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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 than18 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

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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 CHRNB3 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.

References

1. Strong KL, Bonita R. Investing in surveillance: a fundamental tool of public health. Soz Praventivmed. 2004; 49: 269-275.
2. Li TK, Hewitt BG, Grant BF. Alcohol use disorders and mood disorders: a National Institute on Alcohol Abuse and Alcoholism perspective. Biol Psychiatry. 2004; 56: 718-720.
3. Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. Nat Rev Genet. 2005; 6: 521-532.
4. Heath AC, Bucholz KK, Madden PA, Dinwiddie SH, Slutske WS, Bierut LJ, et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. Psychol Med. 1997; 27: 1381-1396.
5. Schuckit MA. Genetics of the risk for alcoholism. Am J Addict. 2000; 9: 103-112.
6. Mowry BJ, Nancarrow DJ. Molecular genetics of schizophrenia. Clin Exp Pharmacol Physiol. 2001; 28: 66-69.
7. Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto mental and addictive disorders service system. Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Archives of General Psychiatry. 1993; 50: 85-94.
8. US Census Bureau Population Estimates by Demographic Characteristics. Table 2: Annual Estimates of the Population by Selected Age Groups and Sex for the United States: April, 2000 to July, 2004 (NC-EST2004-02) Source: Population Division, US Census Bureau Release Date: June 9, 2005.
9. Danese A. A public health genetic approach for schizophrenia. Epidemiol Psichiatr Soc. 2006; 15: 185-193.
10. Karayiorgou M, Gogos JA. Schizophrenia genetics: uncovering positional candidate genes. Eur J Hum Genet. 2006; 14: 512-519.
11. Gejman PV, Sanders AR, Duan J. The role of genetics in the etiology of schizophrenia. Psychiatr Clin North Am. 2010; 33: 35-66.
12. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003; 60: 1187-1192.

13. Soyka M. Alcohol dependence and schizophrenia: what are the interrelationships? Alcohol Alcohol Suppl. 1994; 2: 473-478.

14. Hambrecht M, Häfner H. [Do alcohol or drug abuse induce schizophrenia?]. Nervenarzt. 1996; 67: 36-45.

15. Krystal JH, D'Souza DC, Gallinat J, Driesen N, Abi-Dargham A, Petrakis I, et al. The vulnerability to alcohol and substance abuse in individuals diagnosed with schizophrenia. Neurotox Res. 2006; 10: 235-252.

16. Koskinen J, Löhönen J, Koponen H, Isohanni M, Miettunen J. Prevalence of alcohol use disorders in schizophrenia--a systematic review and meta-analysis. Acta Psychiatr Scand. 2009; 120: 85-96.

17. Jones RM, Lichtenstein P, Grann M, Långström N, Fazel S. Alcohol use disorders in schizophrenia: a national cohort study of 12,653 patients. J Clin Psychiatry. 2011; 72: 775-779.

18. Iyengar SK, Elston RC. The genetic basis of complex traits: rare variants or "common gene, common disease"? Methods Mol Biol. 2007; 376: 71-84.

19. Lander ES. The new genomics: global views of biology. Science. 1996; 274: 536-539.

20. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science. 1996; 273: 1516-1517.

21. Morris CP, Baune BT, Domschke K, Arolt V, Swagell CD, Hughes IP, et al. KPNA3 variation is associated with schizophrenia, major depression, opiate dependence and alcohol dependence. Dis Markers. 2012; 33: 163-170.

22. Zuo L, Wang K, Zhang XY, Pan X, Wang G, Tan Y, et al. Association between common alcohol dehydrogenase gene (ADH) variants and schizophrenia and autism. Hum Genet. 2013; 132: 735-743.

23. Taylor A, Wang KS. Association between DPYSL2 gene polymorphisms and alcohol dependence in Caucasian samples. J Neural Transm. 2014; 121: 105-111.

24. Gelernter J, Kranzler HR, Sherva R, Almasy L, Koesterer R, Smith AH, et al. Genome-wide association study of alcohol dependence:significant findings in African- and European-Americans including novel risk loci. Mol Psychiatry. 2014; 19: 41-49.

25. Horiuchi Y, Arai M, Niizato K, Iritani S, Noguchi E, Ohtsuki T, et al. A polymorphism in the PDLIM5 gene associated with gene expression and schizophrenia. Biol Psychiatry. 2006; 59: 434-439.

26. Li C, Tao R, Qin W, Zheng Y, He G, Shi Y, et al. Positive association between PDLIM5 and schizophrenia in the Chinese Han population. Int J Neuropsychopharmacol. 2008; 11: 27-34.

27. Baritaki S, Rizos E, Zafiropoulos A, Soufla G, Katsafouros K, Gourvas V,et al. Association between schizophrenia and DRD3 or HTR2 receptor gene variants. Eur J Hum Genet. 2004; 12: 535-541.

28. Crocq MA, Mant R, Asherson P, Williams J, Hode Y, Mayerova A, et al. Association between schizophrenia and homozygosity at the dopamine D3 receptor gene. J Med Genet. 1992; 29: 858-860.

29. Le Foll B, Goldberg SR, Sokoloff P. The dopamine D3 receptor and drug dependence: effects on reward or beyond? Neuropharmacology. 2005; 49: 525-541.

30. Lochman J, Balcar VJ, Sťastný F, Serý O. Preliminary evidence for association between schizophrenia and polymorphisms in the regulatory Regions of the ADRA2A, DRD3 and SNAP-25 Genes. Psychiatry Res. 2013; 205: 7-12.

31. Spurlock G, Williams J, McGuffin P, Aschauer HN, Lenzinger E, Fuchs K, et al. European Multicentre Association Study of Schizophrenia: a study of the DRD2 Ser311Cys and DRD3 Ser9Gly polymorphisms. Am J Med Genet. 1998; 81: 24-28.

32. Limosin F, Romo L, Batel P, Adès J, Boni C, Gorwood P. Association between dopamine receptor D3 gene BalI polymorphism and cognitive impulsiveness in alcohol-dependent men. Eur Psychiatry. 2005; 20: 304-306.

33. Sander T, Harms H, Podschus J, Finckh U, Nickel B, Rolfs A, et al. Dopamine D, D2 and D3 receptor genes in alcohol dependence. Psychiatr Genet. 1995; 5: 171-176.

34. Gorwood P, Martres MP, Adès J, Sokoloff P, Noble EP, Geijer T, et al. Lack of association between alcohol-dependence and D3 dopamine receptor gene in three independent samples. Am J Med Genet. 1995; 60: 529-531.

35. Wiesbeck GA, Dürsteler-MacFarland KM, Wurst FM, Walter M, Petitjean S, Müller S, et al. No association of dopamine receptor sensitivity in vivo with genetic predisposition for alcoholism and DRD2/DRD3 gene polymorphisms in alcohol dependence. Addict Biol. 2006; 11: 72-75.

36. Anney RJ, Rees MI, Bryan E, Spurlock G, Williams N, Norton N, et al. Characterisation, mutation detection, and association analysis of alternative promoters and 5' UTRs of the human dopamine D3 receptor gene in schizophrenia. Mol Psychiatry. 2002; 7: 493-502.

37. Fathalli F, Rouleau GA, Xiong L, Tabbane K, Benkelfat C, Deguzman R, et al. No association between the DRD3 Ser9Gly polymorphism and schizophrenia. Schizophr Res. 2008; 98: 98-104.

38. Bodmer W, Bonilla C. Common and rare variants in multifactorial susceptibility to common diseases. Nat Genet. 2008; 40: 695-701.

39. Cirulli ET, Goldstein DB. Uncovering the roles of rare variants in common disease through whole-genome sequencing. Nat Rev Genet. 2010; 11: 415-425.

40. Schork NJ, Murray SS, Frazer KA, Topol EJ. Common vs. rare allele hypotheses for complex diseases. Curr Opin Genet Dev. 2009; 19: 212-219.

41. Liu PY, Zhang YY, Lu Y, Long JR, Shen H, Zhao LJ, et al. A survey of haplotype variants at several disease candidate genes: the importance of rare variants for complex diseases. J Med Genet. 2005; 42: 221-227.

42. Zuo L, Zhang H, Malison RT, Li CS, Zhang XY, Wang F, et al. Rare ADH variant constellations are specific for alcohol dependence. Alcohol Alcohol. 2013; 48: 9-14.

43. Haller G, Kapoor M, Budde J, Xuei X, Edenberg H, Nurnberger J, et al. Rare missense variants in CHRNB3 and CHRNA3 are associated with risk of alcohol and cocaine dependence. Hum Mol Genet. 2014; 23: 810-819.

44. Petrovsky N, Quednow BB, Ettinger U, Schmechtig A, Mössner R, Collier DA, et al. Sensorimotor gating is associated with CHRNA3 polymorphisms in schizophrenia and healthy volunteers. Neuropsychopharmacology. 2010; 35: 1429-1439.

45. Li B, Leal SM. Methods for detecting associations with rare variants for common diseases: application to analysis of sequence data. Am J Hum Genet. 2008; 83: 311-321.

46. Edenberg HJ. Common and rare variants in alcohol dependence. Biol Psychiatry. 2011; 70: 498-499.

47. Maric NP, Svrakic DM. Why schizophrenia genetics needs epigenetics: a review. Psychiatr Danub. 2012; 24: 2-18.

48. McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, Ioannidis JP, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet. 2008; 9: 356-369.

49. Janssens AC, Moonesinghe R, Yang Q, Steyerberg EW, van Duijn CM, Khoury MJ. The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. Genet Med. 2007; 9: 528-535.

50. Craddock N, Sklar P. Genetics of bipolar disorder: successful start to a long journey. Trends Genet. 2009; 25: 99-105.

51. Kraft P, Yen YC, Stram DO, Morrison J, Gauderman WJ. Exploiting gene-environment interaction to detect genetic associations. Hum Hered. 2007; 63: 111-119.

52. Thomas D. Methods for investigating gene-environment interactions in candidate pathway and genome-wide association studies. Annu Rev Public Health. 2010; 31: 21-36.

53. Barc J, Koopmann TT. Genome-wide association studies: providers of candidate genes for identification of rare variants? Europace. 2011; 13: 911-912.

54. Panoutsopoulou K, Tachmazidou I, Zeggini E. In search of low-frequency and rare variants affecting complex traits. Hum Mol Genet. 2013; 22: R16-21.