Published in final edited form as:

Psychiatry Res. 2012 December 30; 200(0): 1044–1046. doi:10.1016/j.psychres.2012.06.001.

Association study of X chromosome SNPs in attempted suicide

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Abstract

We report the results of a high-density attempted suicide association study of the X chromosome, which genotyped 23,141 SNPs on 983 attempters and 1143 non-attempters and generated modest evidence for association for *SH3KBPI* ($P=1.07 \times 10^{-4}$) and *GRIA3* ($P=4.01 \times 10^{-4}$). These findings highlight the need for larger sample sets and meta-analytic approaches.

Keywords

Suicidal behavior; Sex chromosome; GWAS

1. Introduction

Heritability estimates for suicidality range from 30% to 50% (Brent and Mann, 2005; Mann et al., 2009). The heritable component of suicidal behavior can be attributed to the presence of psychiatric disorders, such as mood disorders, and also to the presence of independent heritable factors.

Genome-wide association studies for the attempted suicide phenotype have identified common variants associated with increased risk for this behavior (Perlis et al., 2010; Willour et al., 2011; Schosser et al., 2011). In addition, the secondary analyses identified loci with differential evidence for association in males and females (Willour et al., 2011).

Our initial study focused on SNPs from the autosomal chromosomes. In the current report, we extended our search for attempted suicide loci to the X chromosome by completing an

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psychres.2012.06.001.

association analysis of 23,141 X chromosome SNPs in 983 bipolar disorder (BP) attempters and 1143 BP non-attempters.

2. Methods

The 2126 unrelated European–American bipolar I disorder or schizoaffective disorder–bipolar type subjects that were included in our study were originally ascertained and assessed as part of the NIMH Genetics Initiative for Bipolar Disorder (see supplementary material for details). These samples were subsequently genotyped on the Affymetrix 6.0 SNP array (Affymetrix, Santa Clara, CA, USA), which contains 36,889 SNPs localizing to the X chromosome. After removing poor performing SNPs using standard filtering protocols (Willour et al., 2011), we identified 23,141 SNPs suitable for use in an association study. For our primary analysis, we employed PLINK's (Purcell et al., 2007) logistic regression option and an additive model to perform the association analysis, with the goal of comparing the genotype data from the entire set of 983 attempters to the 1143 non-attempters. We also included covariates representing the three principal components identified by EIGENSTRAT (EIGENSOFT 3.0 software package) and an additional variable distinguishing subjects in the two studies. For the secondary analyses, we stratified the sample by sex and repeated the logistic regression analyses, using 338 attempters and 533 non-attempters in the male analysis and 645 attempters and 610 non-attempters in the female analysis. We used $P < 5.0 \times 10^{-8}$ as the conventional threshold for genome-wide significance and $P < 2.16 \times 10^{-6}$ ($0.05 \div 23,141$) for study-wide significance. The SNP-to-gene annotation used both RefSeq and UCSC genes and was based on dbSNP Build 130 and NCBI build 36.

3. Results

The strongest signal from the association analysis using the entire sample set was located in *SH3KBP1* on Xp22.12 (rs5909133; OR 1.60; $P = 1.07 \times 10^{-4}$) (Table 1). *SH3KBP1* is an adapter protein that has recently been shown to facilitate dopamine receptor endocytosis (Shimokawa et al., 2010). While most of the remaining top ten SNPs map to an intergenic region on Xq22, rs695214 localizes to the *GRIA3* on Xq25 (rs695214; OR 1.58; $P = 4.01 \times 10^{-4}$). *GRIA3* is a glutamate receptor previously implicated in treatment—emergent suicide ideation (Laje et al., 2007; Menke et al., 2008).

Our secondary analyses, which were aimed at identifying sex-specific loci (Supplementary Table), produced non-overlapping top SNP lists. The strongest male signal localized to an intergenic region on Xq25 (rs6648629; OR 0.44; $P = 1.66 \times 10^{-4}$) and the strongest female locus localized to *SH3KBP1* (rs4825317; OR 0.59; $P = 2.23 \times 10^{-5}$).

4. Discussion

In this study, we tested for evidence of association between X chromosome loci and suicidal behavior in BP subjects. Our primary analysis provided modest evidence of association with *SH3KBP1* and *GRIA3*, and additional sex-specific loci were also identified. However, none of these findings met study-wide ($P < 2.16 \times 10^{-6}$) or genome-wide ($P < 5.0 \times 10^{-8}$) significance.

In their recent manuscript, Fiori et al. tested for evidence of association between 37 microsatellite markers and completed suicide in French–Canadian men, identifying two primary regions of association: Xp22–Xp11 and Xq24–Xq27 (Fiori et al., 2011). Our top two SNPs in the male-only analysis map to Xq25, with the second best SNP localizing to the *ODZ1* gene. Schosser et al. also investigated *GRIA3* as a candidate for suicidal behavior, identifying modest evidence for association ($P=0.0023$) that did not withstand correction for multiple testing (Schosser et al., 2011).

There were several limitations to our study. First, our sample size, while considerable, had 80% power to detect a locus of moderate effect (OR of 1.7). Thus, risk loci of smaller effect ($OR<1.7$) may have been missed. Furthermore, our analysis did not include environmental risk factors, which may interact with genetic factors to increase risk. In addition, our analysis, which focused solely on attempted suicide in bipolar disorder, may have missed attempted suicide risk loci specific to other psychiatric disorders, such as schizophrenia or major depression. Finally, we did not use narrower definitions of suicidal behavior, such as requiring subjects to have had high-lethality suicide attempts, which might have increased homogeneity and the evidence for association at specific loci, such as *MAOA*, which is located on Xp11 and has been associated with violent behavior (Brunner et al., 1993). However, narrower phenotype definitions would be most powerfully interrogated in larger sample sets.

Thus, while our analyses do not provide significant support for the presence of common suicidal behavior risk variants on the X chromosome, they do highlight the need for larger samples and meta-analytic studies to conclusively determine the existence and effect of X chromosome suicidal behavior risk loci.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants from the National Institute of Mental Health (MH079240 to V.L.W.) and the American Foundation for Suicide Prevention (V.L.W.).

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Table 1

Top 10 results from the primary X chromosome attempted suicide analysis.

SNP	Location (bp)	Minor/major allele ^a	Minor allele frequency ^b	Gene	Odds ratio ^c	P value
rs5909133	19795569	G/A	0.09	SH3KBP1	1.60	1.07×10^{-4}
rs839382	108740585	C/G	0.39		1.31	1.29×10^{-4}
rs844441	108745328	T/C	0.39		1.31	1.66×10^{-4}
rs12555996	108716207	G/T	0.40		1.30	2.86×10^{-4}
rs2347955	108698358	A/G	0.39		1.29	3.40×10^{-4}
rs839370	108716307	G/A	0.39		1.29	3.48×10^{-4}
rs695214	122224942	A/G	0.08	GRIA3	1.58	4.01×10^{-4}
rs1002116	108708407	G/A	0.39		1.29	4.05×10^{-4}
rs1547612	108710057	A/G	0.39		1.29	4.05×10^{-4}
rs942602	108698011	G/A	0.39		1.29	4.05×10^{-4}

^aThe minor allele as based on the HapMap phase I and II release 24 (<http://hapmap.ncbi.nlm.nih.gov/>) data is listed first.

^bThe frequency of the listed minor allele is calculated based on our combined two data sets.

^cThe odds ratio is provided for the listed minor allele from a logistic regression analysis under an additive model.