a potentially convincing story about how the variant may influence the trait," but few will actually have causal effects. Thus, using evidence-based guidelines such as the ones in the Nature paper will be crucial.

"We believe that these guidelines will be particularly useful to scientists and clinicians in other areas who want to do human genomic studies, and need a defined starting point for investigating genetic effects, " Gunter says.

**More information:** Guidelines for investigating causality of sequence variants in human disease, *Nature*, dx.doi.org/10.1038/nature13127

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