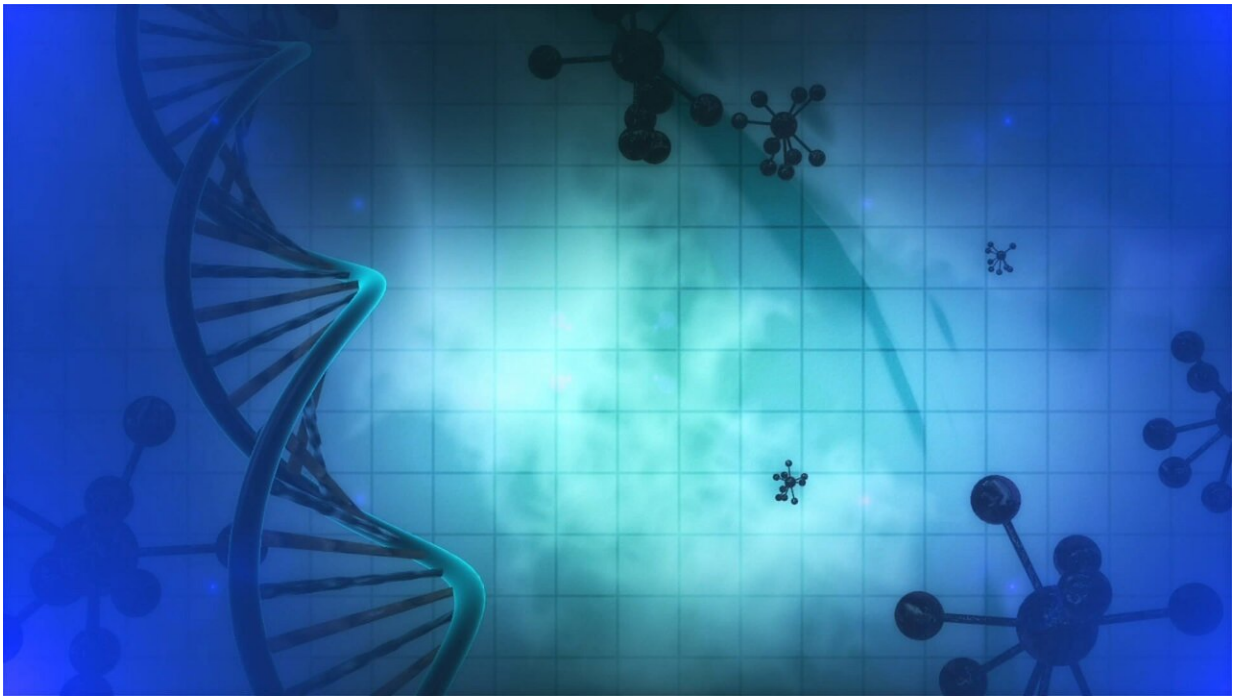
Large study of genetic differences reveals several new targets for variety of diseases

January 14 2020



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While subtle differences in the number of genes copied from one individual and passed down to the next can be found in many healthy people, their role in disease may be much greater than previously thought.

A large, multicenter study led by researchers at Children's Hospital of

Philadelphia (CHOP) compared the genomic data of more than 100,000 people of European ancestry and discovered how relatively rare, albeit recurrent, genetic variations can influence a variety of common diseases.

In addition, existing drugs could be repurposed to target these conditions—ranging from autoimmune diseases to neuropsychological diseases and even cancer—now that the genetic underpinnings of these conditions are known. The findings were published online on January 14, 2019 in the journal *Nature Communications*.

A copy number variation (CNV) is either a gain or loss of genomic information and occurs when the number of copies of a particular gene or genomic region varies from one individual to the next. Rare CNVs are events that often predispose people to medical conditions, whereas more common CNVs are usually well-tolerated and are common in healthy people. However, there are previously established examples in which CNVs can negatively impact a person's health. In fact, prior studies suggest they could have a widespread impact on human health, but most of those studies were based on limited sample sizes, thereby not providing researchers with a complete picture of their true significance.

"This analysis provides us with a dense map of the impact of rare recurrent copy number variations, which represent an important source of genetic variation in our genome, often predisposing us to, and sometimes causing, complex diseases," said senior author Hakon Hakonarson, MD, Ph.D., Director of the Center for Applied Genomics at CHOP. "Our study showed that previous methods are likely not capturing the accurate incidence or prevalence of rare copy number variation regions that directly impact human health."

The study team genotyped 100,028 individuals from populations of European ancestry using either genome-wide SNP arrays or array comparative genomic hybridization platforms. The vast majority (more

than 99%) of the CNV regions uncovered, while individually rare, were recurrent, meaning that they occurred in at least two individuals.

Among these regions that are most clinically relevant are those with homozygous deletions, or the loss of both alleles or both copies of a gene from the same chromosomal pair. The study team identified 375 previously unreported regions like this. In addition to confirming disease -associated CNV regions from previous studies, the researchers discovered several previously unreported regions that match genes that are already of clinical interest, in some cases because drugs that target relevant pathways may already exist.

Some specific regions of interest identified in this study include the chr7p15.3 deletion associated with autoimmune diseases, since it overlaps with the gene that encodes for ITGB8a, a well-established drug target for ovarian cancer; a homozygous deletion region associated with autoimmunity at chr2q34 that that interrupts the coding region of the gene ERBB4, a key oncogene that can be targeted by multiple FDA-approved small molecule inhibitors; and the locus chr19p13.3, which encodes the gene HCN2 and could be a potential target for therapies to treat both epilepsy and pain.

"The number of gene candidates found in our study that warrant further studies establishes the strong correlation between regions of copy number variations and what we already know about the genome," Hakonarson said. "While ongoing, large scale studies focusing on new discoveriers are important, we believe that further investigating these newly identified regions in parallel will continue to yield even more clinically relevant information and accelerate precision medicine."

More information: Yun Rose Li et al, Rare copy number variants in over 100,000 European ancestry subjects reveal multiple disease associations, *Nature Communications* (2020). DOI:

10.1038/s41467-019-13624-1

Provided by Children's Hospital of Philadelphia