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Wolframin gene H611R polymorphism: No direct association with suicidal behavior but possible link to mood disorders ☆

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ABSTRACT

Wolframin gene polymorphisms, including the H611R polymorphism, are reportedly associated with mood disorders and psychiatric hospitalization, but there is disagreement about the association of this specific variant with suicidality and impulsive traits. This study tested the association of the H611R polymorphism with mood disorders, suicidal behavior, and aggressive–impulsive traits. Two hundred and one subjects with mood disorders and 113 healthy volunteers were genotyped for the H611R polymorphism and underwent structured interviews for diagnosis and clinical ratings. All were Caucasians. The H611R polymorphism was associated with mood disorders but not suicidal behavior, aggressive/impulsive traits or suicidality in first-degree relatives. The HR heterozygote genotype was more frequent in mood disorder ($\chi^2 = 7.505$; df = 2; $p = .023$). If this finding will be replicated, the H611R polymorphism may be a possible marker for mood disorders in a psychiatric population, and not just in relatives of Wolfram syndrome probands.

1. Introduction

Wolfram syndrome (WS), a rare autosomal recessive disorder, is caused by a mutation in the gene encoding wolframin (Inoue et al., 1998) on the short arm of chromosome 4 (4p16.1) (Polymeropoulos et al., 1994; Swift and Swift, 2000). Hundreds of sequence variations have been reported in the wolframin gene of which almost 200 appear to be mutations that cause the clinical WS in homozygotes and heterozygotes. Twenty-four mutations have been identified in the wolframin gene, most in exon 8 (Hardy et al., 1999), but dozens of variants in the coding region are benign (Cryns et al., 2003). In patients with WS who are homozygous or compound heterozygous for wolframin mutations, severe psychiatric symptoms were observed. First degree WS relatives had a high probability of carrying a single wolframin mutation and a statistically significant excess of psychiatric hospitalizations, suicidal behavior, completed suicides, and self-reports of mental illness, over spouse controls (Swift and Swift, 2005).

Sequeira et al. (2003) assessed the association of three common polymorphic variations of the wolframin gene (H611R, R456H and I333V) and found a higher frequency of the RR homozygotes but not heterozygotes of the H611R locus in suicide victims. RR genotype was also associated with higher impulsivity, higher novelty seeking and lower persistence (Sequeira et al., 2003). The H611R variant (A1832G), located in exon 8, represents an A/G polymorphism at locus 611, resulting in an amino acid substitution (histidine to arginine) in the wolframin protein. This variant is not associated with WS mutation (Cryns et al., 2003) but may still predispose individuals to psychiatric disorders.

Two studies did not replicate the association of depression or suicidality with the H611R locus (Furlong et al., 1999; Serretti et al., 2003). Furlong et al. (1999) found an association of the A559T heterozygosity with mood disorders but not with the H611R variant in bipolar I, major depressive disorder and control subjects. Serretti et al. (2003), assessed loci H611R, H456R and A559T using a family-based approach with trios of bipolar and unipolar probands and found no association with mood disorders.

This study reexamined the hypothesis that the H611R variant is associated with suicidal behavior and extends the clinical phenotype

Abbreviations: BDHI, Buss–Durkee Hostility Inventory; BDI, Beck Depression Inventory; BG, Brown–Goodwin Aggression Inventory; BHS, Beck Hopelessness Scale; BIS, Barratt Impulsiveness Scale; HAM-17, 17 item Hamilton Depression Rating Scale; PCR, polymerase chain reaction; SIS, Beck Suicide Intent Scale; WS, Wolfram syndrome.

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by quantifying suicidal behavior and including ratings of lifetime severity of impulsive–aggressive traits, and current severity of hopelessness and mood disorders, in a sample of mood disorder subjects and healthy volunteers.

2. Methods

2.1. Subjects

Subjects ($N=201$) were recruited from patients presenting to the research clinics of two university-affiliated psychiatric hospitals for evaluation and treatment of a mood disorder and their clinical and genetic data were used in few other studies on genetics of mood disorders and suicidal behavior . All subjects met DSM-IV criteria for a mood disorder. Healthy volunteers ($N=113$) were recruited through advertisements. Only Caucasian subjects of European origin were included to reduce ethnic variation and the degree of genetic stratification (Malhotra and Goldman, 1999). All subjects were physically healthy on medical evaluation, had no reported symptoms of WS and no known first-degree relatives with the disorder. Written informed consent was obtained and the study approved by the Institutional Review Board.

2.2. Clinical assessment

DSM-IV (APA, 1994) Axis-I and II diagnoses were based on the Structured Clinical Interview SCID-I (Spitzer et al., 1990) and SCID-II (First et al., 1996). Lifetime aggression was rated using the Brown–Goodwin Aggression Inventory (BG) (Brown and Goodwin, 1986), lifetime hostility using the Buss–Durkee Hostility Inventory (BDHI) (Buss and Durkee, 1957) and impulsivity using the Barratt Impulsiveness Scale (BIS) (Barratt, 1994). Depression was evaluated by the Beck Depression Inventory (BDI) (Beck and Steer, 1987) and the 17 item Hamilton Depression Rating Scale, (HAM-17) (Hamilton, 1960). Hopelessness was measured by the Beck Hopelessness Scale (BHS) (Beck et al., 1985). Lifetime suicide attempt history was recorded on the Columbia Suicide History Form (Oquendo et al., 2003), which records all suicide attempts chronologically, including documentation of the method and degree of medical damage. Lethality of the most severe lifetime suicide attempt was scored with the Beck Medical Damage Scale (Beck et al., 1985). Scores range from 0 to 8 with a score ≥ 4 indicating that medical hospitalization was needed. Suicidal intent was measured by the Beck Suicide Intent Scale (SIS) (Beck et al., 1985). Family history of suicide and suicide attempts, and other psychiatric and medical disorders, were recorded. For healthy volunteers, any Axis-I diagnosis on the SCID-NP (non-patient version), suicide attempt and a history of a first-degree relative with a mood or psychotic disorder were exclusion criteria.

2.3. Polymerase chain reaction (PCR)

The H611R polymorphism (dbSNP: 734312) was typed by PCR and *HhaI* restriction enzyme digestion, as described previously (Sequeira et al., 2003) with slight modification in reaction condition. Briefly, a PCR product of 139 bp was obtained using forward primer: 5′-GAGCTCACCAAGATCGCAGT-3′) and reverse primer: 5′-ACACCAGGATGAGCTTGACC-3′). PCR was carried out in a 20 µl volume, containing 100 ng DNA, 40 ng of each primer, 50 mM KCl, 10 mM Tris–HCl (pH 8.3), 2 mM $MgCl_2$, 0.01% gelatin, 200 µM of each dNTP, 4% DMSO, 10 µg BSA and 0.8 U of Red Tag DNA Polymerase (Fisher Scientific). Samples were processed in a Robocycler (Stratagene) and 30 temperature cycles were carried out, consisting of 30 s at 95 °C, 40 s at 56 °C, and 40 s at 72 °C, followed by a final extension step of 72 °C for 4 min. The PCR fragments were digested overnight with *HhaI* restriction enzyme (NE BioLab, MA). The digested PCR products were separated on a 2.5% agarose gel. The assays were carried out blind to clinical status.

2.4. Statistical analysis

SPSS statistical software, edition 12.0 for Windows (2003) by SPSS Inc, Chicago IL was used. Pearson's χ^2 analyses analyzed frequencies of genotypes in clinical subgroups. Student's *t*-test and analysis of variance (ANOVA) compared continuous variables (e.g. rating scales, age) by categorical independent variables (e.g. genotypes, groups), using Bonferroni correction for multiple testing. Power analysis was performed in order to evaluate the power of the sample to detect association to family history of suicidality and mood disorders in first-degree relatives. All tests were two-tailed. Data are reported as mean ± S.D.

3. Results

3.1. Descriptive

The mood disorder group ($N=201$) included 140 (69.7%) females. The mean age was 41.0 ± 14.4 years, 39.4% were married and 42.1% had at least some college education. The primary diagnoses were: major depressive disorder with current major depressive episode ($N=160$, 79.6%) and bipolar disorder with depressed mood ($N=41$, 20.4%). Sixty-eight subjects (33.8%) had attempted suicide at least once. The median lethality score on the Medical Damage Scale for the most lethal attempt for each attempter was 3.0 (range 0–8). Ten subjects (14.9% of attempters) had a lethality score of 7, the highest score possible following a non-lethal attempt. The most frequent methods for suicide were sedative (64.5%) and non-sedative (14.1%) overdoses.

3.2. H611R polymorphism and mood disorders

No significant differences in genotype frequencies were found when comparing across diagnostic subgroups within the mood disorders (major depression or bipolar disorder). Genotype distribution in bipolar disorder was comparable to major depression ($\chi^2=1.42$; df = 2; $p=.49$) (Table 1) and, therefore, subgroup diagnosis was not controlled for in the analyses.

The distribution of genotypes did not deviate from the Hardy–Weinberg equilibrium for the control subjects ($\chi^2=1.03$; df = 1; $p=.31$), and the mood disorder group had an overrepresentation of heterozygotes ($\chi^2=4.32$, df = 1, $p=.04$).

Frequencies of the genotypes differed between the mood disorder and control groups ($\chi^2=7.505$; df = 2; $p=.023$) (Table 1). Inspection of the table suggests that the group difference in genotype is because the HR heterozygote genotype is more prevalent in the mood disorder group and the HH genotype less prevalent.

Table 1
Wolframin (H611R) genotype frequencies in mood disorders subjects and controls.

Phenotype		Genotype *N* (%)			Statistics	
Group		HH	HR	RR	χ^2 (df)	*p*
Controls	($N=113$)	49 (43.4%)	47 (41.6%)	17 (15.0%)	7.50 (2)	.023*
Mood disorders	All ($N=201$)	58 (28.9%)	113 (56.2%)	30 (14.9%)		
	Bipolar disorder ($N=41$)	14 (34.1%)	23 (56.1%)	4 (9.8%)	1.42 (2)	.491
	Other mood disorders ($N=160$)	44 (27.5%)	90 (56.3%)	26 (16.3%)		
	Attempters ($N=68$)	17 (25.0%)	41 (60.3%)	10 (14.7%)	0.71 (2)	.701
	Non-attempters ($N=132$)	40 (30.3%)	72 (54.5%)	20 (15.2%)		

*$p<.05$.