Smoke This: Genetics Research Begins to Uncloud Who Gets Hooked

Another thread was plucked from the tangled web of tobacco addiction recently when a group from the University of Toronto found a genetic defect that seems to protect some people from the hazardous habit of smoking.

"People who carry this mutation are roughly twofold less likely to become smokers," said Rachel Tyndale, Ph.D., a pharmacologist on the study, which appeared in the June 25 Nature.

Around 20 percent of the study population of 400 harbored a defective copy of the gene (called CYF2A6) on chromosome 19, according to the study's investigators. It turns out that this gene is responsible for producing the enzyme that metabolizes around 80 percent of bloodstream nicotine. The lucky one in five makes only half of the enzyme that people with two working copies of the gene make. Hence, heterozygotes metabolize nicotine more slowly.

Speculation

Tyndale and her colleagues speculated that slow metabolizers suffer more nausea, dizziness, and other unpleasant side effects when they first light up. "We believe that this is just tipping the balance to where they find it [smoking] a little bit more aversive or negative," said Tyndale. "And therefore they're that much less likely to pick up their next cigarette or learn to smoke."

So far, the data seems to bear them out. Slow metabolizers get hooked on cigarettes only half as frequently as fast metabolizers. And if slow metabolizers do smoke, they light up 20 percent fewer cigarettes, dropping their risk of lung cancer by a third.

Additionally, slow metabolizers may activate fewer carcinogens, offering further cancer protection. As part of a family of enzymes called cytochrome P450, the CYP2A6 enzyme turns some compounds, such as hydrocarbons found in tobacco smoke, into active carcinogens. "We would anticipate that people who carry defective alleles would activate carcinogens at a slower rate," said Tyndale.

Hint of Protection

News of this gene with an unwieldy name — with its hints of protective effects — spread quickly in research circles. At a National Institutes of Health nicotine addiction conference in July, the finding prompted Alan Leshner, Ph.D., director of the National Institute on Drug Abuse — which funded the research — to say, "We are very excited about the findings from this study and its implications for understanding and treating nicotine addiction."

But other researchers rein in their enthusiasm with a science-reality check. "The finding is preliminary," said Kenneth Kendler, M.D., who researches the heritability of nicotine addiction at the Medical College of Virginia in Richmond. "It has not been replicated by an outside group, and it's only modestly robust. Although it's exciting, prior experience with association studies in complex human traits suggests caution."

Tom Brandon, Ph.D., who designs smoking-cessation programs at H. Lee Moffitt Cancer Center in Tampa, is also cautious, even skeptical about finding a simple genetic cause for addiction. "I don't think we're going to find a gene for smoking, just like we're never going to find a gene for alcoholism. And really, this has been a false and disappointing path. Every few years you read about a gene for alcoholism being discovered, yet it never replicates."

However, additional work from the Toronto group is in press. Due to the publishing journal's strict policies on prepublication disclosure, Tyndale remains tight-lipped about it, although she did say data on nicotine metabolism rates in slow and fast metabolizers is on its way. If the data show slow metabolizers are much slower, the defective allele-anti-smoking link would be strengthened.

Research on people with two defective alleles — possible "super-slow" nicotine metabolizers — could also support the Toronto group's findings. Because just 2 percent of the non-smoking population and even fewer smokers carry two defective alleles, Tyndale envisions a multicenter trial with 10,000 participants. But that's at least a few years away.
Even further out, both Leshner and Tyndale talk about possible gene-based therapies. "Understanding the critical role this enzyme plays in nicotine addiction gives a new target for developing more effective medications to help people stop smoking," said Leshner. For instance, a drug that binds to the enzyme more quickly than nicotine would tie up much of the enzyme. With fewer sites to bind to, more nicotine would be left circulating, causing the same nausea and dizziness that purportedly detracts the slow-metabolizers from smoking. But Tyndale added, "We're a long way from doing that."

**Other Benefits**

Brandon sees other possible benefits. "If we ever reach a point where we can do a genetic test for someone coming in for smoking cessation, it might play a part in determining the most effective treatment for them," he said. "It may be that some treatments will be more effective for people with a certain genetic configuration, and other treatments for other configurations."

The discovery of the defective alleles follows other promising research into genetic influences on smoking behavior. Earlier this year, a team from Yale reported on a particular nicotine receptor protein that plays a role in addiction. And a small study from a group at the University of Texas M. D. Anderson Cancer Center in Houston implicates a dopamine-receptor gene as well. So far, 15 or 20 smoking "candidate genes" have been identified, although none have been characterized as thoroughly as CYP2A6, many more are likely to turn up.

"We really have no idea how many [candidate genes] may be at work. It's also quite possible that genes we don't know about yet... may be involved," said Kendler. He went on to liken the search for smoking genes to "the old story of looking for your keys under the lamplight." Keys might fall outside the circle of light, but people tend to look where it's brightest. So it goes with genetics, where researchers can only look for a smoking connection on the small percentage of genes that are already well characterized.

While that small of circle of light is widening, the influence of environment remains an important — perhaps even primary — focus in smoking research. Reports on smoking from the U.S. Surgeon General and the U.S. Department of Health and Human Services barely mention genetics. And behavioral researchers like Brandon say the web of causes for smoking won't easily be unraveled. "Addictions are such complex disorders," said Brandon. "There are many different reasons people smoke, they start in many different ways, and their patterns are very different."

**Understanding Behavior**

Ohio State University's Karen Ahijevich, Ph.D., who studies nicotine metabolism, agrees that behavioral research is vital. But she understands the appeal of these genetic discoveries. "I think there's always an interest in other explanations for why some people smoke and some don't," she said. "It's appealing to think there are other explanations in addition to the psychosocial factors. This [genetics research] is adding to understanding of behavior."

When asked whether science will ever untangle the web of genetic and environmental influences on smoking, Kendler says, "You are asking for prophecy. I guess I'm a guarded optimist. These are really complex traits, but the power of our methods, both molecular and statistical, are growing by leaps and bounds."

— Brian Vastag

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**Spirituality Returns To the Fold in Medical Practice**

Ten or 20 years ago, medicine largely ignored spirituality and religion in patient management — officially, at least. At most, a doctor might suggest calling the hospital chaplain. Now, at least 40 U.S. medical schools have integrated spirituality education into the required portion of their curricula. By the turn of the century, some authorities expect that nearly all 125 will have done so.

Increasingly, religion and spirituality are now seen as factors in patient relations and in quality of life — attracting increased attention in cancer research and practice.

What the trend signifies, said Dale A. Matthews, M.D., associate professor of medicine at Georgetown University School of Medicine, is "an historic reconciliation between medicine and spirituality." It is not as if they were always apart. Through the centuries, the history of medicine was the history of religion. But then came the discovery of pathogens; and, suddenly, medicine was biomedicine.

According to Matthews, author of "The Faith Factor," a number of things have happened to bring religion back into the picture including a greater interest in spirituality and alternative medicine in the culture at large, as well as disillusionment over medical technology's failure oftentimes to sustain the quality of life.

A return to spirituality and religion is also a recognition of what patients consider important. Studies indicate many cancer patients, in particular, rely on religion and spirituality after their diagnosis. In a University of Michigan study,