Are some people genetically predisposed to alcohol use disorder?

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How much alcohol is too much?

And what makes some people more likely to suffer from alcohol use

disorder, others less?

These questions have been top of mind for researchers who study the effects of alcohol on the human body. One of them is Henry R. Kranzler, a psychiatry professor and director of the Center for Studies of Addiction at the University of Pennsylvania's Perelman School of Medicine.

For more than 20 years, his work has focused on the genetics of substance dependence and whether precision medicine—medicine targeted to an individual's genetic makeup—can help treat addictions.

His work has garnered numerous accolades, so he's only partly joking when he points out that his group's recent research got the ultimate recognition: A study suggesting that alcohol use ages and shrinks the brain was the subject of a "Saturday Night Live" weekend update punchline.

You were one of the researchers on a recent study that found even modest alcohol consumption—a few beers or glasses of wine a week—may carry risks to the brain. What are those risks?

We found that drinking more than about one drink a day was associated with reductions in brain volume, which could have cognitive effects.

I should note that this was a correlational study, meaning that we can't prove that alcohol caused the effect. And it was cross-sectional, meaning it was a snapshot in time. So, we also don't know whether these changes occur directly in response to changes in drinking, including whether they get better when people stop drinking.

But specifically, we found that drinking, on average, one drink per day was associated with lower gray matter volume and lower white matter

volume.

This is important because gray matter is the portion of the brain that contains brain cell bodies, which regulate neural activity. That's where we do our thinking. White matter is the extension of those brain cells and it permits brain regions to communicate with each other. Both gray and white matter are important for all the cognitive processes we're capable of.

In addition to reductions in volume, we saw that the integrity of the white matter, its organization, was more disrupted as the drinking level was increased.

All of which suggests—but we didn't measure it—that these effects are related to poorer cognitive function. We say that alcohol ages the brain because its effects are like those of aging. As we get older, we get cognitively slower.

So, should government guidelines on safe drinking be updated?

Yes. Currently, the National Institute on Alcohol Abuse and Alcoholism recommends that women drink no more than an average of seven drinks a week, and men no more than 14. I would submit that's too much for men, but probably about right for women.

There's other evidence that seven drinks for both genders is an important threshold, although it may be six or eight. For public health purposes, it would be good to know. But with that study, I have reduced my own consumption of alcohol, which is probably the best indicator of the strength of my beliefs.

What has your research discovered about the genetics of alcoholism? Are you more vulnerable to alcohol use disorder if a close relative has it?

The simple answer is, yes.

And the more family members—plus the more closely related they are, parents or siblings more than cousins—the greater the risk.

That was well-known before the current era of molecular genetics. It was based on family history findings and genetic epidemiology. These studies evaluated people and their diagnoses and used mathematical models to determine risk.

Over the past 20 years, since the sequencing of the human genome, this has been borne out. We're beginning to identify the specific variations in DNA that are responsible for the risk. And the number of variations that we know about is growing.

We don't know exactly how many we'll find, ultimately, but we do know that alcohol use disorder is highly polygenic—it involves many different genes.

A person's height, which is also polygenic, is influenced by about 11,000 genes. Alcohol use disorder may be in that ballpark. Everyone has these genes. But there are many forms of a gene.

What differs among people are the variants they have.

Generally, the more risk variants you have, and the fewer protective variants, the more likely you are to have alcohol use disorder.

Does knowing more about the genetic component of alcohol use disorder pave the way for personalized treatment?

We're not at the stage where we can do this yet. But we're getting closer. By looking at the common variants across a person's whole genome we

could do that.

Theoretically, if you genotype a large sample of people with alcohol use disorder you can use the information to calculate a single risk score, which could be used to determine who is going to benefit from a specific type of medication to treat the disorder.

One I've been studying for a while is called topiramate, an anti-seizure medication that may reduce craving and heavy drinking.

We initially thought that a single genotype predicted the response to topiramate treatment. But we found out that it's more complicated than that. So now we've turned to these risk scores.

They are used in other conditions—for breast cancer prognosis, for cardiovascular disease. They're not yet of use in psychiatric conditions, including substance use disorders, but I believe they will be. It's a matter of time and investment to collect large, diverse samples on which to base the calculations.

It holds great promise, and there are a growing number of biobanks that are making this kind of research possible. The UK Biobank, for instance, has 500,000 genotyped individuals. They're now getting data from MRIs on 100,000 of those individuals.

In the U.S., the Million Veteran Program is working to recruit two million veterans to give a blood sample from which DNA will be extracted and analyzed. Veterans also complete questionnaires and give access to their electronic health records, the Veterans Administration's version of which is extensive.

This has been very useful to us in doing the studies to identify the relationship between a trait, like alcohol use disorder, and the genes that

contribute to it.

Given this genetic component, is there a way to pre-screen people to see if they are vulnerable to developing an alcohol use disorder?

Yes, and that's exactly what I was getting at with the polygenic risk scores. These have been used successfully to segment groups into higher or lower risk levels. However, it's not yet developed sufficiently to calculate individual risk for psychiatric disorders for use in a prevention or treatment context.

The predictions are still crude. We still need more information. We need larger and more diverse samples on which to base the calculations for those scores.