Genetic Vulnerability to Eating Disorders and Substance Use Disorders

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Abstract

It is well established that there is substantial comorbidity between eating disorders and substance use disorders. However, it is unclear why these two disorders frequently co-occur. It has been hypothesized that the two disorders may share a common etiology, which could be genetic in nature. There is ample evidence that the eating disorders, specifically anorexia nervosa and bulimia nervosa, and a variety of substance use disorders have a genetic component, yet little research has explored whether these genetic factors are shared. This chapter reviews the current empirical literature indicating that anorexia nervosa and bulimia nervosa and substance use disorders are influenced by genetic factors, as well as preliminary findings exploring whether these disorders indeed share a genetic architecture. We close with suggestions for future research to further elucidate the shared genetic risk between eating disorders and substance use disorders.

Keywords

Anorexia nervosa • Bulimia nervosa • Comorbidity • Eating disorders • Genetics • Substance use disorders

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5.1 Genetic Vulnerability to Eating Disorders and Substance Use Disorders

There is ample evidence suggesting that eating disorders (ED) and substance use disorders (SUD) have a genetic component. In order to discern the familial nature and genetic architecture of these disorders, family, adoption, and twin study designs are utilized. In a family study, risk for a disorder is determined among first-degree relatives of individuals with the disorder (or probands), and this risk is then compared with risk for the disorder in first-degree relatives of individuals without the disorder (or controls). Family studies are often the first step in genetic epidemiology. However, these studies cannot delineate whether a disorder that runs in families is due to genetic or environmental factors. In contrast, adoption studies can explicate the genetic and environmental contributions to observed familiality by comparing similarity for a disorder in biological versus adoptive relatives. If the observed correlations for the disorder are higher among biological relatives, this suggests genetic factors; if the observed correlations are higher among adoptive relatives, this suggests environmental factors.

Twin study designs are also able to elucidate genetic and environmental contributions to familiality. Twin studies decompose the variance of a disorder into genetic and environmental components by comparing the concordance rates of the disorder among identical and fraternal twins. This variance is broken down into additive genetic (i.e., heritability), shared environmental (i.e., environments that increase similarity between twins), and unique environmental factors (i.e., environments that create dissimilarity between twins). However, twin studies are unable to identify which genes are involved in vulnerability towards a disorder.

Finally, molecular genetic approaches can identify specific genes that influence vulnerability towards a disorder. The dominant approach in the molecular genetics field changes rapidly and has included linkage, candidate gene, and genome-wide association studies (GWAS). Linkage studies are used to identify regions in the genome that may harbor genes that predispose individuals to a disorder and are advantageous in that they can be useful for narrowing down the search of the entire human genome to specific regions. Candidate gene studies explore the association between a specific genetic variant and a disorder. If the variant and disorder are correlated, an association is assumed between the two; however, candidate gene association studies require investigators to select a specific gene for analysis based on a hypothesized association between the pathophysiology of the trait and the gene of interest. Due to the necessity of this a priori hypothesizing, candidate gene studies are limited by existing knowledge of the underlying biology of a disorder.

More recent advances in molecular genetic technology have enabled GWAS, which do not focus on one specific gene or set of genes but examine the entire genome. GWAS are able to explore 300,000–1,000,000 genetic markers across the entire human genome; therefore, they have the ability to identify novel genetic variants that may be involved in the vulnerability to a disorder without needing a priori knowledge. An important consideration in GWAS, however, is that very large sample sizes are necessary. Because an entire sweep of the genome is

conducted, a large number of comparisons are made, requiring a greater level of statistical significance ($p < 10^{-8}$).

Here we review the latest empirical evidence suggesting that there is a genetic vulnerability to ED, SUD, and their comorbidity. We provide an overview of family, twin, and molecular genetic study findings for each disorder, as well as initial findings exploring the genetic overlap between ED and SUD. For ED, we focus on anorexia nervosa (AN) and bulimia nervosa (BN); for SUD, we focus on alcohol use disorder (AUD), nicotine dependence, and illicit drug use disorders because these disorders are most commonly explored for their comorbidity and genetic vulnerability. We conclude by discussing burgeoning approaches in the field and ways these approaches can answer important questions about the genetic etiology of this comorbidity.

5.2 Family Studies of Eating and Substance Use Disorders

Initial family studies revealed that ED and SUD aggregate in families. For example, family members of probands with AN are approximately 11 times more likely to develop AN (Strober, Freeman, Lampert, Diamond, & Kaye, 2000). Further, there is a shared familial transmission between AN and BN, such that there is increased risk for BN in relatives of those with AN and vice versa (Lilenfeld et al., 1998; Strober et al., 2000; Walters & Kendler, 1995). The relative risk for BN in females with a relative with AN has been reported at 12.3, whereas females who have a relative with BN have a reported relative risk of 4.2 for developing AN (Strober et al., 2000).

SUD also aggregate within families (Wang, Kapoor, & Goate, 2012). Relatives of individuals with an illicit drug use disorder are at a 4.5-fold greater risk for having an illicit drug use disorder compared with controls, whereas relatives of probands with AUD are twice as likely to have AUD (Merikangas et al., 1998). The familial aggregation of illicit drug use disorders also appears greater among relatives of females than relatives of men, which may suggest a greater familial loading among females (Merikangas et al., 1998). Similar to ED, a cross-familial transmission is suggested between SUD classes (Rietschel & Treutlein, 2013). The prevalence of certain illicit drug use and nicotine disorders is greater in relatives of probands with alcohol dependence than relatives of controls (Bierut et al., 1998; Nurnberger et al., 2004).

Family studies have provided convincing evidence that ED and SUD aggregate within families. Several reports have also suggested cross-familial transmission between ED types and SUD classes. This indicates the familial vulnerability towards these disorders may exist at a general level, while additional factors may play an important role in which ED or substance class disorder emerges.

5.3 Adoption Studies of Eating and Substance Use Disorders

To date, no adoption studies of ED diagnosis have been conducted. In contrast, several adoption studies have examined the familiality of SUD and, in general, suggest that genetic factors play an important role in their familial aggregation (Wang, Kapoor, et al., 2012). However, when exploring the number of diagnostic criteria met for substance dependence in probands, genetic effects were null for familial transmission for alcohol dependence until five criteria were met, whereas only one criteria was necessary for genetic effects to be evident for drug dependence (Yates, Cadoret, Troughton, & Stewart, 1996).

5.4 Twin Studies of Eating and Substance Use Disorders

Twin studies have corroborated the familial nature of ED and SUD. Heritability estimates have ranged from 28 to 74 % for AN and from 28 to 83 % for BN, with the remaining variance attributable to unique environmental factors (Trace, Baker, Penas-Lledo, & Bulik, 2013). For SUD, results have suggested that genetic factors are highly involved. For example, genetic factors have been implicated for alcohol, nicotine, cannabis, stimulant, and cocaine abuse or dependence. In regard to alcohol dependence, heritability estimates typically range between 40 and 60 % (Wang, Kapoor, et al., 2012), with an average heritability of 57 % (Sullivan, Daly, & O'Donovan, 2012). The average heritability for nicotine dependence is similar, estimated at 67 % (Sullivan et al., 2012), whereas heritability estimates range between 30 and 80 % for illicit substance dependence (Wang, Kapoor, et al., 2012).

Twin research has also examined whether the genetic risk factors for an SUD are specific or nonspecific. If these factors are nonspecific, they would predispose individuals to misuse a range of substances, whereas specific factors would predispose an individual to misuse a specific substance or substance class. In general, results suggest that the genetic risk for an SUD is not substance specific, but is a general factor predisposing individuals to a range of SUD (Kendler, Jacobson, Prescott, & Neale, 2003; Kendler, Myers, & Prescott, 2007; Tsuang et al., 1998). Thus, environmental factors (e.g., peer group, access to substances) likely impact which substance is used.

5.5 Molecular Genetic Studies of Eating and Substance Use Disorders

A significant number of reports have examined the association between specific genetic variants and ED and SUD independently. The following section will review molecular genetic studies that have been conducted within the ED field and within the SUD field, with candidate gene studies focusing on those genetic variants that may be most relevant for the comorbidity between ED and SUD.

5.5.1 Linkage Studies

Few linkage studies of ED exist, although there are more reports for SUD. For ED, studies have found several linkage peaks on various chromosomes: for AN, chromosomes 1 (Devlin et al., 2002; Grice et al., 2002), 2, and 13 (Devlin et al., 2002) have been implicated, whereas for BN, chromosomes 10 and 14 (Bulik et al., 2003) have been implicated. The greater number of linkage studies for SUD compared with ED is due, in part, to the higher prevalence of some SUD. As discussed in a review (Wang, Kapoor, et al., 2012), a number of linkage peaks have been identified for alcohol dependence including regions in chromosomes 4 and 14.

Over 20 linkage studies have been conducted for nicotine dependence and have been reviewed in detail elsewhere (Li, Ma, & Beuten, 2004). A recent meta-analysis implicated a region on chromosome 17 for a combined measure of smoking-related behaviors, whereas suggestive linkage was identified at chromosome 5 for a measure of nicotine dependence (Han, Gelernter, Luo, & Yang, 2010). Additional linkage studies have been reported for cannabis, including linkage to regions on chromosomes 1, 2, 3, 8, 9, and 14 for cannabis dependence and related constructs (Agrawal, Hinrichs, et al., 2008; Agrawal, Pergadia, et al., 2008; Ehlers, Gizer, Vieten, & Wilhelmsen, 2010; Han et al., 2012; Hopfer et al., 2007). Finally, other SUD linkage peaks have been identified including chromosomes 9 and 12 for cocaine dependence (Gelernter et al., 2005) and chromosome 14 for opioid dependence (Lachman et al., 2007).

5.5.2 Candidate Gene Studies

5.5.2.1 Dopamine Genes

The dopamine system has been extensively studied in SUD, as it is known to be involved in reward, motivation, motor activity, cognition, emotion, and food intake. For ED, studies have suggested that the A1 allele in the TaqIA polymorphism (i.e., rs1800497) in the dopamine D2 receptor gene/ankyrin repeat and kinase domain containing 1 (*DRD2/ANKK1*) gene are associated with sensation-seeking among women with bulimia-spectrum disorders who also experienced childhood sexual abuse (Groleau et al., 2012). In contrast, other research has suggested that as the number of A2 alleles of the TaqIA polymorphism increases, the greater the association with purging AN (Bergen et al., 2005). Additional research has focused on the association between ED and polymorphisms in the catechol-O-methyltransferase (*COMT*) gene; however, results are inconclusive. Some studies suggest that the Val allele of the Val158Met polymorphism (i.e., rs4680) is significantly associated with AN (Frisch et al., 2001; Mikolajczyk, Smiarowska, Grzywacz, & Samochowiec, 2006) and BN (Yilmaz, Kaplan, Zai, Levitan, & Kennedy, 2011), whereas others suggest that the Met allele is associated with AN (Michaelovsky et al., 2005) or that there is no association between alleles in this polymorphism and ED (Brandys et al., 2012). Although there are other genes in the dopamine system, less research has investigated their association with ED.

Numerous studies have demonstrated an association between genetic variants in the dopamine system and alcohol dependence. Two meta-analyses (Munafo, Matheson, & Flint, 2007; Smith, Watson, Gates, Ball, & Foxcroft, 2008) on approximately 40 studies investigating the TaqIA polymorphism, the most widely studied polymorphism in the addiction literature, indicated that the A1 allele was significantly associated with alcohol dependence. On the other hand, a recent meta-analysis of the Val158Met polymorphism did not find a significant association with alcohol dependence (Tammimaki & Mannisto, 2010).

For nicotine dependence, meta-analyses have indicated that the A1 allele increases risk for nicotine dependence (Li et al., 2004; Munafo, Clark, Johnstone, Murphy, & Walton, 2004), whereas the Val allele significantly increases risk for smoking (Tammimaki & Mannisto, 2010). Two specific groups of alleles across multiple polymorphisms (i.e., haplotype) in the *COMT* gene have also been shown to be differentially protective against smoking in African-American women and European-American men (Beuten, Payne, Ma, & Li, 2006).

No study has examined associations between cannabis abuse or dependence and variants in dopamine genes, but there is evidence to suggest that the TaqIA polymorphism increases risk for a cannabis-related "high" at an earlier age in adolescent boys compared with their peers who did not have the A1 allele (Conner et al., 2005). Furthermore, a meta-analysis has suggested that the Val allele of the Val158Met polymorphism is associated with increased risk for cannabis abuse (Tammimaki & Mannisto, 2010). For other illicit drugs, the A1 allele of the TaqIA polymorphism is associated with greater heroin consumption and resistance to treatment outcome; however, findings on psychostimulants are conflicting. No significant associations between the Val158Met polymorphism and opioid addiction or stimulant abuse have been observed (Tammimaki & Mannisto, 2010). However, other variants in the *COMT* gene, as well as additional genetic variants in the dopamine system (*DRD2/ANKK1*, dopamine transporter (*SLC6A3*), and dopamine β hydroxylase (*DβH*)), have been associated with cocaine abuse or dependence (Haile, Kosten, & Kosten, 2007).

Taken together, candidate gene studies on genetic variants in the dopamine system and their association with ED and SUD implicate similar genetic risk factors. Although several replication studies have been conducted for alcohol and nicotine dependence, more studies are needed to understand whether genetic variants in the dopamine system confer risk for other SUD, as well as AN and BN.

5.5.2.2 Serotonin Genes

One of the most widely studied systems in psychiatric research is the serotonin system because it has been associated with aggression, sleep, personality, mood and appetite regulation. Extant research within the ED and SUD fields has examined genetic variants on two separate serotonin genes. For ED, most studies have focused on a single polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*), *5-HTTLPR*. Two meta-analyses reported that individuals who had at least one copy of the short allele were more likely to have AN compared with individuals who had two copies of the long allele (Calati, De Ronchi, Bellini,

& Serretti, 2011; Lee & Lin, 2010). There were no significant associations between this polymorphism and BN (Lee & Lin, 2010). Several studies have also examined the association between a promoter region polymorphism (-1438G/A, rs6311) of *HTR2A* and AN. Although an initial meta-analysis reported an absence of an association between this genetic variant and AN (Ziegler et al., 1999), a more recent meta-analysis indicated an association (Gorwood, Kipman, & Foulon, 2003).

For AUD two meta-analyses have reported that the short allele of *5-HTTLPR* is significantly associated with alcohol dependence (Feinn, Nellissery, & Kranzler, 2005; McHugh, Hofmann, Asnaani, Sawyer, & Otto, 2010). The G allele of the -1438G/A polymorphism in the *HTR2A* gene was also significantly associated with alcohol dependence in a sample of Japanese individuals whose *ALDH2* gene, a gene with established connections to alcoholism, was inactive (Nakamura et al., 1999). Moreover, the presence of the G allele in -1438G/A distinguished alcohol-dependent patients from heroin-dependent patients when the individuals were also carriers of the *5-HTTLPR* short allele (Saiz et al., 2009). Although findings with *5-HTTLPR* appear robust, additional work is necessary to confirm the association between this *HTR2A* polymorphism and alcohol dependence.

Studies examining *5-HTTLPR* and nicotine dependence or related phenotypes have been mixed. As reviewed elsewhere (Herman & Balogh, 2012), some studies report an association with the short allele, others with the long allele, and still others report no association. However, the A allele of the -1438G/A polymorphism in the *HTR2A* gene is associated with tobacco smoking (Polina, Contini, Hutz, & Bau, 2009). Finally, minimal work has explored associations between these two serotonin genes and other drug disorders, and those that do exist are mixed (Herman & Balogh, 2012).

In sum, genetic variants in the serotonin system may influence risk for ED and some SUD. However, replication is essential to fully understand the extent to which these variants contribute to individual vulnerability to these disorders.

5.5.3 Genome-Wide Association Studies

To date, only four GWAS of ED exist. In general, these studies have not found genome-wide significant *p*-values for any single-nucleotide polymorphism (SNP) and AN (Nakabayashi et al., 2009; Wang et al., 2011) or eating disorder symptomatology (Boraska et al., 2012; Wade et al., 2013). Although no GWAS for BN diagnosis currently exist, a GWAS examining a BN spectrum phenotype, which included items asking about self-induced vomiting, binge eating, and bulimia, also showed no significant findings (Wade et al., 2013). These negative findings are likely due to small sample sizes, limiting the ability to detect significant associations. Lastly, one report did identify a region, which included a recurrent 13q12 deletion, only observed among AN women of European ancestry and not control women (Wang et al., 2011).

There are many more GWAS for SUD than for ED. Studies of alcohol dependence have yielded findings that survived genome-wide significance and included SNPs in or near the *C12orf51* gene (Baik, Cho, Kim, Han, & Shin, 2011; Wang, Foroud, et al., 2012) and a SNP (rs1789891) that lies between the *ADH1B* and *ADH1C* genes (Frank et al., 2012; Treutlein et al., 2009). However, some GWAS have not reported significant associations between common SNPs and measures of alcohol dependence (Bierut et al., 2010; Heath et al., 2011; Kendler et al., 2011).

GWAS of nicotine dependence have been the most successful of any psychiatric disorder. The most robust finding comes from three GWAS of smoking-related phenotypes, where SNPs located in nicotinic acetylcholine receptor subunit genes (e.g., *CHRNA5*, *CHRNA3*, and *CHRNB3*) reached genome-wide significance (Liu et al., 2010; Thorgeirsson et al., 2010; The Tobacco and Genetics Consortium, 2010). GWAS of illicit drugs have reported a significant association between two genetic variants in the *ANKFN1* gene (rs1019238 and rs1431318) and cannabis dependence (Agrawal et al., 2011), and differential associations by ethnicity for heroin addiction such that rs10494334 was significantly associated with heroin addiction among European-Americans, whereas in African-Americans, rs950302 in the *DUSP27* gene was associated with heroin addiction (Nielsen et al., 2010).

In general, with the exception of smoking-related phenotypes, GWAS have not been successful in identifying genetic risk factors for ED and SUD. Those SNPs that have emerged have not been in dopaminergic or serotonergic genes. Differences between candidate gene and GWAS findings could result from multiple factors, including the fact that the threshold for significance in GWAS is so high.

5.6 Genetic Vulnerability to Eating and Substance Use Disorder Comorbidity

Given the significant comorbidity between ED and SUD and the strong familiality involved in each, it has been hypothesized that the disorders share a familial vulnerability, albeit genetic or environmental. Similar to the approaches described above, family, twin, and molecular genetic study designs can be used to elucidate whether ED and SUD share a genetic etiology.

5.6.1 Family Studies of Eating and Substance Use Disorder Comorbidity

Family studies have assessed whether ED and SUD aggregate together within families. Initial reports observed an increased likelihood of an SUD in first-degree relatives of probands with BN (Holderness, Brooks-Gunn, & Warren, 1994). However, when proband SUD was controlled for, findings indicated that BN and SUD were transmitted independently (Kaye et al., 1996; Lilenfeld et al., 1997, 1998; Schuckit et al., 1996). Limited reports have explored the prevalence of ED in relatives of those with an SUD or the impact of family history of ED on SUD

vulnerability, but in general, findings also suggest independent transmission (Harrell, Slane, & Klump, 2009; Nurnberger et al., 2004; Schuckit et al., 1996; von Ranson, McGue, & Iacono, 2003).

5.6.2 Twin Studies of Eating and Substance Use Disorder Comorbidity

Similar to the twin design discussed above, bivariate twin designs are used to decompose the correlation between two disorders into genetic and environmental components. These models can also yield the genetic and environmental correlations between the disorders. These correlations represent the correlation between the genetic and environmental factors influencing disorder one (e.g., ED) and the genetic and environmental factors influencing disorder two (e.g., SUD). If the correlations are estimated at 1.0, this would indicate complete overlap.

To date, four studies have explored the genetic overlap between BN and SUD, including AUD and illicit drug use disorders, and, in contrast to family studies, indicate a shared familial association. The first report applied a multivariate twin model to the lifetime history of six psychiatric disorders including BN and alcoholism (alcohol dependence or problem drinking) to elucidate the genetic overlap among these six disorders (Kendler et al., 1995). Although findings revealed that a majority of the genetic liability to alcoholism was independent from the other five disorders (including BN), there was evidence of a small amount of genetic overlap with BN (6 %).

Expanding on this first investigation, Baker, Mitchell, Neale, and Kendler (2010) explored the genetic correlation between a BN symptom count and several SUD including AUD, regular smoking (defined as ever engaging in an average of at least seven episodes of smoking per month), and illicit drug use disorder. Findings suggested small-to-moderate overlap in the genetic factors contributing to the BN symptom count and all SUD examined. The strongest genetic correlation was observed between BN and AUD, estimated at 0.53, whereas the genetic correlation between BN and any illicit drug use disorder was estimated at 0.37 and regular smoking estimated at 0.35.

Examining shared genetic liability between broadly defined BN diagnosis, any illicit drug use disorder, and AUD corroborates findings. Utilizing this broader definition of BN diagnosis, a genetic correlation of 0.39 was observed between BN and an illicit drug use disorder (Baker, Mazzeo, & Kendler, 2007), which is quite similar to the genetic correlation reported above. Confirming previous findings in a large, population-based study of female twins from Sweden, the genetic correlation between BN and AUD was estimated at 0.23 (Trace, Thornton, et al., 2013). Although this correlation is lower than previously reported, the confidence intervals overlap.

Providing further evidence of a shared genetic component between ED and SUD, shared genetic risk has been observed between binge eating, inappropriate compensatory behaviors, and alcohol misuse. Specifically, a genetic correlation of

0.61 and 0.31 was estimated between problematic alcohol use and inappropriate compensatory behaviors and binge eating, respectively (Slane, Burt, & Klump, 2012). A larger investigation corroborated these findings and found significant genetic overlap between alcohol dependence and binge eating and between alcohol dependence and inappropriate compensatory behaviors (estimated genetic correlations of 0.26 and 0.32, respectively) (Munn-Chernoff et al., 2013). These findings suggest that the comorbidity between ED and SUD may be more related to specific ED symptoms as opposed to a specific diagnosis, which would explain why SUD are more common in individuals with a binge-purge-type ED. Clearly, further work is needed exploring the genetic relationship between specific ED symptoms and SUD and to further delineate the inconsistencies in findings across family and twin studies.

5.6.3 Molecular Genetic Studies of Eating and Substance Use Disorder Comorbidity

To date, no molecular genetic studies have explored whether there is a cross-disorder association between ED and SUD. Linkage studies for these disorders independently have shown overlap in linkage peaks (e.g., chromosomes 1 and 14), whereas candidate gene association studies have shown independent associations between similar genetic variants in the dopamine and serotonin systems and ED and SUD. However, in the absence of cross-disorder analyses, we are unable to discern whether the observed overlap in linkage peaks and genetic variants contributes to the comorbidity between ED and SUD. Nonetheless, despite this lack of cross-disorder association analyses, it is likely that at least some of the same genetic variants in dopamine and serotonin genes influence liability to both ED and SUD and their comorbidity. Clearly, this is an area worth further exploration.

5.7 Conclusion and Future Directions

Despite an extensive amount of literature showing that the comorbidity between certain ED and SUD is high, the reasons for this comorbidity are unclear. It has long been hypothesized that ED and SUD share a common etiology, which may include shared genetic influences. Although the results of family studies have been inconsistent, twin studies uniformly suggest there is at least a small amount of overlap in genetic risk. Moreover, two promising studies suggest that the symptoms of binge eating and inappropriate compensatory behaviors may be the "genetic link" between ED and SUD—which may account for some of the inconsistencies observed across the literature.

Further, although numerous studies have investigated whether genetic variants contribute to ED and SUD, more work is needed to identify genetic variants that contribute to their comorbidity. Genes in the dopamine and serotonin systems may be important, as well as other genes that have accumulated less evidence (e.g.,

genes in the opioid system, such as *OPRD1*). Future studies should focus on genetic variants in these key neurotransmitter systems and the shared association between binge eating and/or inappropriate compensatory behaviors and SUD.

An additional important next step in identifying the genetic factors influencing comorbidity between ED and SUD is to implement cross-disorder association analyses, specifically cross-disorder GWAS. Cross-disorder GWAS would allow for the identification of shared genetic variants that transcend diagnostic categories and are shared between comorbid disorders—an approach that has been highly successful in identifying shared genetic variants between schizophrenia, bipolar disorder, and major depression (Smoller et al., 2013). This type of cross-disorder analysis would answer important questions as to whether certain genetic variants contribute to the liability to both ED and SUD.

Finally, understanding the genetic factors that increase vulnerability for the comorbidity between ED and SUD not only have important implications for our understanding of etiology, but also have important implications for prevention, detection, and treatment. For example, prevention efforts can be developed for those at genetic risk (e.g., those with first-degree relatives with an ED or comorbid ED-SUD). Ultimately, a thorough understanding of the genetic architecture of this comorbidity will enrich our ability to prevent, detect, and treat these disorders independently, as well as their comorbidity.

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