Focusing on the Roots of Nicotine Addiction:  
The Genetic Aspects of Cigarette Smoking  

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As has been pointed out numerous times, there are some individuals who use alcohol, tobacco or other drugs of abuse and become substance abusers—continuing to drink, smoke or inject themselves with a drug(s) of abuse even though doing so causes them serious problems. Others are able to limit or avoid use of these harmful substances well before they become abusers or addicts. To clarify the role that genes play in predetermining those individuals who are more vulnerable to a substance of abuse, twin studies are a first step in exploring genetic and environmental factors which result in the development of dependence and addiction. If genes significantly influence the risk for abuse, identical (monozygotic) twins who share the same genes will tend to be alike (concordant) in their response to a particular agent of abuse. On the other hand, fraternal twin pairs who only have 50 percent of their genes in common will be less concordant. By comparing the degree of concordance in monozygotic as compared to dizygotic twin pairs, scientists can estimate the extent to which genes influence vulnerability to a specific drug of abuse.

With regard to tobacco use, researchers report increasing evidence that a large part of the significance in concordance for tobacco use in monozygotic twins as compared to dizygotic twins is their vulnerability to nicotine addiction. Studies of tobacco use by more than 3,000 male twin pairs at St. Louis University revealed that genetic factors made a stronger contribution (61%) to nicotine dependence than did environmental factors (39%). Similarly, at the Medical College of Virginia a study of 949 female twin pairs found that genetic factors played a more important role (78%) than
did environmental factors (22%) for smoking initiation. Furthermore, for nicotine
dependence the concordance rate in monozygotic twin pairs was found to be 72% as
compared to only 28% for dizygotic twin pairs. Based on these findings, it is clear the
genetic factors play an important role in a person’s vulnerability to smoking tobacco and
in particular this is due to the individual’s dependence on the nicotine component in
tobacco.

With knowledge that nicotine is the specific chemical identified with vulnerability
to tobacco addiction, it should now be possible for researchers to explore variations in
DNA sequences, in the alleles of specific genes, to learn more about the mechanism(s)
believed to regulate the chemical changes in our body due to the use of this addictive
agent. One brain chemical which nicotine appears to stimulate to provide the pleasurable
effects of tobacco use is dopamine, and researchers have been investigating several genes
and their alleles involved in dopamine metabolism and their influence on smoking
behavior. The precise nature of this link remains controversial, but as has been noted,
many of the neurophysiological processes that underlie nicotine addiction are common to
addictive drugs with diverse pharmacologic actions including the opiates, alcohol,
marihuana and cocaine.

Two genes in the dopamine metabolic pathway, for example, that appear to
influence smoking behavior by affecting dopamine metabolism are SLC6A3 and in
particular DRD2. What has been found is that an allelic variation, a polymorphism, in
the gene DRD2 is due to a change of one nucleotide-from a cytosine to adenine-at a
precise position, 32 806 in the DRD2 gene. This allele has been found to be twice as
common in smokers as in nonsmokers. In addition, this polymorphism is also found
more frequently in smokers who start smoking earlier in life and among those unable to stop smoking.

At present, the exact mechanism by which an allele exerts its effects on an individual’s predisposition to tobacco addiction is unknown. What is known is that individuals with one or more variant alleles have been found to have a reduced number of dopamine receptors in their brain’s corpus striatum. One hypothesis under consideration is that a decreased number of dopamine receptors may be evidence of an inherited dopamine deficit which is restored by nicotine.

There is, as well, evidence of genetic variation in other genes affecting nicotine metabolism including the cytochrome P450 enzymes and other cytochromes as well. The largest gap in our knowledge appears to be at the primary site of nicotine action in the brain, at the acetylcholine receptor. To proceed further apparently requires closer definition of the complex interaction between nicotine and its receptor as well as the receptor subtypes important in the addiction pathway(s). What is evident is that researchers are now focused on identifying the many genes important to tobacco addiction and looking for the biochemical mechanisms which result in addiction to nicotine.

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