The Genomics of Smoking & Addiction

INTRODUCTION:

Growing knowledge and improving techniques in the field of genomics is doing much to improve personalized health and medicine, where knowledge of an individual’s genetic disorders and predispositions and how these factors interact to shape the individual’s phenotype allows doctors to apply treatments, therapies, and prevention strategies more effective in their ability to tailor medicine to the individual than ever before. In addition, however, expertise in genomics also improves population-level approaches to health. How is the field of genomics informing the field of public health and epidemiology (“the science of studying causes, and effects of health and disease conditions in defined populations,” according to Wikipedia)? One example is how genomics is expanding scientists’ and administrators’ understanding of smoking behaviors. Smoking is a quintessential public health issue. The smoking behavior of one individual, which may be influenced by several endogenous and exogenous factors and greatly affects the health of the individual, can also become an environmental influence on the health of other individuals and even whole micro-populations. But how does knowledge of genomics help public health officials better understand smoking behavior and develop strategies to prevent smoking?
LITERATURE REVIEW AND FINDINGS IN THE FIELD OF GENOMICS:

Much research has been done regarding the relationship between genes and cigarette smoking. Though individual loci have small effects on complex behaviors such as smoking, the general consensus in peer-reviewed research literature is that genes indeed play a role in the causation of cigarette smoking\(^1\). Even a brief review of published research reveals that the prevailing method of studying the effect of genes on smoking behaviors has been and continues to be twin studies that compare the relative variability of genotype with that of the environment. Evidence suggests that the presence of the same trait, be it persistent smoking or smoking cessation, because it has been found that both members of a pair of twins (concordance) is greater in monozygotic (identical) twins than in dizygotic (fraternal) twins. According to such research there is a significant genetic contribution to smoking initiation, although there is also a strong influence of environmental factors, and whether it is the genetic factors or the environmental factors that determines smoking behavior varies greatly from population to population.

Several studies have also confirmed a strong genetic influence on smoking persistence as well, which is of greater concern than smoking initiation because it is smoking persistence that leads to the most damaging health effects of smoking. Because there is such consistent evidence for the heritability of smoking behaviors, scientists have also carried out studies attempting to identify the genetic and biological mechanisms of tobacco use and addiction. Very few studies have directly addressed the effect of genes on smoking cessation\(^2\), but since the other aspects of smoking behavior are influenced by


genes, it is not an unreasonable to expect that smoking cessation behavior is likewise influenced by genes.

In 2011 behavioral science researcher Jason D Boardman, along with several other researches wondered why, despite the widespread acceptance among U.S. populations of the harmfulness of smoking and extensive public relations campaigns designed to mitigate the social/cultural factors that cause smoking, the occurrence of regular smoking is not decreasing as quickly as is it could. Boardman and his colleagues conducted research exploring the effect of public policy on the extent to which genes influence smoking desistance. Using a sample of adult twins (n mz = 363, n dz = 233) from a large population registry, they estimated Cox proportional hazards models that describe similarity in the timing of smoking desistance among adult twin pairs. They showed that identical twin pairs are significantly more likely to quit smoking within a similar time frame compared with fraternal twin pairs. Boardman and his fellow researchers found that genetic factors determining smoking cessation and avoidance increase in importance following restrictive legislation on smoking behaviors, saying “These findings support the social push perspective and make important contributions to the social demography and genetic epidemiology of smoking as well as to the gene-environment interaction literatures.” The experimenters took a sample of 6,000 twin pairs from the birth registry of the Commonwealth of Virginia, using a survey to identify the twin pairs they would use: twin pairs in which both twins reported having smoked daily at some point in their lives and in which the first to quit did so between the years 1960 and 1980. Limiting their focus to the twin pairs that met these criteria reduced the sample set from 6,000 to 363 monozygotic (MZ), that is, identical, pairs and 233 same-sex dizygotic (DZ) (fraternal) pairs from the larger study. Pairs were extensively surveyed about their general lifestyle and especially their smoking habits. They found that identical twins had more concordance (presence of a given smoking trait, be it onset, persistence, or cessation) than same-sex fraternal twins. The researchers found that twin pairs who resemble each other in their education tend to quit smoking
within a similar time frame compared with twin pairs who differ from each other in their education. “In other words, this crude indicator of the social environment is highest when the genetic factors are the lowest and is non-existent when genetic factors are most noticeable. Taken together, these findings provide strong support for the social push hypothesis.” That is, the model that posits that removing the social and cultural causes of smoking will reveal the presence of genetic influences of the behavior, with removal of social causes leaving genes as a remaining main cause of the behavior. Looking to identify the genes themselves that influence smoking and where they are located, several researchers have done very interesting genome-wide association studies.

In one study, for example, carried out by Ming D. Li, et. al, noting a need to replicate preexisting gene-association studies of smoking in populations other than Caucasians, analyzed 32 single-nucleotide polymorphisms (SNPs) in CHRNA5/A3/B4 to determine their ties to smoking initiation “(SI), smoking quantity (SQ), and smoking cessation (SC)” in a sample population of 8,842 Koreans. They found 7 SNPs that were each associated with at least one smoking-related phenotype in the total sample (SI: $P = 0.015\ 0.023$; SQ: $P = 0.008\ 0.028$; SC: $P = 0.018,0.047$). They also found “a spectrum of haplotypes formed by three consecutive SNPs located between rs16969948 in CHRNA5 and rs6495316 in the intergenic region downstream from the 59 end of CHRN4 associated with these three smoking-related phenotypes...” Significantly, the researchers noted these SNPS and combinations of alleles at different loci of the genes have much stronger influence on smoking initiation and smoking quantity than on smoking cessation, possibly providing a clue to why those who are genetically (rather than or in addition to culturally and socially) disposed to become smokers may have a difficult time quitting. The genetic impetus/predisposition to start and continue to smoke might be quite a bit stronger than any biological disposition to quit smoking. As a whole, the researchers concluded that the associations of variants in the CHRNA5/A3/B4 cluster with smoking behaviors in the Korean smoker samples provide strong evidence for the contribution of this cluster to the cause of smoking behaviors in this Asian population.
A similar replicated results like those mentioned above in Italian populations\textsuperscript{3}, where researchers noted a link between the CHRNA5-A3-B4 gene cluster region and heavy smoking.

In another study, researcher Katherine Siminovitch, et al performed a genome-wide association study for a Brazilian population sample to determine what genes might be linked to smoking behavior in this group, stating in the published results, “Although several studies pointed to different candidate genes for smoking, there is still a need for replication especially in samples from different countries. We investigated whether 21 positive signals for smoking behavior from these studies are replicated in a sample of 531 blood donors from the Brazilian population.”\textsuperscript{4} They found that two of the SNPs studied by previous researchers, in the SLC1A2 (rs1083658) and ACTN1 (rs2268983) genes, were associated with smoking behavior in the population sample. The SLC1A2 (rs1083658) and ACTN1 (rs2268983) genes play an important role nicotine dependence by affecting the glutamate system. Glutamic and acid and its associated receptors in the brain are heavily involved in the brain’s excitatory and inhibitory signals to the body\textsuperscript{5}. These genes are also involved in synaptic plasticity, and as such, the researches state, are “biologically plausible candidates that merit further molecular analyses so as to clarify their potential role in smoking behavior.”

Another gene association study, seeking to identify the underlying genetic mechanisms of smoking behavior, has identified yet another gene that is involved in an individual’s predisposition to


\textsuperscript{5} \url{http://en.wikipedia.org/wiki/Glutamate_receptor}
begin and continue smoking. The authors examined 2,339 adolescents from a Chinese Han population in the Wuhan Smoking Prevention Trial that took place in Wuhan, China, from 1998 to 1999. The researchers investigated 57 genes to determine their link with the dopamine pathway and smoking initiation. They also looked at an independent sample of 603 Caucasian adolescents in California that had been studied as part of the Children's Health Study (Southern California, 1993–2009). In the Wuhan Smoking Prevention Trial cohort, a SNP (rs2298122) was found in the calcyon neuron-specific vesicular protein gene (CALY) that was correlated with smoking initiation in females (odds ratio = 2.21, 95% confidence interval: 1.49, 3.27; $P = 8.4 \times 10^{-5}$), and they replicated the association in females from the Children's Health Study cohort (hazard rate ratio = 2.05, 95% confidence interval: 1.27, 3.31; $P = 0.003$). Analyzing the results, the researchers suggested that the CALY gene “may influence smoking initiation in adolescents, although the potential roles of underlying psychological characteristics that may be components of the smoking-initiation phenotype, such as impulsivity or novelty-seeking, remain to be explored”.

All these studies and the dozens more like them leave no doubt about the significant influence genes have on smoking behavior, but how is this knowledge helping public health officials and investigators in the field to improve public health and prevent smoking?

APPLICATIONS OF GENOMICS IN SMOKING PREVENTION:

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According to researchers Hall, Wayne D., et. al, some of the most obvious applications of this knowledge to improving individual and public health may not actually be feasible\(^7\). For example, they point out screening people for alleles suspected of being linked to a predisposition for smoking behavior, because as they state in their paper, “research to date has not identified commonly occurring alleles that are strongly predictive of developing nicotine addiction. Nicotine addiction is likely to involve multiple alleles of small effect that interact with each other and with the environment.” In other words, there is no single or clearly identifiable genetic or environmental factor that determines smoking behavior and nicotine dependency.

On the other hand, although results from attempts made by researchers to use genetic information to tailor nicotine addiction to an individual’s needs have failed to yield promising results, and population-level policy approaches, such as using legislation such as taxes to de-incentivize smoking and reduce opportunities to smoke, have been more effective, it is very possible that in the near future that more research about the distinctive interactions between genes and environment in certain populations and communities may provide more tools and knowledge for reducing smoking behavior and its associated health risks.

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