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The trace amine associated receptor (*TAAR6*) gene is not associated with schizophrenia in the Irish Case-Control Study of Schizophrenia (ICCSS) sample

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ABSTRACT

To replicate previous association between *TAAR6* and schizophrenia, including our own finding in the Irish Study of High Density Schizophrenia Families (ISHDSF) sample, we genotyped 12 single nucleotide polymorphisms (SNPs) in the Irish Case-Control Study of Schizophrenia (ICCSS) sample. Only rs9389020 provided nominal evidence for association ($p<0.0228$), which did not withstand the permutation testing ($p<0.2196$). The combined odds ratio from ISHDSF and ICCSS samples [OR (95%CI)=1.0564 (1.0078-1.1074); $p=0.02$], while nominally significant, did not survive correction for multiple testing. Here we demonstrate that *TAAR6* is not associated with schizophrenia in the ICCSS sample.

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1. Introduction

The *TAAR6* gene, located on 6q23.2, has been reported to be associated with schizophrenia (SCH) and bipolar (BP) illness, but the results remain inconclusive (Duan et al., 2004; Jamra et al., 2005). Duan et al. (2004) were first to report a positive association between *TAAR6* and SCH in North American Caucasian and African-American families. Another study found a positive association between BP and *TAAR6* in a German case-control sample (Jamra et al., 2005). A third positive association between *TAAR6* and SCH and BP was reported from a Korean case-control sample (Pae et al., 2008). Similarly, Vladimirov et al. (2007) observed a nominally significant positive association on single marker and haplotypic levels between *TAAR6* and SCH in the Irish Study of High Density Schizophrenia Families (ISHDSF) (Vladimirov et al., 2007).

Alongside these positive reports, several studies reported no association between *TAAR6* and SCH or BP in a Chinese family based study (Duan et al., 2006), a Japanese case-control study (Ikeda et al., 2005), an Arab-Israeli family sample (Amann et al., 2006), a Caucasian family sample(Liu et al., 2007) and another large case-control sample from European ancestry(Sanders et al., 2008). The discrepancies in these observations require further study in order to explore the involvement of this gene as a liability factor for SCH.

Here we attempted to replicate our recently reported positive association between *TAAR6* and SCH in a second Irish Case-Control Study of Schizophrenia (ICCSS) sample. We identified one marker, rs9389020, to be nominally associated with SCH which did not remain significant after permutation testing.

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2. Methods and materials

2.1. Marker selection and genotyping

Based on the linkage disequilibrium (LD) pattern, twelve SNPs covering a region of 71.5 kb were selected for genotyping and analyzed for association with SCH. Polymorphisms with previously reported signals (rs4305745, rs6933874, rs6937506, rs12189813, and rs9389011) were also included in the analysis (Table 1). A high throughput genotyping method based on multiplex PCR and SNP analyses were performed with the GenomeLab SNPstream genotyping platform (Beckman Coulter Inc. Fullerton, CA) and its accompanying SNPstream software suite. The average genotyping success was 97.4%. Hardy-Weinberg equilibrium (HWE) was assessed for all markers using HAPLOVIEW v4.0 and, no deviations were observed. Definition of LD blocks was based on the confidence interval method using the Haploview default settings (Gabriel et al., 2002).

2.2. Sample

The ICCSS sample is composed of 627 affected cases and 1021 controls. Affected subjects were collected from in- and out-patient psychiatric facilities in the Republic of Ireland and Northern Ireland and were eligible for inclusion if they had a diagnosis of SCH or have poor-outcome schizoaffective disorder (PO-SAD) by DSM-III-R criteria. Controls were selected from several sources, including blood donation centers and were included if they denied a lifetime history of SCH. Both cases and controls were included only if they reported all four grandparents as being born in Ireland and/or United Kingdom.

2.3. Statistical analysis and power calculation

The single-marker association analysis was performed using HAPLOVIEW v4.1. In addition to reconstructing haplotypes and providing case and control frequencies, the newest implementation includes a permutation test (set at 10000 for these analyses) to assess empirical significance. The haplotype association analysis was performed using the log-likelihood ratio test implemented in UNPHASED version 3.0.611(Dudbridge, 2003).

In order to derive a summary statistic for rs93989020 across this and our previous study (Vladimirov et al., 2007), we applied a fixed-effects approach to combining odds ratios (Mantel and Haenszel, 1959). For the family-based studies, a Haplotype-based Haplotype Relative Risk (HHRR) design was used (Falk and Rubinstein, 1987; Terwilliger and Ott, 1992). The HHRR statistic compares the number of times a given parental allele ('risk' allele) is transmitted versus non-transmitted. In population based samples, we construct an odds ratio comparing case to control allele frequencies. The equivalence of odds ratios generated from family and population-based studies has been previously addressed (Kazeem and Farrall, 2005).

Power analysis was performed using procpower implemented in SAS9.1v and shows that this sample has 80% power to detect association with odds ratios of 2.3 and 1.5 for allele frequency of 0.1 and 0.5, respectively.

3. Results

The major allele of rs8192624, rs8192625 rs12189813 and rs9389011 were reported to be associated with SCH and BP (Duan et al., 2004; Jamra et al., 2005; Vladimirov et al., 2007). In our study on a single marker level, only rs9389020 shows nominal evidence for association ($\chi 2 = 5.508$, df = 1, $p = 0.0228$), and rs9389011 shows a trend ($\chi 2 = 3.07$, df = 1, $p = 0.0782$). These two polymorphisms, located 70 kb and 42 kb telomeric from *TAAR6*, are in low LD with each other and not in LD with markers in the *TAAR6* gene. The four markers located in *TAAR6* (Table 1) did not show any evidence for association.

The HapMap and the ICCSS sample data show a similar LD pattern (Fig. 1A and B) of the region, which is characterized by two LD blocks interspersed with regions of very low LD. The first LD block consists of four markers located telomeric from *TAAR6* and centromeric from *TAAR5*. Of these, rs4305745 was originally identified as associated with SCH (Duan et al., 2004). The second LD block consists of two markers flanking the TAAR2 gene. Of these, rs9389011 was reported to be nominally associated with SCH by Vladimirov et al. (2007).

In this study the haplotype analysis was conducted in two stages: in the first stage rs8192622, rs8192624, rs8192625 and rs7772821 markers located in the *TAAR6* gene were tested for an association in two, three and four haplotype

Table 1

Name	Position (bp)	Obs HET	Pred HET	HW pval	%Geno	MAF	SNP alleles	Case-control freq.	Chi square	*P* value	Perm P
rs8192622	132933231	0.093	0.091	0.5811	99.6	0.048	C>T	0.051–0.042	1.214	0.2705	0.9472
rs8192624	132933946	0.148	0.149	0.9402	99.4	0.081	G>A	0.085–0.074	1.179	0.2776	0.9524
rs8192625	132934025	0.137	0.134	0.5652	97	0.072	G>A	0.073–0.071	0.081	0.7756	1
rs7772821	132934199	0.234	0.242	0.2459	97.8	0.141	T>G	0.143–0.137	0.238	0.626	0.9998
rs4305745	132935405	0.507	0.496	0.4258	95.6	0.455	A>G	0.456–0.453	0.041	0.8401	1
rs6903874	132938603	0.313	0.318	0.5919	95.9	0.198	T>C	0.202–0.190	0.66	0.4166	0.9938
rs7765655	132939551	0.374	0.372	0.9454	95.9	0.247	G>A	0.755–0.749	0.147	0.7013	1
rs3813354	132952327	0.151	0.15	0.7635	99.2	0.081	G>A	0.920–0.916	0.216	0.6422	1
rs12189813	132969195	0.494	0.476	0.1518	98.2	0.39	G>C	0.391–0.390	0.02	0.9896	1
rs9389011	132976272	0.33	0.362	0.011	94.5	0.237	T>C	0.773–0.744	3.102	0.0782	0.5454
rs9389015	132985129	0.488	0.498	0.4612	97.1	0.468	C>T	0.476–0.452	1.75	0.1859	0.851
rs9389020	133004746	0.4	0.416	0.127	98.6	0.295	T>C	0.719–0.680	5.185	0.0228	0.2196

On single marker analysis level only rs9389020 located telomeric from *TAAR2* gave a nominal evidence for an association which does not survive permutation testing. The permuted *P* value is a result of 10000 permutations.