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Scientists find gene interactions that make cocaine abuse death eight times more likely

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Scientists have identified genetic circumstances under which common mutations on two genes interact in the presence of cocaine to produce a nearly eight-fold increased risk of death as a result of abusing the drug.

An estimated one in three whites who died of cocaine exposure is a carrier of variants that make cocaine abuse particularly deadly.

The variants are found in two genes that affect how dopamine modulates brain activity. Dopamine is a chemical messenger vital to the regular function of the central nervous system, and cocaine is known to block transporters in the brain from absorbing dopamine after its release.

The same dopamine genes are also targeted by medications for a number of psychiatric disorders. The researchers say that these findings could help determine how patients will respond to certain drugs based on whether they, too, have mutations that interact in ways that affect dopamine flow and signaling.

The scientists had previously identified a total of seven mutations on two dopamine-related genes, some of which were linked to the risk for cocaine abuse death. Years of molecular genetics studies showed that the mutations had specific functions – a single variant alone was associated with an almost three-fold increase in risk of dying of cocaine abuse – and led researchers to hypothesize that the variants probably interacted because the genes themselves relied on each other for proper function.

A statistical analysis that dissected the complex interactions among the variants combined with cocaine exposure revealed gene-gene-environment interactions that would dramatically increase the risk of death from cocaine abuse.

"Finding an impact factor of 8 just blew us away," said Wolfgang Sadee, professor of pharmacology and director of the Program in Pharmacogenomics at Ohio State University and senior author of the study. "Beyond that, this represents a new paradigm. Going forward, we can ask whether such interactions do exist between variants that may be a normal variation in the population. These kinds of interactions may underlie the genetics of behavior."

These specific findings apply primarily to whites. The researchers found that a different combination of variants affect the risk of cocaine abuse death in African Americans, and that in this population, some of the variants had protective properties.

The research is published in the online journal *Translational Psychiatry*.

The mutations are mostly single-nucleotide polymorphisms, or SNPs (pronounced "snips"). Each gene contains two alternative forms – called alleles – that are functionally identical in most people. However, in some cases, the activity level, or expression, of an allele can differ from its partner allele in a single gene.

The SNPs described here are on two genes: the dopamine receptor D2, which is a target for antipsychotic drugs, and the dopamine transporter DAT, the main target of cocaine and amphetamines.

The variants' clinical relevance was determined in earlier work led by Sadee that analyzed human brain autopsy tissues of people who had died of cocaine overdose and from age-matched drug-free controls.

The variants identified in this work are harder to detect and analyze than many mutations because these variants have no role in making protein; they exist in deeper and often overlooked regions of genes. Sadee's lab has designed a technique to predict and determine their functions based on measurements of how much messenger RNA, a carrier of genetic information, each specific allele expresses.

Having a defined set of a manageable number of variables then made a statistical analysis both possible and a critical step to more fully understanding the effects of these variants. First author Danielle Sullivan, a doctoral student in biostatistics at Ohio State, built logistic regression models to search for the main effects and interactions among the variants associated with the higher risk of cocaine death.

"A combination of variants turned out to have a high effect on the risk of dying. That is called epistasis – a gene-gene-environment interaction that is seen only when there is that extra stimulus, in this case the cocaine," Sadee said. "It's a three-way system, which is incredibly complex unless you know beforehand that these variables are all related to each other."

Sadee said consideration of how gene-gene-environment interactions affect the impact of single genes could help solve the mystery of "missing heritability." Scientists know that genes are behind the causes of many diseases and conditions, but to date have been unable to document the complete genetic history of any given disease.

More immediately, what he has discovered about these variants is likely to increase understanding of numerous psychiatric disorders and improve the effectiveness of medical therapies for these problems. Dopamine-related conditions include attention deficit-hyperactivity disorder, bipolar disorder, phobias, anxiety and schizophrenia.

"The gene-gene interaction that we've reported here, eliciting what might be a 'perfect dopamine storm' under cocaine stimulation, could well contribute to other conditions and affect response to drugs such as antipsychotics and amphetamines," Sadee said.

Clinical studies led by his lab so far suggest that gene-gene interactions occurring without an environmental stimulus such as cocaine do appear to help predict response to certain medications.

He is also extending the research to a handful of other genes that affect signaling in the brain.

"Each gene gives us new combinations, each one has novel variants that can be tested in this way. And they may be considered normal variations – they're not associated with a disease process, but if there are multiple variants together, they may push this whole system in the direction that makes disease more likely or influences individual response to circumstances like stress or drugs," Sadee said.

Provided by The Ohio State University