Smoking

The burden of smoking on our society is remarkable. Estimates are that as many as 1 in 10 of all deaths are smoking related. Deaths aside, billions of dollars are spent yearly in the U.S. on treating smoking related disorders including upper respiratory tract infections, myocardial infarction, and age-related macular degeneration. Smoking clearly ranks among the most pressing of health care issues in the U.S., and is an increasingly important health care issue world-wide. Even a small decrease in the rate of smoking in the U.S. would confer major benefits, not only on the suffering of individual smokers but on the entire economy. What can genomics bring to bear on this issue? Quite a lot, including insights on the genetic underpinnings of addiction behavior, disease risk associated with smoking, and novel approaches to smoking cessation.

Twin studies have long shown that inheritance plays an important role in smoking behavior, with heritability estimates of over 50% for both smoking and the ability to quit smoking. Anecdotally, each of us has probably experienced the hale and hearty 90 year old who has smoked two packs a day, since "before you were born" as well as the 50 year old smoker with oxygen and steroid dependant COPD. Perhaps some readers have wondered about the possibility of a genetic basis for this variable response to a toxic environmental insult.

In rare cases, the source of the genetic contribution to the effects of smoking is clear– single gene Mendelian disorders like alpha-one antitrypsin deficiency show a very strong gene-environment interaction. Until recently, sorting out the more subtle interactions between common genes variants and smoking was fraught with difficulties – mainly because the environmental factor frequently so strongly outweighs the genetic contributions to the development of disease. Multiple studies demonstrating a correlation between various genes, health conditions, and smoking have been published; few of these early studies were widely replicated. More recently the techniques used in so-called genome-wide association studies have begun to unravel this Gordian knot.

This unraveling began with the discovery of the gene variations associated with macular degeneration in 2005-2006, for which both genetics and smoking are clear risk factors. Since then the unraveling has accelerated. Recently, three simultaneously published studies have examined variable genetic markers known as single nucleotide polymorphisms –SNPs-, spread across the genome, and their relationship to smoking and several health conditions. The three studies identified a region on chromosome 15 as an important contributor to the genetic component of smoking related disease risk. The markers fall in a "gene cluster" consisting of nicotinic acetylcholine receptor genes, with several other genes interspersed, and were associated with nicotine dependence, smoking quantity, peripheral arterial disease, and lung cancer. As is the case with many variants identified through genome-wide association studies, these variants each confer only a small increase to an individual's risk, albeit with a high degree of statistical certainty. Unsurprisingly, one of the research groups concluded that the effect on lung cancer risk

was mediated indirectly through changes in smoking behavior. Intriguingly, the authors of the other two studies concluded that the risk of lung cancer conferred by these markers might be mediated directly: in some way, changes in DNA present in lung tissue and associated with these SNPs makes it more likely for a tumor to occur. Further studies are needed to sort out which of these mechanisms is correct, but these early studies give a tantalizing look at the underpinnings of some of the variability noted among smokers, and a window on potential new therapeutic approaches.

Much also is being learned about the influence genetic variation has on the effectiveness of various approaches to smoking cessation. For example, evidence is mounting that people become addicted to smoking for differing reasons, and that the reasons may be, at least in part, genetically based. At some point, health care providers will probably be able to use genetic information to guide more individualized approaches to smoking cessation for their patients. A number of studies suggest that variations in genes associated with nicotine metabolism alter the effectiveness of types of nicotine replacement therapies. Similarly, studies have shown that individuals with variants in genes in pathways associated with dopamine metabolism seem to respond to pharmacologic interventions differentially. These emerging insights will very likely lead to novel therapeutic compounds. Even modest gains in the effectiveness of smoking cessation interventions would produce important health improvements.

We are just scratching the surface of the intersection of smoking, health and genomics – this research will help blaze the trail for a better understanding of other important environmental influences on disease (e.g., high-fat diet, air pollution, alcohol use). The intersection of genes and the environment is a major focus of study for the NHGRI and NIH, as in the Genes and Environment Initiative (GEI see http://www.genome.gov/19518663). One can safely predict that as we become increasingly sophisticated in our ability to conduct large genome-wide association studies novel interactions will be found between genetic variants, smoking, and other smoking related disorders like stroke, myocardial infarction, and COPD. Though genomic discoveries will never provide a complete solution to the monumental and complex problem smoking presents to society, small victories will come with time, and make a difference in the lives of many.