Genetic trait could triple odds of whites' susceptibility to heavy cocaine abuse

December 21 2010, by Emily Caldwell

(PhysOrg.com) -- Nearly one in five whites could carry a genetic variant that substantially increases their odds of being susceptible to severe cocaine abuse, according to new research.

This genetic variant, characterized by one or both of two tiny gene mutations, alters the brain's response to specific chemical signals. In the study, led by Ohio State University researchers, the variant was associated with a more than threefold increase in the odds that carriers will be susceptible to severe cocaine abuse leading to fatal overdosing, compared to non-carriers.

Among whites, one or both mutations were found in more than 40 percent of autopsy brain samples taken from people who had abused cocaine, compared to 19 percent of samples from people who lived drug-free. Overall, one in five samples from whites in the control group and one in two to three samples in the cocaine overdose group contained the genetic variant, compared to one in eight African Americans, in whom the variant is less prevalent.

The mutations – either alone or in combination – affect how dopamine modulates brain activity. Dopamine, a neurotransmitter, is a chemical messenger vital to the regular function of the central nervous system. Previous research has established that cocaine blocks dopamine transporters from absorbing dopamine after its release, leaving the chemical outside the brain cells and creating a feeling of euphoria.

In people who carry one or both of the mutations, the function of a gene responsible for transmitting dopamine signals in the brain is altered. Researchers speculate that this altered gene function sets up a vicious circle of chemical signals that could lead to a craving for a substance that can maintain elevated levels of dopamine in the brain.

The researchers say many questions about cocaine abuse susceptibility remain unanswered: Do the mutations increase the chances someone will try cocaine in the first place? Or do they deepen the cocaine craving and lead to heavy abuse? And how strong is the overall effect of this trait?

But what the research does show is the first strong connection in brain tissue between the mutations and the presence of severe cocaine abuse.

“We now have both good biological rationale and clinical association showing that this has an impact on the way cocaine abuse might progress or might be initiated,” said Wolfgang Sadee, professor of pharmacology and director of the Program in Pharmacogenomics at Ohio State and senior author of the study. “We have found a frequent variant in one of the key candidate genes that can affect cocaine abuse, but more importantly, it also opens the avenue to explore how this variant affects response to therapies for a variety of psychiatric disorders that involve dopamine.”

The research appears online and is scheduled for later print publication in the journal Neuropsychopharmacology.

The mutations described in this study are single-nucleotide polymorphisms, or SNPs (pronounced “snips”). Each gene contains two alternative forms – called alleles – that are 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. Each small difference is a SNP.

SNPs have become the primary study target of Ohio State's Program in Pharmacogenomics. But the mutations Sadee studies aren't just any SNPs. Up until about 10 years ago, most biological research focused on these tiny mutations in areas of genes that produce proteins. But Sadee's lab explores the role of SNPs that are present earlier in a gene's existence, located in regions called introns.

A better understanding of the human genome has led scientists to determine that about 90 percent of the mutations that can lead to disease or govern behavior actually are located in these deeper and often overlooked regions of genes, and that they regulate the genes' functions long before protein production begins.

In this work, Sadee and colleagues examined allele differences in a gene called dopamine receptor D2. This receptor has a short form and a long form, each of which has a distinct function in the process of regulating dopamine after it is released so its levels stay normal in the brain.

In people who carry these polymorphisms, however, the ratio of the short form to long form of the gene is disrupted. One mutation shortens the short form, and the other lengthens the long form. When this happens with either one or both of the SNPs, most of the short form of the gene is wiped out, and the receptor's dopamine regulatory role malfunctions.

Sadee's lab identified these SNPs and showed in previous studies that their presence influenced cognitive processing, another brain function that is affected by dopamine. The researchers then turned to behaviors and disorders associated with dopamine regulation, including cocaine abuse.

To test the clinical relevance of the SNPs, the researchers examined human brain autopsy tissues of people who had died of cocaine overdose

and from age-matched drug-free controls. The researchers used a technique that measures for what is known as allelic messenger RNA expression imbalance, which was developed in Sadee's pharmacogenomics core lab.

Among whites, more than 40 percent of the samples taken from people who had abused cocaine contained these polymorphisms, compared to less than one in five of the drug-free brain samples.

The finding suggests that whites with at least one of these mutations are 3.4 times more likely to be susceptible to cocaine abuse than are whites without either mutation. The study suggested that whites with both mutations, known as homozygous carriers, are at even higher risk for susceptibility to cocaine abuse, but the results were not significant when subjected to statistical analysis, meaning this higher risk could occur just as often by chance.

Sadee noted that more research is needed to collect enough evidence to merit a warning to people who might be at higher risk for sensitivity to cocaine. "But this work is pointing in the right direction. There is very little in the genetics literature that points as strongly to a specific problem as this paper does," he said.

No test currently exists for these polymorphisms. Sadee said the scientific community wants to ensure that all SNPs that are considered potential biomarkers for genetic traits must first be carefully vetted to ensure there is ample evidence of risks or benefits associated with each mutation before testing is available.

Because the dopamine receptor D2 is a primary target for nearly all antipsychotic drugs, Sadee and colleagues are now investigating how these mutations might affect carriers' response to drugs that act on this gene.

“We now have found that this gene contains frequent variants that affect some fundamental behavior. There are a few other genes that do, too. Now we want to look at how those genes interact,” Sadee said. “On top of that, in some psychiatric disorders there are treatments that depend on the dopaminergic system, and only 50 percent are effective. So now the question becomes, would these SNPs, together with another gene, predict whether or not somebody responds to these treatments or becomes worse?”

This work is supported by the National Institutes of Health.

Provided by The Ohio State University