

Review Article

Genetic Factors for Alcohol Dependence and Schizophrenia: Common and Rare Variants

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Introduction

Alcohol dependence (AD) is a complex disease, with devastating effects on individuals, families and society. It is estimated that 76.3 million people worldwide suffered from alcohol use disorders (AUD) [1]. In the United States (US), more than 18 million adults (7% of the population) have been diagnosed with AUD including alcohol abuse or dependence [2]. Family, twin, and adoption studies have indicated that genetic and environmental factors and their interactions contribute to the development of AD, with a heritability of more than 0.5 [3-5].

Schizophrenia (SCZ) is a mental disorder characterized by auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with significant social or occupational dysfunction. It is estimated that 1% of the population may suffer from SCZ worldwide [6]. Approximately 2.4 million US adults (about 1.1 percent of the population aged 18 and older in a given year) have SCZ [7,8]. SCZ is a multifactorial disorder characterized, to a large extent, by the contribution of multiple susceptibility genes, which may interact, in a stochastic manner, with epigenetic processes and environmental factors [9,10]. SCZ is known to be a multifactorial disorder with a demonstrated heritability of 80% in family studies and meta-analysis of multiple twin studies [11,12].

Epidemiological studies have shown that there is a high alcohol/substance use disorder comorbidity rate in SCZ; however, the interrelationship between AD and SCZ is very complex. Previous study has suggested that chronic AD alone can result in a chronic, SCZ-like psychosis (alcoholic hallucinosis) which cannot be distinguished from SCZ on the basis of psychopathological or clinical symptoms; however, recent clinical and epidemiological studies have pointed at a significantly increased prevalence for substance

abuse and dependence in SCZ, especially of alcohol [13]. However, the hypothesis that substance abuse causes SCZ is not generally supported [14]. Recently, one study has reported that individuals with SCZ are at increased risk for developing substance abuse disorders [15]; while another study has indicated that approximately every fifth patient with SCZ has lifetime AUD diagnosis [16]. More recently, it is suggested that AUDs are a common sequela of SCZ [17].

Common variants

The common-disease common-variant (CDCV) hypothesis proposes that common disease/common traits are most likely due to common variants with small to modest effects on disease/trait. Candidate gene and genome-wide association studies (GWASs) may have greater power to detect common variants with small effects [18-20]. The SCZ comorbid with AUD may be partly due to shared common genetic variants. For example, it has been reported that KPNA3 may contribute to the genetic susceptibility to SCZ as well as other psychiatric disorders including opiate dependence and AD [21]. Furthermore, common alcohol dehydrogenase (ADH) variants may confer risk for both SCZ in African-Americans and autism in European-Americans [22]. Moreover, the DPYSL2 gene at 8p22-p21 has been implicated in multiple psychiatric disorders such as Alzheimer's disease, AD and SCZ [23]. Recently, a GWAS identified PDLIM5 as a new locus for AD [24]; which has previously been reported to be associated with SCZ [25,26].

However, for some other genes, the results are inconsistent. For example, it has been suggested that the dopamine D (3) receptor gene (DRD3) is a candidate for a number of psychiatric conditions including SCZ, bipolar disorder and alcohol and drug abuse [27-31]. Some positive associations [32,33] support the involvement of DRD3 in the development of addiction to alcohol. However, other studies in French, Korean and Caucasian populations report no association of DRD3 with AD [34,35]. Furthermore, two studies suggest that neither the coding nor the regulatory region of DRD3 plays a major role in predisposition to SCZ [36,37].

Rare variants

Recently, there is increasing evidence showing that multiple rare variants may underlie susceptibility to common diseases/traits [18]. It has been suggested that multiple rare gene variants, each with moderate to high penetrance, could play an important role in common diseases [38-40]. To identify rare variants, genetic and genomic data (from such as candidate gene studies and GWASs) have been used. So far, GWASs, focusing mainly on common SNPs, have detected over 2000 loci that were associated with diseases and traits. However, many identified SNPs have very small effect sizes and the proportion of heritability explained by common variants is only modest. Although GWASs using tag SNPs are a powerful approach for detecting common variants, they are underpowered for detecting associations with rare variants. However, rare haplotypes/variants are

important for disease susceptibility and cannot be ignored in genetics studies of complex diseases. It has been reported that rare haplotypes in association studies may play an important role in influencing disease susceptibility and thus should not be ignored in the design and execution of association studies; which has profound implications for association studies and applications of the Hap Map project [41]. For example, using SNP data, a rare variant constellation across the entire ADH gene cluster is found to be significantly associated with AD in European-Americans, European-Australians and African-Americans [42]. Another study shows that rare variants in CHRN3 or CHRNA3 may confer risk for AD or cocaine dependence using SNP data [43] but common SNPs in CHRNA3 genotype are associated with negative symptoms in the SCZ sample [44].

However, an effective way to identify rare variants is through direct sequencing [45]. Although rare variants may be important in understanding the biology of common diseases, clearly establishing their associations with disease is often difficult. Association studies of such variants will be becoming increasingly common as large-scale sequence analysis of candidate genes has become feasible. Currently, few results have been reported about shared genes with rare variants between AD and SCZ using genomic data or sequence data.

Future directions

It has been suggested that both the common disease, common variant (CD/CV) hypothesis and rare variant (CD/RV) hypothesis are correct, depending on the gene and disease examined [18]. These two hypotheses are not mutually exclusive. For example, if variation in a gene has an impact on a biological process or disease, there will be a spectrum of variations with a spectrum of effects, including common variants of small effects and rare variants of large effects. In AD, both GWAS and sequencing are critical if we are to progress in our understanding of the disease and our ability to better treat patients [46]. In SCZ, there is accumulating evidence that both common genetic variants with small effects and rare genetic lesions with large effects determine risk of this disease. For example, thousands of common SNPs, each with a small effect, cumulatively could explain about 30% of the underlying genetic risk of SCZ; while rare and large copy number variants (CNVs) with high but incomplete penetrance, variable in different individuals, could explain about additional 30% of SCZ cases [47].

GWAS is a screening procedure to identify the location of pathogenically relevant variations. Nonetheless, when considered singly, polymorphisms with such small effect sizes may be no use for individual risk prediction [48]. However, a robust finding of associations can contribute to major advances in the understanding of disease pathogenesis, whatever the effect size is, because it may pin down with a high degree of confidence a protein product that lies at some point in the disease pathway [48]. It is suggested that if a large number (e.g. >100) of susceptibility polymorphisms of small effects are identified, considering them together may provide useful individual-level risk prediction [49,50].

Furthermore, complex diseases such as AD and SCZ result from the interplay of many genetic and environmental factors. Much of the heritability remains unexplained in these studies. If some of the unexplained heritability in GWASs is due to interactions, then one goal might be to use interactions to discover novel genes/regions

[51,52]. This could be due to the involvement of environmental factors in the manifestation of these disorders, alone or in association with genetic variants (gene-environment interaction). In addition, complex diseases can follow a polygenic model in which the disease only manifests when a whole combination/series of frequent variants, each carrying a small effect, are co-inherited [53].

The allelic architecture of complex diseases/traits may be due to a combination of multiple common and rare variants. It has been suggested that targeted genotyping arrays and next-generation sequencing technologies at the whole-genome and whole-exome scales are increasingly employed to access sequence variation across the full minor allele frequency (MAF) spectrum [54]. Current findings of the genetic risks of AD and SCZ emerging from GWASs support a highly polygenic model displaying the full spectrum of causal alleles that includes the extremes of rare, penetrant alleles as well as common alleles of small effects. However, little is known about the extent to which rare variants contribute to the heritability of complex diseases. Importantly, rare and potentially deleterious variants may not be detected by GWASs. In order to create a comprehensive catalogue of common and rare variants in individuals with psychiatric disease such as AD and SCZ, it will be useful to combine the results of GWASs, gene-gene and gene-environment interactions, with the recent rapid advances in next generation sequencing (NGS) technologies, including whole exome sequencing, transcriptome sequencing, and whole genome sequencing.

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