Genetics of Substance Use Disorders

Cassie Yu, MD, Jon McClellan, MD*

KEYWORDS

- Genomics • Genome-wide association • Alcohol • Nicotine • Addiction
- Alcohol dehydrogenase • Aldehyde dehydrogenase
- Nicotinic acetylcholine receptors

KEY POINTS

- Substance abuse disorders are highly familial, with heritability estimates of 40% to 60%.
- Functional missense mutations in genes coding for alcohol-metabolizing enzymes (*ADH1B* and *ALDH2*) are associated with adverse responses to alcohol and are protective against alcohol dependence.
- A functional missense mutation in the nicotinic acetylcholine receptor *CHRNA5* decreases receptor sensitivity to nicotine and increases the risk for nicotine dependence.
- Substance abuse seems to be characterized by extreme genetic heterogeneity, most of which remains unexplained.

INTRODUCTION

Substance abuse and dependence are highly heritable, and seem to have a strong genetic component. However, to date few definitive genetic variants moderating substance abuse risk have been identified. These conditions are characterized by substantial clinical heterogeneity and psychiatric comorbidity. Further, the expression of genetic vulnerability toward substance abuse depends in part on complex interactive social and cultural factors. Marked heterogeneity and the influence of environmental risk and protective factors complicates gene discovery.

In this article, we review contributions of genetics research on substance use disorders, starting with family, twin, and adoption studies. We then examine the genetics of alcohol, nicotine, and illicit drug use disorders individually. We also review issues underlying the basic genomic architecture of complex disease, and discuss strategies to guide future research characterizing genetic mechanisms underlying these conditions.

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Department of Psychiatry, University of Washington, Box 356560, Seattle, WA 98195, USA
* Corresponding author.
E-mail address: drjack@uw.edu

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FAMILY, TWIN, AND ADOPTION STUDIES

Substance abuse disorders are highly heritable.[1] Rates of substance abuse disorders are substantially increased in first-degree relatives of individuals with substance dependence (including opiates, cocaine, cannabis, and/or alcohol), as compared with controls.[2] In general, the use of alcohol, nicotine, and cannabis is strongly influenced by social and environmental factors during adolescence, with genetic factors playing an increasingly important role as substance use persists and progresses into young and middle adulthood.[3]

Twin and adoption studies suggest relatively stronger genetic versus environmental influences of alcohol use disorder. Rates of alcohol dependence were found to be significantly higher in a cotwin of an affected monozygotic twin pair, as compared with a cotwin of an affected dizygotic twin pair.[4] Children of alcoholics adopted by nonalcoholics and reared in a nondrinking environment have a higher risk of developing alcohol problems, as compared with children of nonalcoholics adopted by the same parents.[5]

Family and twin studies also support the role of genetic factors for smoking initiation and nicotine dependence.[6] Kendler and colleagues[7] demonstrated that male twin pairs have similar rates of tobacco use whether raised together or apart. In female twin pairs, the heritability estimates for tobacco use were higher in more recent birth cohorts, suggesting that, as cultural prohibitions for smoking relaxed, genetic factors played a greater role in women's smoking habits.

Although less well-studied, twin, family, and adoption studies also support the importance of both genetic and environmental factors for illicit substance use and abuse, including cannabis.[1] Specific patterns of substance abuse tend to correlate within families.[2]

However, because many people who misuse one drug misuse multiple drugs, distinguishing specific versus general risk factors of addiction is challenging.

GENETIC ARCHITECTURE OF COMPLEX DISEASE

The prevailing model for much of psychiatric genetic research continues to be based on the common disease–common variant hypothesis. This model holds that common risk variants found in all human populations collectively confer a substantial portion of disease susceptibility for complex disease. Each variant risk allele confers a small effect, and by itself is not sufficient to cause disease. The total burden of risk variants, in combination with environmental risk factors, is hypothesized to explain the development of disease in most individuals.

Research over the past decade has challenged the common disease–common variant hypothesis. Complex disorders, including neuropsychiatric conditions, seem to be characterized by extreme genetic heterogeneity. Rare deleterious variants, including de novo mutations, or mutations that arose in recent generations, substantially contribute to disease risk. The common disease-rare variant model suggests that common illnesses are the collective sum of individually rare damaging mutations, such that most affected individuals or families may have a different genetic cause.[8]

Of course, rare and common alleles both contribute to disease risk and normal human variation. The genomic architecture of any illness or trait must stem from the same evolutionary forces that shape the human genome. In this regard, the nature of substance abuse presents an interesting dialectic. Although substance abuse and dependence are conceptualized clinically as categorical disorders, physiologic, psychological, and behavioral responses to psychoactive substances vary widely among humans. The ability to tolerate and metabolize substances is an adaptive trait,