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Polymorphisms in the Serotonin Receptor Gene HTR2A Are Associated With Quantitative Traits in Panic Disorder

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Anxiety disorders and specifically panic disorder (PD) are caused by complex interactions of environmental and genetic factors. The latter comprise many different genes, from which those involved in serotonergic neurotransmission have received particular attention. Here we report the results from an association candidate-gene approach, where we analyzed 15 single nucleotide polymorphisms (SNPs) within the gene coding for the serotonin-receptor 2A (HTR2A) in patients suffering from PD and a control sample. We found that the SNP rs2296972 shows an association between the number of T-alleles and severity of symptoms in PD. By performing tests according to the Fisher product method (FPM), an association between HTR2A and the personality trait reward dependence could be shown. Most pronounced effects were observable for the SNPs rs2770304, rs6313, and rs6311. Furthermore, the polymorphisms rs3742278, rs2296972, and rs2770292 form a haplotype, which may be associated with higher susceptibility for PD. These results further underline a possible important role of genetic variations within the system controlling serotonergic neurotransmission for the development and course of disease in PD. © 2007 Wiley-Liss, Inc.

KEY WORDS: genetics; anxiety; psychiatry; association; SNP

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INTRODUCTION

Panic disorder (PD) is an anxiety disorder characterized by recurrent attacks of intense fear whereas frequency and severity of the attacks varies between patients. Typically, symptoms such as palpitations, dyspnea, chest pain, or fear of dying are included. Agoraphobia often coincides with PD and is defined by a cluster of phobias embracing fears about being in situations, from which escape might be difficult. Avoidance behavior in the context of agoraphobia often results in considerable limitations concerning job-related issues and social life of the patient. Life-time prevalences of PD between 0.4% and 2.9% have been described for different countries and cultures [Weissman et al., 1997; Narrow et al., 2002]. Twin and family studies on genetic epidemiology of PD and related behavioral phenotypes show an estimated heritability of about 50% [Hettema et al., 2001; Kessler, 2002]. Inheritance does not follow a mendelian pattern, but suggests a complex interplay of different genetic variants and environmental conditions [Vieland et al., 1996]. Several studies have examined disturbances of serotonergic signaling in the context of anxiety disorders [Abrams et al., 2005; Keck et al., 2005b]. Particularly alterations in the serotonin-receptor 2A (HTR2A) gene and expression have been suggested as risk factors for the development of affective disorders [Massou et al., 1997; Islam et al., 2004]. The gene coding for HTR2A spans over 20 kb, it is located on chromosome 13q14-q21 and consists of three exons and two introns [Chen et al., 1992]. Recent studies on a possible association of genetic variants of HTR2A and PD phenotypes, however, have yielded inconclusive results. In Estonian and Japanese samples a significant association between the diagnosis PD and the rs6313 polymorphism within HTR2A could be shown [Inada et al., 2003; Maron et al., 2005]. A study analyzing Caucasians from Canada and Germany, in contrast, found no evidence for this association [Rothe et al., 2004]. In order to elucidate reasons for these inconsistent results we conducted a further case-control study with 154 German PD patients, but extended this approach by additionally considering information about disease severity and about personality traits discussed as predisposing for the development of PD [Ampollini et al., 1999; Johnson et al., 2006; Ongur et al., 2005].

METHODS

Patients

The PD sample consisted of 154 consecutive referrals to our Anxiety Disorders Outpatient Clinic for diagnosis and treatment of PD with agoraphobia (87.4%) or PD without agoraphobia (12.6%), as their primary psychiatric diagnoses (Table I). Anxiety disorders due to a medical or neurological condition were exclusion criteria. Patients who suffered from generalized anxiety disorder, depressive symptoms or presented with a comorbid axis II disorder at the time panic attacks started were excluded from this study. Diagnosis was ascertained by trained psychiatrists according to the

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TABLE I. Composition of the Examined Patient and Control Sample, Matched for Age and Gender

	N	Mean age	SD	Sex (% women)
Controls	347	38.2	10.6	68.6
PD patients	154	39.8	12.5	70.8

Structured Clinical Interview for DSM-IV (SCID) [First et al., 1997]. All patients underwent a clinical examination including EEG, ECG, detailed hormone laboratory assessment and most received cranial nuclear magnetic resonance imaging. Additionally, each PD patient underwent standardized tests for personality traits (TPQ [novelty seeking, harm avoidance (HA) and reward dependence; Cloninger, 1987; German version: Weyers et al., 1995] and EPQ-RK [psychoticism, extraversion, and neuroticism; Eysenck and Eysenck, 1991; German version: Ruch, 1999]), which were conducted during a time period where no panic attacks had occurred for at least 2 weeks. For assessment of severity of PD the "Panic and Agoraphobia scale" (PAS) total score was used reflecting the symptoms during the worst episode [Bandelow, 1995]. Self-reported ethnicity was recorded using a questionnaire asking for nationality, first language, and ethnicity of the subject and all four grandparents. All patients were Caucasian and 87% of German origin.

Controls

A control sample (n = 347) matched for ethnicity, sex, and age of the PD patient sample was recruited (Table I). Controls were selected randomly from a Munich-based community sample and screened for the absence of anxiety and affective disorders using the Composite International Diagnostic Screener [Wittchen, 1999]. Only individuals negative in the screening questions for the above-named disorders were included in the sample. Controls were not tested for personality traits and PAS was not applied.

The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians University in Munich and is compliant with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all subjects.

DNA Preparation

On enrolment in the study, 40 ml of EDTA blood was drawn from each participant and DNA was extracted from fresh blood using the Puregene whole blood DNA-extraction kit (Gentra Systems, Inc., Minneapolis, MN).

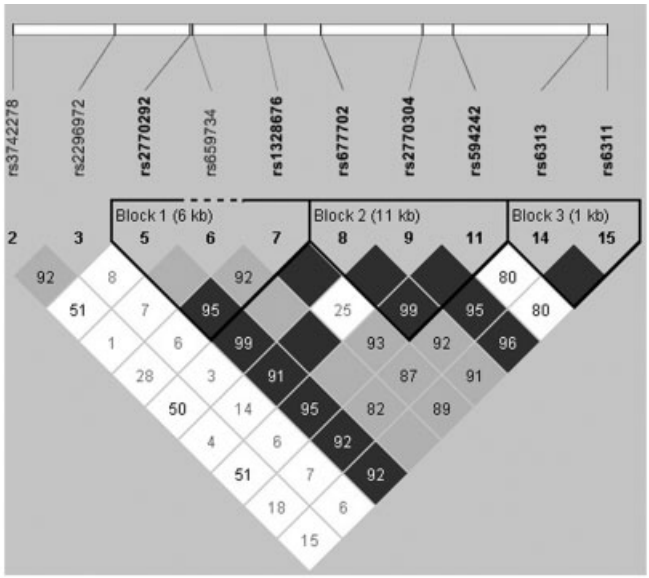
Single Nucleotide Polymorphism (SNP) Selection and Genotyping

A total of 15 SNPs within the HTR2A-gene were selected from publicly available databases (e.g., dbSNP http://www.ncbi.nlm.nih/). A SNP search tool developed at the Institute for Human Genetics, Technical University Munich and GSF-National Research Centre for Environment and Health, was used to download SNP sequences (http://ihg.gsf.de/ihg/snps.html). For all SNPs the July 2003 Human Reference Sequence (hg16, University of Santa Cruz, http://genome.ucsc.edu/) was used. Genotyping was performed on a MALDI-TOF mass-spectrometer (MassArray® system) with the Spectrodesigner software package (Sequenom™, San Diego, CA) for primer selection and the homogeneous mass-extension process for producing primer extension products [Binder et al., 2004]. Only unambiguous results from spectroscopy were used for further analysis, resulting in a lower number of tested patients and controls than primarily

TABLE II. Analyzed SNPs of the HTR2A-Gene

SNP-ID	Position on Chr 13	Function	Alleles	Amino acid exchange	Observed heterozygosity		Predicted heterozygosity according to HWE		HWE *P*-value		% Genotyped		Minor allele frequency		Used for analysis (Y/N)
					Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	
rs6308	46307049	Coding on exon 3	C/T	V/T	0	0	0	0	1	1	99.6	99.2	0	0	N
rs3742278	46317578	Intron	A/G	—	0.225	0.317	0.206	0.289	0.299	0.499	98.3	98.4	0.117	0.175	Y
rs2296972	46326472	Intron	G/T	–	0.419	0.421	0.423	0.421	0.978	1	99.6	99.2	0.303	0.302	Y
rs2246127	46328480	Intron	C/T	—	0.463	0.25	0.45	0.469	0.864	0.434	69.8	6.6	0.341	0.375	N
rs2770292	46333107	Intron	C/G	—	0.364	0.35	0.339	0.349	0.387	1	98.3	98.4	0.216	0.225	Y
rs659734	46333284	Intron	C/T	—	0.082	0.108	0.079	0.102	1	1	98.3	98.4	0.041	0.054	Y
rs1328676	46339610	Intron	C/G	—	0.45	0.469	0.432	0.443	0.66	0.729	98.3	92.6	0.316	0.332	Y
rs677702	46344499	Intron	C/T	—	0.352	0.339	0.332	0.334	0.504	1	99.1	96.7	0.21	0.212	Y
rs2770304	46353366	Intron	C/T	—	0.429	0.496	0.431	0.428	1	0.149	98.3	92.6	0.314	0.31	Y
rs1475196	46353624	Intron	G/T	—	0	0	0	0	1	1	98.3	93.4	0	0	N
rs594242	46356053	Intron	C/G	—	0.368	0.363	0.374	0.368	0.909	1	98.3	92.6	0.249	0.243	Y
rs2070035	46364450	Intron	A/C	—	0	0	0	0	1	1	99.6	100	0	0	N
rs6304	46364550	Coding on exon 2	A/G	V/I	0	0	0	0	1	1	99.6	100	0	0	N
rs6313	46367941	Coding on exon 1	C/T	S/S	0.509	0.509	0.487	0.487	0.602	0.803	98.7	95.1	0.418	0.418	Y
rs6311	46369479	Promoter	C/T	—	0.506	0.513	0.486	0.484	0.648	0.683	98.3	95.9	0.418	0.41	Y

Positions according to the July 2003 Human Reference Sequence (UCSC Version hg16; http://genome.ucsc.edu/). All SNP Information was retrieved from dbSNP (http://www.ncbi.nlm.nih.gov/) and GeneCards (http://www.genecards.org).



R-square-values for pairwise measures

	rs2296972	rs2770292	rs659734	rs1328676	rs677702	rs2770304	rs594242	rs6313	rs6311
rs3742278	0.058	0.012	<0.01	<0.01	0.011	<0.01	0.014	<0.01	<0.01
rs2296972		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
rs2770292			0.013	**0.541**	**0.958**	0.107	**0.779**	0.177	0.175
rs659734				0.085	0.013	0.102	0.015	0.023	0.033
rs1328676					0.57	0.014	**0.598**	0.264	0.27
rs677702						0.121	**0.816**	0.169	0.167
rs2770304							0.149	0.302	0.31
rs594242								0.154	0.151
rs6313									**0.994**

Fig. 1. Linkage disequilibrium (LD) -analysis of ten polymorphic SNPs (Table II) using HAPLOVIEW. R^2-values are indicated for pairwise measures [Barrett et al., 2005]. Pairs of SNP with evidence for strong LD are colored dark grey, for minor LD light grey and those with evidence for recombination are marked white, numbers indicate D-prime values. LD blocks are displayed representing 95% confidence bounds on D' [Gabriel et al., 2002]. In the table below the corresponding r^2-values are listed, values >0.5 are typed in bold.

genotyped. Thus in the haplotype analysis the number of completely genotyped sets of SNPs was 220 for the controls and 121 for the patients. Genotyping was performed at the Genetic Research Center GmbH, Munich, Germany. All primer sequences are available upon request.

Statistical Analysis

HAPLOVIEW [Barrett et al., 2005] was used for pairwise calculations of linkage disequilibrium (LD) and generation of 95% confidence bounds on D-prime (D′) [Gabriel et al., 2002]. The Fisher product method (FPM) with 1,000 permutations was used for combining tests [Fisher, 1932]. All haplotype analyses were performed using the COCAPHASE and QTPHASE modules of UNPHASED [Dudbridge, 2003]. To correct for multiple testing, a sliding-window approach was applied. Nominal *P*-values were multiplied by the overall number of tests performed on the analyzed SNPs (all possible haplotype combinations and FPM, n = 56).

RESULTS

Within the HTR2A-gene a total of 15 SNPs with an average distance of 4.5 kb were genotyped. Allele frequencies were tested for consistency with Hardy–Weinberg equilibrium (HWE) both in the patient and the control sample (Table II). Those 10 SNPs which were polymorphic, were tested for associations with the clinical diagnosis PD, severity of PD as measured with PAS, and associations with personality traits. HAPLOVIEW calculation of pairwise measurements of LD between all SNPs revealed three LD blocks [Gabriel et al., 2002] and a r-square value of 0.058 for the two SNPs rs3742278 and rs2296972 (Fig. 1).

Single-locus analysis according to the allele-dosage model showed a monotone association between the number of T-alleles of the intronic SNP rs2296972 and severity of PD (nominal *P*-value: 0.00051, corrected *P*-value: 0.029, see Fig. 2). Multi-allelic haplotype analysis did not show significant associations of other examined polymorphisms within HTR2A for disease severity and combining testing according to the FPM [Fisher, 1932] did not yield a significant result either.

Personality of the patients was evaluated with the standardized personality questionnaires EPQ-RK and TPQ. By applying the FPM [Fisher, 1932], an association between the 10 polymorphic SNPs within HTR2A and TPQ measurements of the personality trait reward dependence (RD) could be shown (*P*-value after 1,000 permutations: 0.013). The most profound effects within HTR2A were observable for the SNPs rs2770304, rs6313, and rs6311. For rs2770304 a nominal *P*-value of 0.0006 resulted ($P = 0.034$ after correction for multiple testing, Fig. 3). As described earlier [Spurlock et al., 1998] and consistent with our calculations of LD, the silent

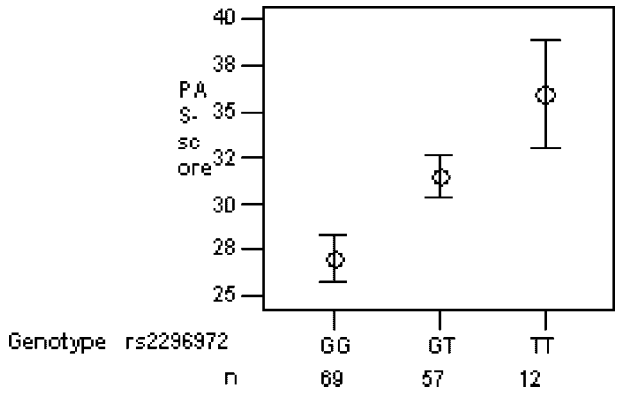


Fig. 2. The Number of T alleles of rs2296972 is associated with increasing severity of PD (P-value after correction for multiple testing = 0.029, n = 138). Displayed are mean PAS-values ± 1 SE.

exonic SNP rs6313 and the −1438 promotor polymorphism rs6311 are almost in complete LD ($r^2 = 0.98$, Fig. 1). Results of a single-locus analysis suggested a monotone association between the number of T-alleles and psychometric values of the TPQ personality trait RD for both rs6313 and rs6311 (nominal P-value: 0.009, significance was lost after correction for multiple testing, Fig. 3). Analysis of multi-allelic haplotypes did not reveal significant associations.

By performing a single-locus analysis according to the allele-dosage model, a nominal association between the intronic SNP rs3742278 and the clinical diagnosis PD could be detected (nominal P-value 0.011, OR 1.8), but significance was lost after correction for multiple testing. Haplotype analysis showed an association of the intronic SNPs rs3742278, rs2296972, and rs2770292 to the clinical diagnosis PD. The most pronounced effect is present for the haplotype G_G_C with an odds ratio of 2.53 against A_G_C for development of PD (Table III). The nominal P-value for this association was 0.01, after correction for multiple testing significance was lost. Combining testing according to the FPM [Fisher, 1932] did not show significant associations with cases and controls.

DISCUSSION

We here report associations of different quantitative traits in PD with polymorphisms of the HTR2A-gene.

Analysis of the SNP rs2296972 showed an association with severity of symptoms ($P = 0.029$). PD patients, who reported more severe symptoms, tended to have the less frequent allele suggesting a gene-dose effect (Fig. 2). An analysis of multi-allelic haplotypes did not increase significance of the mentioned association with disease severity. The fact, that combining testing with the FPM did not yield a significant association either and rs2296972 is an intronic SNP, might indicate LD with a causal variant at a locus still to be identified.

Furthermore, we find an association of the 10 polymorphic SNPs within HTR2A (Table II) with the personality trait RD ($P = 0.013$ after correction for multiple testing) by using combining testing according to the FPM [Fisher, 1932]. Within HTR2A the strongest single-locus associations were observable for the intronic SNPs rs2770304, rs6313, and rs6311 (Fig. 3). Even so, most studies suggest HA as a possible vulnerability factor for PD [Saviotti et al., 1991; Wiborg et al., 2005]. RD was reported as altered in PD only in few studies [Ampollini et al., 1999; Ongur et al., 2005]. One possible explanation for our finding of genetic association with RD but not with HA might be the inclusion criteria of our sample. Since HA has been discussed as associated with the presence of personality disorders [Mulder et al., 1999], our sample

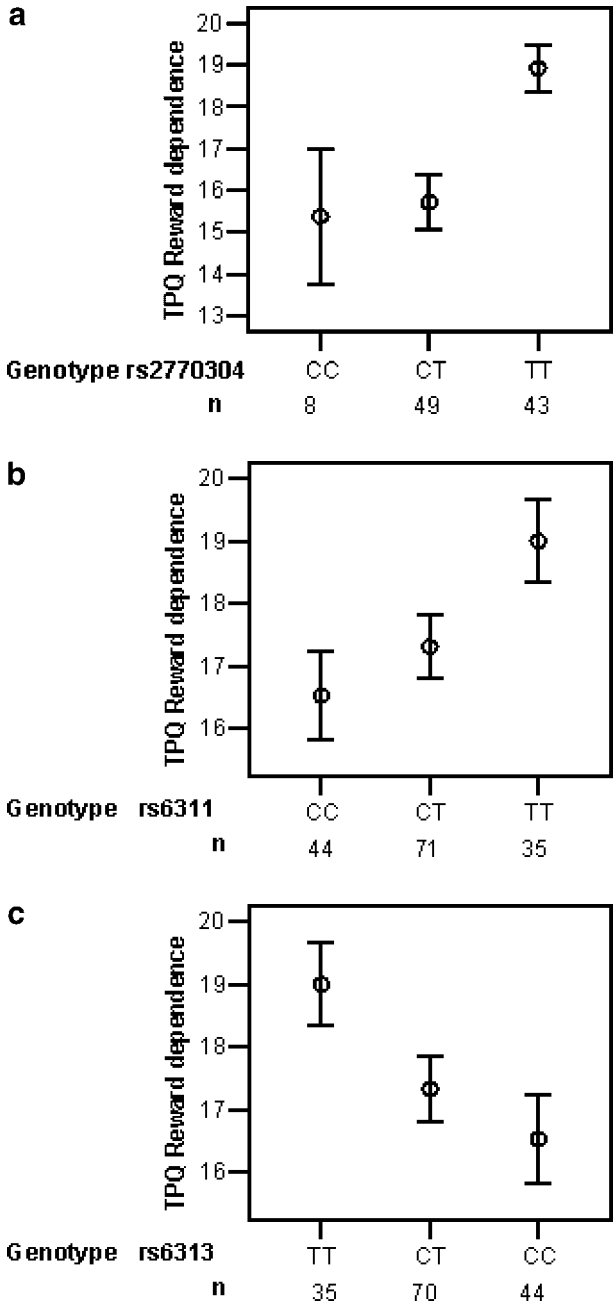


Fig. 3. Allele-associations of the SNPs rs2770304, rs6311 and rs6313 with TPQ-scores for the personality trait RD. Displayed are mean TPQ-RD - values ± 1 SE. rs2770304: P-value after correction for multiple testing = 0.034; n = 100. rs6313 and rs6311: nominal P-values = 0.009; not significant after correction for multiple testing; n = 149 and 150.

selection might explain the lack of associations with HA, as comorbid axis II disorders were an exclusion criteria. For anxiety-related personality traits associations of genetic polymorphisms have been described so far for the GABA(A) alpha 6 receptor, literature for associations with the serotonin transporter gene promoter (5-HTTLPR) is controversial [Lesch et al., 1996; Ebstein et al., 2002; Lang et al., 2004; Sen et al., 2004b]. A meta-analysis on the role of 5-HTTLPR variations in anxiety-related personality scores confirmed associations with the personality trait neuroticism [Sen et al., 2004a].

TABLE III. Haplotype Analysis of the SNPs rs3742278, rs2296972, and rs2770292, Reference Haplotype Is A_G_C, DF = 6, LRS = 16.779, Nominal *P*-value = 0.010 (Significance Is Lost After Correction for Multiple Testing)

	Controls		PD patients		
Haplotype	N = 220	Rel. frequency	N = 121	Rel. frequency	OR
A_G_C	104	0.46	44	0.36	1
A_G_G	29	0.13	21	0.17	1.75
A_T_C	56	0.24	29	0.24	1.25
A_T_G	14	0.06	6	0.05	1.02
G_G_C	21	0.09	22	0.18	2.53
G_G_G	5	0.02	0	0	n.a.
G_T_C	0	0	1	0.01	n.a.

In terms of case-control associations, a haplotype combination with an odds ratio of up to 2.53 resulted, which comprised the intronic SNPs rs3742278, rs2296972, and rs2770292 (Table III). However, after correction for multiple testing this association turned out to be not significant. A single-allele association of the SNP rs3742278 with the clinical diagnosis of PD does not reach the level of significance either after correction for multiple testing. For Estonian and Japanese patient samples [Inada et al., 2003; Maron et al., 2005], associations to the clinical diagnosis PD have been described for the synonymous exonic SNP rs6313, which is in complete LD to the promoter polymorphism rs6311 [Spurlock et al., 1998]. In a Caucasian patient sample from Canada and Germany, however, no evidence for this association could be found [Rothe et al., 2004]. A recent linkage study could identify a LD for PD in the chromosomal region 13q, which also comprises the HTR2A-gene [Hamilton et al., 2003]. Our failure to observe an association between rs6313 and the diagnosis PD is consistent with the study by Rothe et al. [2004]. We suppose, that the discrepancy between our data and the results from Japanese and Estonian patients, where an association between clinical diagnosis of PD with the SNP rs6313 could be observed [Inada et al., 2003; Maron et al., 2005], is most probably an effect due to the different ethnic backgrounds of the patient samples and thus difference in LD structure.

Recent studies demonstrated the interference of serotonin-neurotransmission with the endocrine stress reaction, indicating a possible key function of HTR2A. For rats it has been reported, that application of an HTR2A-agonist results in increased secretion of ACTH and corticosterone in limbic brain areas [Van de Kar et al., 2001]. Moreover, glucocorticoid receptors may have a repressive role concerning activation and expression of HTR2A [Islam et al., 2004]. Dysfunction of the HPA system and the subsequent disbalance of different neuroendocrine parameters, such as central serotonergic neurotransmission, have been shown to play a central role in the development of affective disorders, including PD [Holsboer, 2000a,b; Keck et al., 2005a]. The close connection between serotonin metabolism and HPA-axis is further underlined by the efficacy of SSRIs for treatment of PD [Heydorn, 1999].

The findings presented in this study suggest the involvement of serotonin transmission and in particular HTR2A genotype with the risk to develop PD, disease severity, and reward dependence in PD. Only Caucasian patients were included in order to minimize genetic heterogeneity and all significant SNPs showed allele frequencies consistent with HWE. Our finding of associations between SNPs of the HTR2A-gene with different anxiety-related phenotypes appears to be in line with earlier reports. Discrepancies with the studies published by Inada et al. [2003] and Maron et al. [2005] regarding the associated loci within HTR2A are possibly due to differences in LD structure as ethnically different populations were examined. Further finemapping and resequencing of this region seems promising to identify a possible causal variant in LD with so far known associated loci.

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