Perspective

The Genetics of Addiction: Where Do We Go From Here?

ABSTRACT. We have made tremendous progress in understanding the genetic epidemiology of substance use problems. We understand a good deal about the genetic architecture of substance use disorders with respect to other psychiatric conditions, and how genetic influences change across development and as a function of the environment. We are further behind in identifying specific genes involved in substance use disorders. However, rather than blindly charging ahead with expensive gene identification efforts, our field would benefit from more thoughtful discussion about what strategies to pursue—both genetic and environmental—to have the greatest impact on reducing substance use problems. (*J. Stud. Alcohol Drugs, 77,* 673–675, 2016)

IT IS NOT UNCOMMON TO HEAR DISPARAGING remarks about slow progress in the genetics of addiction. However, the fact that there is now widespread acceptance that substance use disorders are genetically influenced is in itself a remarkable advancement, in light of the historical view of substance use problems as a moral deficit. Accordingly, I begin this commentary by taking stock of how far we have come in understanding genetic influences on substance use before turning my attention to two areas that remain the great unknowns and the surrounding issues to which our field should pay more attention.

What we know

Genetic influences affect substance use and substance use disorders but largely are not specific to substance use outcomes. Numerous large-scale twin studies have documented the importance of genetic influences on how much people use substances (alcohol, tobacco, other drugs) and the likelihood that users will develop problems (Verhulst et al., 2015). However, twin studies also robustly demonstrate that genetic influences affect multiple forms of substance use (alcohol, illicit drugs) as well as externalizing behaviors such as adult antisocial behavior and childhood conduct disorder. In fact, the majority of genetic influence on substance use outcomes appears to be through a general predisposition that broadly influences a variety of externalizing disorders (Kendler et al., 2003) and is likely related to behavioral undercontrol and impulsivity, which is a heterogeneous construct in itself (Dick et al., 2010). Parsing the exact mechanisms through which genes affect externalizing behavior will require closer collaborations between the fields of behavior genetics and cognitive neuroscience and may provide targets for future intervention efforts.

The importance of genetic influences on substance use outcomes changes across time. Genetic influences on substance use appear to increase steadily across adolescence, with early experimentation with substances being more environmentally influenced, and genetic factors increasing in importance as individuals move from initiation and experimentation to more established patterns of use (Pagan et al., 2006). Further, the predisposition for substance misuse appears to manifest earlier in development as conduct problems. Specific genes that have been associated with adult alcohol dependence have been shown to affect behavior problems earlier in development (Dick et al., 2006, 2009). Multiple independent twin samples have found that the general externalizing predisposition comes online earlier in development and that genes more specific to substance use problems show up later (Kendler et al., 2011; Meyers et al., 2014). Interestingly, although we know a lot about how the predisposition for substance use manifests from early adolescence through young adulthood, we know relatively little about what happens after that.

Historically, it has been challenging to obtain funding to study alcohol use and problems longitudinally beyond the mid-20s, which seems an important gap in the literature considering that so many life changes that are likely to affect substance use (marriages, divorces, child-bearing, career changes, other life stressors) happen beyond young adulthood. We know that individuals' substance use patterns have trajectories that can include escalation and de-escalation, remission, and relapse. Studying how genetic influences affect substance use beyond early adulthood, and what factors predict different trajectories of use and remission, is an area in need of further research that could have important implications for prevention and intervention.

The importance of genetic influences changes as a func-

tion of the environment. Nowhere is this more true than in the area of addiction, where a particular environment (access to a substance) is crucial for an individual's genetic predisposition to affect substance use outcomes. A number of environments that influence access to substances and/or opportunity to use among adolescents, including parental monitoring (Dick et al., 2007a, 2009, 2011) and peer substance use (Button et al., 2009; Dick et al., 2007b; Olfson et al., 2014), have been shown to moderate the importance of genetic influences on adolescent substance use. The environments and mechanisms by which gene–environment interaction (G × E) effects operate beyond adolescence are not well understood and remain an important area of study. Our initial efforts to extend studies of G × E to emerging adulthood suggest that G × E effects are not nearly as systematic as those evidenced in adolescence, perhaps a result of the many developmental processes and pressures that come into play during emerging adulthood (Arnett, 2000).

What we don't know

What are the specific genes that influence substance use and substance use problems? The good news is that we have made a lot of progress in understanding how genetic influences affect substance use; the bad news is that we have not made nearly as much progress in figuring out what those specific genes are. There are considerable differences of opinion among very smart people in the field about how many genes have been "found" that influence substance dependence, with some individuals stating that beyond the genes influencing alcohol metabolism, there are few robustly associated genes. Others are more optimistic that additional genetic effects reported in the literature are "real." I tend to fall in the latter camp.

The challenge is that because the individual genes affecting alcohol use and dependence have such small effects on their own—and there are likely thousands of variants that affect risk, not all of which will be present in any given affected individual—it is incredibly difficult to detect individual associations in the first place at statistically controlled levels and the likelihood is reduced that these associations will replicate in independent samples even if they are "real" effects. Parallel to other areas in psychiatry (Purcell et al., 2009), polygenic risk scores predict alcohol outcomes but account for only a small amount of the variance (Salvatore et al., 2014). Advances in the genetics of schizophrenia, where one could argue the greatest progress in psychiatric genetics has been made (Ripke et al., 2013), clearly indicate that large sample sizes will be necessary to identify specific genes and begin to account for nonnegligible amounts of variance.

However, there are notable differences between alcohol problems and schizophrenia, which should give us pause when considering how successful this strategy will be as applied to substance problems. Alcohol misuse has a considerably stronger environmental component, with potentially far greater etiological heterogeneity. Although larger samples do help get around these issues, at some point one must evaluate the cost:benefit ratio of pouring vast resources into the collection, genotyping, and analysis of samples to identify specific genes. To what end are we willing to pursue this strategy—especially when there are known environmental prevention, intervention, and treatment strategies, to include public policy—that can have a profound effect on reducing problematic substance use? I think that our field could benefit from a more honest, thoughtful reflection on where we invest our time and energies if the ultimate goal is to reduce substance problems.

How will genetic information translate into prevention and intervention? In my mind, this is another crucial question that is too rarely discussed. It is often stated that identifying specific genes will lead us to a greater understanding of the underlying biology, eventually enhancing our ability to prevent and treat disorders. Genome-wide association studies of Crohn's disease uncovering previously unknown association with autoimmune genes is held up as an example of how large-scale genetic studies can be informative about underlying disease etiology (Graham & Xavier, 2013). But with substance problems having such a strong environmental component, I wonder whether the focus on genetic etiology (and the potential to inform prevention/intervention) is coming at the expense of environmental etiology (and the potential to inform prevention/intervention).

I do think that advances in genetic epidemiology about the pathways by which genetic predispositions unfold can be used to inform prevention, even without the identification of specific genes (Dick & Hancock, 2015). For example, knowing that there are both internalizing and externalizing pathways to alcohol problems suggests that one-size-fits-all prevention efforts can be improved. Knowing that conduct problems and other indices of behavioral disinhibition are early manifestations of a predisposition that later leads to substance problems can point toward targets for prevention/intervention. Similarly, identifying specific environments that reduce the expression of risky genetic predispositions can create focus areas for prevention/intervention. However, without more cross-talk between scientists who work in addiction genetics and those who work in prevention/intervention, the potential for translation will not be reached. I believe the field could benefit tremendously from deeper collaboration between basic and applied scientists and practitioners, and that as a field we must constantly re-evaluate the "why" (Sinek, 2009) behind our work. As researchers, we are trained to pay careful attention to the details of our work. I think we too often forget to ask similarly hard questions about the big picture.

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Conflict of Interest Statement

The author declares that she has no conflicts of interest.

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