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Genome-wide linkage scans for major depression in individuals with alcohol dependence

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Abstract

Major depression is more prevalent among individuals with alcoholism than in the general population. Twin studies have found a moderate degree of genetic correlation for alcohol dependence (AD) and major depression (MD), suggesting the existence of loci that confer susceptibility to both disorders. The aim of the present study was to conduct genome-wide linkage analyses to identify loci and to replicate prior evidence for linkage to MD, and to search for linkage regions that may confer risk to the co-occurrence of depression and alcoholism in a sample of sib-pairs affected with AD. A set of 1020 microsatellite markers (average marker spacing of 4 cM) were genotyped in 1289 subjects, which consisted of 473 informative families for analysis of depressive traits and 626 sibling pairs for analysis of symptoms of MD and AD. For univariate linkage results for depression, there were six regions (1q, 2p, 4q, 12q, 13q, and 22q) with multipoint LOD scores in excess of 1.00; the highest peak was on chromosome 4q32.3 near marker D4S2952 (LOD = 2.17, $p = 0.0008$) for

Contributors

Authors K.S.K. and C.A.P. designed the study and authors D.W. and D.G.P. assisted for sample collection. Author BP was responsible for genotyping. Author M.C.N. assisted with the genetic analyses, and author P.H.K. conducted analyses and wrote the draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest statement

All other authors declare that they have no conflicts of interest.

symptoms of MD. Bivariate linkage analysis of symptoms of MD and AD identified only one region at 22q11.21 with LOD > 1, which overlapped with the region for symptoms of MD. Several of these regions replicate previously reported linkage results for major depression and emotion-related traits and events, such as neuroticism and suicide attempts. These identified genomic locations, together with results from prior studies, indicate potential regions of interests that may contain susceptibility loci to the risk of depression among individuals with alcohol dependence.

Keywords

Emotional related trait; Quantitative genetics; Susceptibility loci

1. Background

Co-occurrence of major depressive disorder (MD) with alcohol dependence (AD) is frequently observed in both national epidemiologic surveys (Kessler et al., 1997; Grant et al., 2004) and clinical studies (Schuckit et al., 1997; Lynskey, 1998), which has substantial impacts on individuals and society (Burns and Teesson, 2002). Both MD and AD are clinically and etiologically heterogeneous conditions with moderate to high heritability (37–70%) Heath et al., 2002; Kendler et al., 2006. Evidence coming from twin studies supports common liability from genetic predisposition for the two disorders (Prescott et al., 2000). However, efforts to study genetic influences on each of the two disorders have not yielded many conclusive implications (Jabbi et al., 2008; Kalsi et al., 2009).

Genomic regions that are identified by linkage analyses can be targeted for more extensive genetic analyses. We are aware of only one prior published linkage study of MD and AD (Nurnberger et al., 2001) using a ‘alcoholism or depression’ phenotype. Several previous linkage studies for major depression have been conducted with divergent linkage results (Zubenko et al., 2003; Camp et al., 2005; McGuffin et al., 2005), which rarely point to a convincing region for further examination. Our goal in this report was to attempt to add to the literature by conducting both univariate and bivariate genome-wide linkage analyses for depression phenotypes in the Irish Affected Sibpair Study of Alcohol Dependence (IASPSAD, Prescott et al., 2005). In this sample, nearly 70% of the individuals with AD had a lifetime diagnosis of MD, raising the question of whether region is alcohol-specific or encompasses genes with pleiotropic effect for depression. We aimed to identify loci for depression and to see whether we could replicate prior evidence for linkage to MD as well as identify linkage regions that confer susceptibility for the co-occurrence of MD and AD.

2. Materials and methods

The IASPSAD was conducted in Ireland and Northern Ireland to recruit AD families, for which probands met the DSM-IV (American Psychiatric Association, 1994) criteria for AD. All participants, including probands, parents, and siblings were interviewed by clinically-trained interviewers using the SSAGA (Bucholz et al., 1994) to obtain AD and ADsx (the sum of the endorsed AD criteria). Lifetime MD and MDsx (the sum of the endorsed MD criteria) were based on the SCID (Spitzer and Williams, 1985). There were 1248 individuals (64.3% males) from 591 families who completed the interview. More details of the study design, sample ascertainment, and clinical characteristics are described elsewhere (Prescott et al., 2005).

All but seven individuals provided DNA samples ($N = 1407$) with the majority of blood samples (15% of the brush samples). Blood samples from 66 volunteer control subjects recruited in Ireland were used to obtain allele frequency estimates. A 1020-marker autosomal genomewide screen was conducted by deCODE Genetics using their standard panel of polymorphic

microsatellite markers. The average marker spacing was 4 cM, and average heterozygosity in our sample was 72.5%. Details of the laboratory methods and error-checking are provided elsewhere (Prescott et al., 2006). After data cleaning, 1289 samples were included in the analyses, resulting in 473 informative families and 626 sibling pairs for univariate and bivariate linkage analyses, respectively.

Univariate linkage analyses were conducted using the non-parametric method in the Merlin program for MD and MDsx (Abecasis et al., 2002). A bivariate MDsx–ADsx linkage model was employed using variance components method in the Mx program (Neale et al., 2004). The model was specified with the variance and covariation of traits partitioned into components of quantitative trait locus (QTL), familial or background additive genetics, and residual effects. We corrected the ascertainment inherent in selecting the presence of lifetime AD in bivariate analysis using US lifetime prevalence estimates¹ (Kessler et al., 1994). Followed the suggestions of Lander and Kruglyak (Lander and Kruglyak, 1995) the importance of reporting all potential linkage regions exceeding a LOD score of 1, we reported these linkage peaks as regions of interests in Table 1.

3. Results

Comorbid MD diagnosis in males (70.5%) was not significantly different from that in females (72.6%). The correlation between ADsx and MDsx was modest ($r = 0.25$), in part reflecting the limited range of ADsx. Univariate linkage results for AD and ADsx phenotypes in the present sample have been published previously (Prescott et al., 2006). For univariate MD and MDsx linkage results, there were six regions (1q, 2p, 4q, 12q, 13q, and 22q) with multipoint LOD scores in excess of 1.00. The highest peak was on chromosome 4q32.3 near marker D4S2952 (LOD = 2.17, $p = 0.0008$) for MDsx. The highest linkage peak did not exceed a genome-wide significant level (Kruglyak and Lander, 1995).

Bivariate linkage analysis of MDsx–ADsx identified 22q11.21 with LOD score greater than 1, suggesting the possibility of susceptibility loci in this region that may exert pleiotropic effects on symptoms of MD among AD individuals. However, this peak exhibited high specificity for MDsx than ADsx, with MDsx/ADsx QTL variance ratio of ~100 at marker D22S427, which explained about 3.8% of the variance of MDsx and negligible for the variance of ADsx. Therefore, even if there were gene loci that increase the risk for AD at this region, their effects were too small to be meaningfully detected. For the six linkage regions aforementioned in univariate depression analyses, the MDsx/ADsx QTL variance ratio ranged from approximately 10–100. These regions exhibited specificity for depression rather than for severity of alcohol dependence.

4. Discussion

Using this IASPSAD sample, ascertainment and primary genome scan analyses focused on AD and alcohol-related traits (Kuo et al., 2006; Prescott et al., 2006); however, given twin data suggesting a significant genetic correlations between AD and MD (Prescott et al., 2000), conducting secondary analyses using this sample would also be informative for exploring the existence of chromosomal regions linked with MD. In this relatively large and culturally and ethnically homogeneous IASPSAD sample, we reported a few linkage regions of interests that may harbor genes for developing MD. Although none of them reached genomewide significance, the peaks for univariate MD and MDsx overlap with several regions identified in previous linkage studies for MD at 1q, 2p, 12q22, and 13q (Abkevich et al., 2003; Middeldorp

¹ For ascertainment correction, as the population prevalence data were not available for Ireland, we used US lifetime prevalence estimates of 20.2% for males and 8.2% for females (Kessler et al., 1994).

et al., 2008), for recurrent MD at 13q31.1–13q31.3 (McGuffin et al., 2005), and for recurrent early-onset MD at 1q43, 12q, and 13q (Zubenko et al., 2003). In addition, past studies have suggested for substantial overlap of the genetic factors influencing liability to a wide range of internalizing disorders (Hettema et al., 2006). Comparing our results to those from linkage scans of suicide attempts (Willour et al., 2007), neuroticism (Beem et al., 2006), bipolar disorder (Marcheco-Teruel et al., 2006), panic disorder (Gelernter et al., 2001), and anorexia nervosa (Devlin et al., 2002) indicates some overlap with our reported regions.

Regions obtained from linkage analyses can be used to identify candidate genes for further genetic analysis. Our strongest signal at 4q32.3 contains the NPY genes family that has been implicated in depression, such as NPY1R and NPY5R. NPY is an endogenous pro-neurogenic peptide with neuroprotective effect and plays important roles in stress regulation, anxiety, depression and epilepsy. Patients with depression show decreased NPY concentration in serum (Hashimoto et al., 1996) and the cerebrospinal fluid (Heilig, 2004). In addition, several familial candidate genes for psychiatric disorders locate within 5 Mb of the nearest marker for each peak of our linkage regions, including CHRM3 (1q43), TPH2 (12q21.1), COMT and MAPK1 (22q11.21), and ADRA2B (2p13–q13).

In sum, although the linkage evidence for our reported regions was not especially strong in terms of statistical significance, prior biological and genetic association evidence of a number of genes that located within these regions provides support for these linkage results. The aforementioned genes are plausible candidates that may confer genetic susceptible risk to depression or other emotional related traits.

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Table 1

Locations of markers in susceptible linkage regions with LOD score ≥ 1 for depression trait.

Chromosome	Marker	Position	cM	LOD_MD	LOD_MDsx	LOD_MDsx-ADsx
1	D1S2670	1q43	237.6	1.02 ($p = 0.019$)		
2	D2S388	2p11.2	85.9		1.04 ($p = 0.01$)	
4	D4S2952	4q32.3	166.7		2.17 ($p = 0.0008$)	
12	D12S1052	12q21.1	75		1.24 ($p = 0.008$)	
13	D13S271	13q31.1	84.3	1.00 ($p = 0.019$)		
22	D22S427	22q11.21	17.0			1.38 ($p = 0.02$)
	D22S1638	22q11.21	17.4	1.68 ($p = 0.003$)		

Note: Marker position was determined using the UCSC Genome Browser assembled in March 2006.
MD, major depressive disorder; MDsx, symptom counts of MD; and MDsx-ADsx, bivariate analysis for symptom counts of MD and AD.