NEWS

Many people with harmful genetic variants show no ill effects

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Most adults with genetic variants tied to certain conditions, such as heart disease or cancer, go undiagnosed, according to a study of more than 50,000 people[1].

The variants' silence leaves these people unaware of their risk of developing the conditions later in life, says lead investigator **David Carey**, director of the Weis Center for Research at Geisinger Health System in Danville, Pennsylvania.

Carey's team looked for genetic variants associated with 27 chronic conditions. The list of conditions does not include autism, but does include tuberous sclerosis complex. As many as **half of all people with tuberous sclerosis complex** have autism. Other teams are studying the same population to gauge the effects of variants linked to autism.

"The value lies in the huge population, all captured within the same healthcare system. It's really fantastic," says **Dan Arking**, associate professor of genetic medicine at Johns Hopkins University in Baltimore, Maryland, who was not involved in the new work.

The variants in the study are clinically significant: Some increase the risk of the linked condition by up to 70 percent. But variants interact with many other genetic and environmental factors, and these interactions may cause the condition's features to be more or less severe — or even absent.

"People used to say anytime there is a [spontaneous] variant or something really rare, that it must cause disease," says Arking. The new study instead suggests that, on the contrary, some rare variants have weak ties to conditions such as autism, he says. The results appeared 23 December in *Science*[2].

Action items:

Carey and his team looked at data from the **MyCode Community Health Initiative**, launched in 2007 by Geisinger Health System in central Pennsylvania. MyCode researchers have collected DNA samples and up to 14 years' worth of medical records from the participants.

The researchers probed the 50,726 participants' genomes for inserted or deleted sequences, and for single nucleotide variants, called SNVs, in the code. Their analysis revealed that each individual harbors about 21,409 SNVs, consistent with findings from previous studies.

The researchers then narrowed their analysis to 76 genes known to contribute to life-threatening conditions such as cancer or cardiovascular disease. The list includes three genes **tied to tumor growth** and to autism: **PTEN**, **TSC1 and TSC2**. (Clinicians are obligated to counsel individuals with variants in any of these 76 genes.)

Nearly 4 percent of the general population carries variants in at least one of these genes, the researchers found. But more than one-third of these people show no symptoms and have no family history of the linked condition. For example, most of the individuals who carry a variant linked to an inherited condition that causes high cholesterol have normal cholesterol levels, according to a second study by Carey's team in the same issue of *Science*.

Subtle signs:

The findings could mean the individual will develop the condition later in life — or not, Carey says. Other variants in her genome might mitigate the risk, he says.

"We generally look at one gene at a time, but we have about 20,000 genes and they all work in concert," Carey says. "We're not sophisticated enough yet to be able to tease out all the genetic interactions, but we know that they exist."

Last year, another team of researchers used the MyCode data to show that genetic changes tied to autism also **crop up in many people without the condition**. At the **2016 American Society of Human Genetics annual meeting** in Vancouver, Canada, last year, they presented results showing that about 2,000 of the MyCode participants carry large deletions or duplications of genetic material associated with autism, intellectual disability or schizophrenia. But less than 5 percent of this group has received treatment for any of the conditions.

The finding suggests that genetic variants can confer features so subtle that they go unrecognized well into adulthood. Researchers could study this group to understand the mildest end of the autism spectrum.

"This cohort could help us describe the full picture of autism, the breadth of the phenotype," says **Christa Lese Martin**, director of the Autism and Developmental Medicine Institute at Geisinger Health System in Lewisburg, Pennsylvania. Martin was a lead investigator on the autism

study but was not involved in the new work.

About 125,000 people have enrolled in MyCode so far. By early next year, researchers expect to have sequencing data for 90,000 of the individuals.

REFERENCES:

1. Dewey F.E. *et al. Science* Epub ahead of print (2016) **PubMed**
2. Abul-Husn N.S. *et al. Science* Epub ahead of print (2016) **PubMed**