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Review article

Genetic influences on conduct disorder

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ABSTRACT

Conduct disorder (CD) is a moderately heritable psychiatric disorder of childhood and adolescence characterized by aggression toward people and animals, destruction of property, deceitfulness or theft, and serious violation of rules. Genome-wide scans using linkage and association methods have identified a number of suggestive genomic regions that are pending replication. A small number of candidate genes (e.g., *GABRA2*, *MAOA*, *SLC6A4*, *AVPR1A*) are associated with CD related phenotypes across independent studies; however, failures to replicate also exist. Studies of gene-environment interplay show that CD genetic predispositions also contribute to selection into higher-risk environments, and that environmental factors can alter the importance of CD genetic factors and differentially methylate CD candidate genes. The field's understanding of CD etiology will benefit from larger, adequately powered studies in gene identification efforts; the incorporation of polygenic approaches in gene-environment interplay studies; attention to the mechanisms of risk from genes to brain to behavior; and the use of genetically informative data to test quasi-causal hypotheses about purported risk factors.

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1. Introduction

Conduct disorder is a psychiatric disorder of childhood and adolescence characterized by aggression toward people and animals, destruction of property, deceitfulness or theft, and serious violation of rules. The worldwide prevalence of conduct disorder is 3.2% (Canino et al., 2010) and was responsible for more than 5.75 million years of healthy life lost according to the Global Burden of Disease Study 2010 (Erskine et al., 2014). The impact of the disorder reaches far beyond the personal and financial costs incurred by affected children/adolescents and their families. For example, in the United States, the estimated public cost in terms of mental health, general health, education, and juvenile justice services for a child diagnosed with conduct disorder exceeds 70,000 USD over a 7-year period (Foster and Jones, 2005).

Understanding the etiology of conduct disorder is central to the goal of developing effective prevention and intervention efforts aimed at reducing its global burden. Familial factors have long been implicated in conduct disorder (Costello and Angold, 2001). The field of behavioral genetics has attempted to formalize these initial observations by disentangling the degree to which those familial influences can be ascribed to genetic or environmental factors. Our goal here is to provide an overview of this area of research. We begin with a summary of the latent genetic studies of conduct disorder and conduct disorder clinical criteria, which permit an estimation of the degree to which genetic and environmental influences contribute to variation in outcomes. Next, we review efforts to identify specific, measured genes associated with conduct disorder, ranging from candidate gene approaches to genome-wide scans of conduct disorder and related behaviors. We then turn to the study of gene-environment interplay for conduct disorder. Understanding how environmental risk and protective factors interface with genetic predispositions to predict conduct disorder is a particularly active, albeit controversial, area of research. Lastly, we close with a discussion of four key ways to move this area of research forward in the future.

There have been many genetically informed studies of conduct disorder and related/component behaviors such as aggression, externalizing behavior, psychopathy, and callous-unemotional traits. Accordingly, our review is selective rather than exhaustive. To the extent possible, we focus on genetically informed studies that are consistent with the Diagnostic and Statistical Manual Revised Third Version and Fourth Version (DSM-III-R and DSM-IV) (American Psychiatric Association, 1987, 1994) definition of conduct disorder as "a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated." Conduct disorder diagnoses are typically given to individuals under 18 years of age; accordingly, we focus on studies of conduct disorder in individuals < 18 years. We note, however, that research on the molecular genetics of conduct disorder is still in its infancy, and there are very few studies of conduct disorder according to the strict DSM criteria. Thus, in our review of gene identification efforts for conduct disorder we opted to include larger scale meta-analytic findings of phenotypes closely related to conduct disorder, including aggression and antisocial behavior.

2. Heritability of conduct disorder: twin studies

Most behavioral outcomes have some degree of genetic influence (Polderman et al., 2015), and conduct disorder is no exception. Conduct and related externalizing disorders (e.g., substance use and abuse) are among the most active areas of behavioral genetic research. In view of this, there are already several excellent reviews of the heritability of conduct disorder and broadband antisocial behavior (Burt, 2009; INSERM Collective Expertise Centre, 2005; Polderman et al., 2015; Rhee and Waldman, 2002). We provide highlights from this literature, where samples of twins are often used to estimate heritability. Twin studies permit the partitioning of latent genetic and environmental influences via comparison of the phenotypic correlations of monozygotic (MZ) and dizygotic (DZ) twin pairs. Additive genetic, shared environmental, and non-shared environmental influences can be estimated owing to the fact that both types of twins are exposed to the same rearing environment, but that MZ twins share all of their genetic variation, while DZ twins share half of their genetic variation, on average. Shared environmental influences refer to experiences or events that both twins experience that make them more similar (e.g., growing up in the same neighborhood). Non-shared environmental influences refer to experiences or events that one individual experiences, but not his/her co-twin (e.g., having different friends). When the MZ correlation for a variable is larger than the DZ correlation, this suggests that there are genetic influences. When the DZ correlation for a variable is approximately half of the MZ correlation or lower, this suggests that there are no shared environmental influences. Finally, when the DZ correlation for a variable is more than half of the MZ correlation, this suggests the presence of shared environmental influences.

In a quantitative review of twin studies from the past fifty years, Polderman et al. (2015) report that ~50% of the variance in conduct disorder (broadly measured with over 200 phenotypes in 147,974 monozygotic twin pairs and 192,651 dizygotic twin pairs) is attributable to additive genetic influences. Interestingly, and in contrast to other disorders on the externalizing spectrum (Krueger et al., 2002), the results from this meta-analysis also suggest that shared environmental factors account for a significant (14%) proportion of the variance in conduct disorder (Polderman et al., 2015). To focus more narrowly on conduct disorder, we also present heritability estimates obtained from large-scale (n > 1000) population and community-based twin studies that have used reliable and valid measures of conduct disorder symptomatology or diagnoses according to DSM-III-R or DSM-IV criteria. Analyses in community and population-based samples are more likely to provide unbiased estimates of heritability compared to clinically ascertained samples, where affected individuals are over-represented. Conduct disorder is relatively common, and thus there is sufficient variation to provide reliable estimates of its heritability in population and community-based samples.

Table 1 summarizes the standardized variance component estimates for genetic, shared environmental, and non-shared environmental influences (i.e., h^2, c^2, and e^2, respectively) on conduct disorder. These studies are quite consistent in showing that genetic influences account for a modest to moderate amount of the variance in conduct disorder. In one large study of 5600 individuals from male-male and female-female twin pairs who were ascertained from a population-based registry, there was also evidence that common environmental factors accounted for a significant (32%) proportion of the variance in conduct disorder (Kendler et al., 2003) mirroring the results of the Polderman et al. (2015) meta-analysis of broad conduct disorder phenotypes.

Oftentimes twin studies are conducted using data collected at a single assessment in order to estimate the degree to which genetic and environmental influences account for variation in a behavior or trait. However, it should be noted that heritability estimates are not static, and can change over time. This is especially important to consider for a behavior like conduct disorder, for which there is some evidence for differences across development (Loeber et al., 2000; Moffitt, 1993). This raises two potential questions from a genetic perspective: First, does the degree to which genetic influences account for variance in conduct disorder change across time; and second, are the genes that contribute to conduct disorder earlier in

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