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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.

Keywords

SCH; association; *TAAR6*; gene; case-control; sample

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 and co-workers (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).

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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.

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 rs9389020 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 70kb 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 (Figure 1A and 1B) 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 and colleagues (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 combinations respectively. No significant haplotype association was observed. Similarly, the markers defining the first and second LD blocks were tested for association and again no haplotype was significantly associated with SCH within each individual set of analyses (data not shown). In the second stage of analysis we have used rs9389020 which shows nominal significance for association as an anchor in combination with SNP markers in the *TAAR6* gene. This approach has been successfully applied to identify significant haplotypes (Duan et al., 2004; Liu et al., 2007; Vladimirov et al., 2007). The anchored haplotype analyses show all three markers in *TAAR6* to be associated with SCH when analyzed in combination with rs9389020 (Suppl. Table 1). All associated haplotypes were composed of the minor allele at rs8192622, rs8192624 and rs8192625 and the major allele of rs9389020. However, none of these haplotypes withstand permutation testing, possibly due to low observed frequency in cases (0.028%) and in controls (0.015%).

Since in ISHDSF rs9389020 gave a trend towards association we performed combined analysis (ISHDSF and ICCSS samples) to establish if the increased power will strengthen the observed association. The combined odds ratios from the family-based [OR (95%CI) = 1.0362 (0.8350–1.286)] and population-based [OR (95%CI) = 1.0581 (1.0086–1.110)] samples yielded a combined odds ratio [OR (95%CI) = 1.0564 (1.0078–1.1074); $p=0.02$], which while nominally significant, did not survive any approach to correction for multiple testing.

4. Discussion

TAAR6 is in a region where most markers are in very low LD with each other, which is consistent with the LD map of this locus retrieved from the HapMap project (Figure 1B). During the course of this work several independent studies attempted to replicate the original finding for association between *TAAR6* and SCH. Of these five were negative and four were positive. The first two negative replications were performed in 235 family trios from the Han Chinese population (Duan et al., 2006) and in two independent sets of Japanese case-control samples (Ikeda et al., 2005); the third negative study used 53 Arab Israeli families with previous

evidence for linkage to 6q13–26 in a region containing the *TAAR6* gene (Amann et al., 2006). The fourth study, attempted to replicate the original report by performing a family-based association of all nine *TAAR* genes in a sample from Caucasian ancestry. In it, Liu and co-workers identified two polymorphisms rs8192624 and rs8192625 located in the coding sequence of *TAAR6* to be nominally associated with (BP) (Liu et al., 2007). They also identified a four marker haplotype located downstream from *TAAR6* to be associated with BP. This haplotype contained rs12189813 marker, which was shown to be significantly associated with SCH (Vladimirov et al., 2007), but which was not significant in Liu's study.

Finally, in a recent report, 648 SNPs located into functional regions of fourteen candidate SCH genes including the *TAAR6* gene were tested for association with SCH in a large case-control (1,870 cases and 2,002 controls) sample from European ancestry. In this study *TAAR6* was represented by rs8192625 which gave a nominal point-wise significance ($p < 0.03$), and which did not withstand experiment-wise or gene-wide significance (Sanders et al., 2008). None of the other analyzed genes showed significant association with SCH as well. Several factors, some pointed out by the authors, might have influenced these negative results such as nature of the tested sample (e.g. case-control vs familial sample), lack of precise diagnosis, phenotypic and/or locus heterogeneity and insufficient power, although all negative reports claimed to be adequately powered.

Of the positive reports, an extended two marker haplotype (rs7772821 and rs12189813) containing the *TAAR6* 3'UTR was identified to be associated with SCH in a family based sample from Ireland (Vladimirov et al., 2007). Vladimirov and colleagues study is of particular interest as ISHDSF sample was collected from the same region (Kendler et al., 1996) as ICCSS sample. Both samples are relatively large, with similar LD structure and enough power to detect association. In ISHDSF, rs12189813 and rs9389011 were significantly associated with SCH and rs9389020 showed a trend towards association ($p = 0.054$). In ICCSS, rs9389020 is nominally associated whereas rs9389011 and rs12189813 did not show evidence for association ($p = 0.0782$, $p = 0.98$, respectively). The combined analysis at single marker level for rs9389020 was nominally significant ($p = 0.024$) but it did not withstand correction for multiple testing. In ISHDSF the most significant two markers haplotype was represented by the major alleles of rs7772821 (in 3'UTR of *TAAR6*) and rs12189813. When the other 3 markers in the *TAAR6* gene were included in the analysis, all three four and five marker haplotypes, represented by the major alleles of these polymorphisms, were significant as well.

In the ICCSS sample the most significant two marker haplotype is composed of the minor allele of rs8192622 and major allele of rs9389020, although this haplotype does not survive correction for multiple testing. The inclusion of *TAAR6* markers in two, three, four and five marker haplotypes retained the signal, although in contrast to ISHDSF sample, these haplotypes were composed of minor alleles of the *TAAR6* markers and major allele of rs9389020. A plausible explanation for this observation could be attributed to the very low LD between markers and that likely none of the studied markers is the casual variant (Lin, 2007). The LD pattern is modulated by recombination rate, genetic drift, selection balance and mutation rate (Mullerova and Hozak, 2004) and the mutation rate in the *TAAR6* region has been reported to be higher than average (Duan et al., 2004).

Another interesting question is the reconciliation between the previously observed positive association of *TAAR6* in the family ISHDSF sample versus the negative association observed in this case-control study. An explanation for failed replication could be the nature of studied sample (familial vs. case-control). Multiplex SCH families are relatively rare, and affected individuals in such families may carry different and perhaps highly penetrant risk variants. There also remains a possibility that the multiplex families have some degree of cryptic relatedness, in which case our prior observations may reflect a founder effect. Finally, there is

also a possibility that our own findings in the ISHDSF sample might be false positive. Further work will be needed to understand and explain the association differences between ISHDSF and ICCSS samples.

A second study found *TAAR6* to be associated with BP in two independently analyzed samples from the German population (Jamra et al., 2005). In a Korean case-control sample, five polymorphisms located in the *TAAR6* gene and 3'UTR were tested for association and one marker rs6903874 was significantly associated with SCH and BP (Pae et al., 2008). The authors also identified one haplotype, containing rs6903874, to be significantly over-represented in SCH and BP cases and a second haplotype to be under-represented in BP cases (Pae et al., 2008). In the current study rs6903874 was not associated with SCH in our ICCSS sample.

Since all of these studies were performed in different ethnic groups, a possible explanation for the non-replication is differences either in the presence or the frequency of a liability allele between different populations. The high-risk allele might have a very different pattern of both LD and association across different populations and marker sets useful in one study may not be useful in another (Nakajima et al., 2002; Neale and Sham, 2004).

At the time of preparation of this manuscript several genome-wide association studies (GWAS) for SCH and BPD were published. The clinical antipsychotic trials of intervention effectiveness (CATIE) study used the Affimetrix 500K chip genotyping platform and a custom 164K fill-in chip to genotype 738 SCH cases and 733 group-matched controls from a US population based sample (Sullivan et al., 2008). In their stage 1 analysis, the authors did not identify any SNP or multimarker combination of SNPs to achieve genome-wide significance. A second GWAS study was more fruitful (O'Donovan et al., 2008), and the authors identified a strong evidence for association in the *ZNF804A* gene on chromosome 2, which remained positive after replication in two additional samples. Two additional intergenic loci on 11p14.1 and 16p13.12 also provided a strong evidence for association. The third GWAS study was supported by the Wellcome Trust Case Control Consortium (WTCCC) was conducted in a large sample (2000 cases and 3000 combine controls) collected within Great Britain and one polymorphism at 16p12 gave evidence for an association with BPD, but which was not supported in independent replication (2007).

None of these GWAS studies had hinted at *TAAR6* to be associated with SCH. As stated by the authors of these studies, failure to detect association signal does not provide conclusive exclusion of any given gene identified so far. Factors like incomplete coverage of common variants, modest effect size ($OR < 1.2$) inadequate power, allelic and locus heterogeneity could all affect our ability to detect genetic association.

In summary, the present study did not support a strong association of the *TAAR6* gene with SCH. At single marker level, only rs9389020 gave nominal evidence for association and this does not survive permutation testing. The anchored haplotype analysis gave nominally significance evidence for association, which also did not withstand permutation testing.

Overall, the evidence for association of *TAAR6* with SCH is fairly weak. The positive markers show only nominal significance and these results are not significant after permutation or other approaches for multiple test correction. Thus we conclude that, if *TAAR6* does contribute to liability for SCH, this contribution is relatively small and may vary significantly between samples.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

1A represents the LD map of *TAAR6* region in the HAPMAP data set and 1B the LD map of *TAAR6* region in the ICCSS sample. The coloring is based on the D' confidence interval method using Haploview default settings and reflects the LD strength; the values represent r^2 .

Table 1

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.

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
rs693874	132938603	0.313	0.318	0.5919	95.9	0.198	T>C	0.202-0.190	0.66	0.4166	0.9938
rs7565655	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
rs1289813	132969195	0.494	0.476	0.1518	98.2	0.39	G>C	0.391-0.390	0.02	0.9896	1
rs9599011	132976272	0.33	0.362	0.011	94.5	0.237	T>C	0.773-0.744	3.102	0.0782	0.5454
rs9599015	132985129	0.488	0.498	0.4612	97.1	0.468	C>T	0.476-0.452	1.75	0.1859	0.851
rs9599020	133004746	0.4	0.416	0.127	98.6	0.295	T>C	0.719-0.680	5.185	0.0228	0.2196