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Invited review

A glimpse into the future – Personalized medicine for smoking cessation

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ABSTRACT

The devastating consequences of tobacco smoking for individuals and societies motivate studies to identify and understand the biological pathways that drive smoking behaviors, so that more effective preventions and treatments can be developed. Cigarette smokers respond to nicotine in different ways, with a small number of smokers remaining lifelong low-level smokers who never exhibit any symptoms of dependence, and a larger group becoming nicotine dependent. Whether or not a smoker transitions to nicotine dependence has clear genetic contributions, and variants in the genes encoding the α5-α3-β4 nicotinic receptor subunits most strongly contribute to differences in the risk for developing nicotine dependence among smokers. More recent work reveals a differential response to pharmacologic treatment for smoking cessation based on these same genetic variants in the α5-α3-β4 nicotinic receptor gene cluster. We anticipate a continuing acceleration of the translation of genetic discoveries into more successful treatment for smoking cessation. Given that over 400,000 people in the United States and over 5 million people world-wide die each year from smoking related illnesses, an improved understanding of the mechanisms underlying smoking behavior and smoking cessation must be a high public health priority so we can best intervene at both the public health level and the individual level.

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1. Nicotine dependence – a major public health problem

Smoking is the greatest modifiable contributor to premature death in the U.S. and the world (Mokdad et al., 2004; World Health Organization, 2011; Centers for Disease Control, 2012a), and cigarette use will kill one in two long-term smokers (Centers for Disease Control, 2010). Each year over 400,000 people in the United States die of smoking related illnesses (Centers for Disease Control, 2008), and because of increasing cigarette use in developing nations, it is predicted that the worldwide death toll from smoking will increase from the current 5.4 million persons per year to more than 8 million persons per year by 2030 (World Health Organization, 2011). The economic burden of smoking is correspondingly high. In the United States alone, annual costs are estimated at $96 billion in direct medical expenses and $97 billion in lost productivity (Centers for Disease Control, 2008). These important public health issues and associated economic costs motivate studies to identify and understand biological pathways that drive smoking behaviors so that more effective prevention and cessation treatments can be developed.

A revolution of genetic technologies is underway, and these new scientific tools can be brought to bear on the study of smoking behaviors and nicotine dependence. Millions of genetic variants (or single nucleotide polymorphisms; SNPs) can be assessed in the human genomes of tens of thousands of individuals, and the genetic examination of smoking behaviors can be undertaken on a scale not possible 10 years ago. These new technologies have facilitated investigations of many complex diseases, and thousands of new genetic findings have been made in the past decade (Hindorff et al., 2009, 2013). Modern genetic studies have significantly impacted our understanding of illnesses such as obesity, diabetes, and heart disease, and also nicotine dependence and smoking related illnesses. Specifically relevant here, recent genetic findings show promise to improve clinical care for smoking cessation.

2. Development of nicotine dependence – a multi-step process

Nicotine is the compound in tobacco that is primarily responsible for the maintenance of smoking behaviors and the

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development of dependence (Stolerman and Jarvis, 1995), and many people with severe smoking related illnesses remain unable to stop smoking due to the addictive nature of nicotine (Centers for Disease Control, 2013). To develop nicotine dependence, a person passes through a series of behavioral steps, and both environmental and genetic factors influence each transition. The first step in the development of nicotine dependence is the initiation of smoking, which occurs with the use of a first cigarette. The next step in this process is taken when an individual passes the threshold of smoking 100 cigarettes over a lifetime, and becomes a "smoker," a definition that has been employed in large-scale epidemiological studies (Bondy et al., 2009). These early steps of smoking behavior typically occur in adolescence and are strongly influenced by environmental factors such as peer smoking, cigarette access, and cigarette cost (Kobus, 2003; Hoffman et al., 2006; Centers for Disease Control, 2012b). As cigarette use continues, smoking behaviors become more established, and a range of different smoking patterns is seen. At one end of behavior, some smokers remain lifelong low level cigarette users, or "chippers", who never develop any symptoms of dependence. At the opposite extreme of behavior, some people increase their use of cigarettes, smoke cigarettes more intensively, and become addicted, heavy smokers. The addicted smokers also have the least success with smoking cessation. Twin studies convincingly demonstrate that a substantial contribution of genetic factors determines whether one becomes a lifelong light smoker or a nicotine dependent, heavy smoker (Li, 2006).

Fig. 1 shows data from the Collaborative Genetic Study of Nicotine Dependence (COGEND) where we tracked the number of people who transition through each step in this model of the development of nicotine dependence. We assessed individuals in the Detroit and St. Louis communities, 25–44 years of age, and we asked about their smoking history. Slightly over half of those queried reported smoking at least one cigarette in their lifetime; of those who smoked one cigarette, 58% continued using cigarettes and smoked 100 cigarettes in their lifetime. Among these smokers, 45% went on to develop nicotine dependence, defined by a score of 4 or more on the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991), and an additional third of smokers had some symptoms of nicotine dependence. A minority of smokers, 20%, reported low levels of smoking that never escalated to dependence. This differential response to smoking, with a small number of smokers remaining lifelong low level smokers who never exhibit any symptoms of dependence, and another group of smokers becoming nicotine dependent, heavier smokers, identifies two extremes of smoking behaviors. These extremes mark people who are differentially susceptible to the addictive component of cigarettes (nicotine) and have very different rates of smoking cessation. This step of whether a smoker transitions to nicotine dependence has clear genetic contributions. In fact, within just the past few years, several specific genetic variants differentiating these groups of light smokers versus heavy smokers have been successfully identified.

3. Nicotinic acetylcholine receptor subunit genes – targets for genetic studies

Genetic variation in the genes encoding the nicotinic acetylcholine receptor subunits strongly contributes to differences in the risk of developing nicotine dependence among smokers. The most compelling genetic association with nicotine dependence is in the chromosomal region 15q25 that encompasses the α5-α3-β4 nicotinic acetylcholine receptor subunit gene cluster (*CHRNA5-CHRNA3-CHRNB4*) (Saccone et al., 2007). Many independent studies have validated this association with nicotine dependence and with other smoking behavioral phenotypes such as cigarettes smoked per day (Berrettini et al., 2008; Thorgeirsson et al., 2008). Large-scale studies of over 73,000 European-ancestry individuals in genome-wide association (GWA) meta-analyses unequivocally identify this region as associated with heavy smoking ($p = 5.57 \times 10^{-72}$) (Liu et al., 2010; Thorgeirsson et al., 2010; Tobacco and Genetics Consortium, 2010).

One method to dissect and understand these findings is to compare genetic variant associations across diverse human populations. Genetic risk factors that are consistent across European, Asian, and African populations point to variants that are more likely to cause biologic changes, which in turn lead to disease association. The chromosome 15 region containing the *CHRNA5-CHRNA3-CHRNB4* gene cluster has very different genetic architecture across these three populations, and these differences have been leveraged to narrow down potential functional association signals. In a large, international, collaborative meta-analysis, the association between variation in the *CHRNA5-CHRNA3-CHRNB4* genes and smoking quantity was examined in over 22,000 smokers of European, Asian, and African descent. Despite the diverse genetic backgrounds across these populations and the widely varying frequencies of the risk variation, from 5% to over 35%, the variant rs16969968 is clearly associated with heavy smoking behavior across all populations. This consistent association across populations of various ancestries provides evidence that rs16969968 is most likely a causative functional variant that alters the susceptibility to nicotine dependence (Chen et al., 2012a).

4. α5 nicotinic acetylcholine receptor subunit gene – biologic function

Taking these consistent genetic association findings to the next step, laboratory studies point to potential biological mechanisms

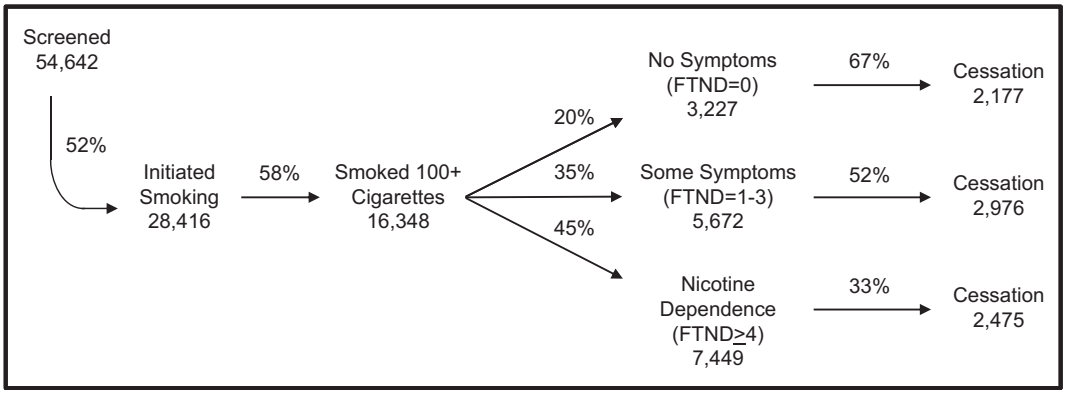

Fig. 1. Smoking behaviors in the COGEND screening sample.