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Are TMEM genes potential candidate genes for panic disorder?

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We analysed single nucleotide polymorphisms in two transmembrane genes (TMEM98 and TMEM132E) in panic disorder (PD) patients and control individuals from the Faroe Islands, Denmark and Germany. The genes encode single-pass membrane proteins and are located within chromosome 17q11.2–q12, a previously reported candidate region for PD. Three single nucleotide polymorphisms (rs887231, rs887230 and rs4795942) located upstream and within TMEM132E showed a nominal significant association with PD primarily in the Danish cohort. No nominal significant associations were observed between TMEM98 and PD. Our data indicate that TMEM132E might contribute moderately towards the risk of developing PD. \textit{Psychiatr Genet} 24:37–41 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

Panic disorder (PD) is a mental disorder influenced by genetic factors as well as environmental factors (Klauke \textit{et al.}, 2010; Schumacher \textit{et al.}, 2011). A variety of genetic studies of PD have been carried out. However, the results have been inconsistent (Maron \textit{et al.}, 2010). Recently, we reported results from a genome-wide association study in a Faroese case–control cohort, suggesting chromosome 17q11.2–q12 comprising the amiloride-sensitive cation channel 1 (ACCN1) gene as a candidate region and gene for PD (Gregersen \textit{et al.}, 2012). The 17q11.2–q12 region also comprises two transmembrane protein genes (TMEM132E and TMEM98). One of the microsatellite markers (D17S1842) associated with PD in our previous study is located within TMEM132E (Gregersen \textit{et al.}, 2012). Interestingly, another TMEM gene, TMEM132D located on chromosome 12, has been identified as a novel candidate gene for PD (Erhardt \textit{et al.}, 2011, 2012; Quast \textit{et al.}, 2012). The TMEM genes encode single-pass membrane proteins and may have functions essential to neuronal cells (Oh-hashi, 2010). In the current study, we aimed to follow up on the 17q11.2–q12 region by analysing single nucleotide polymorphisms (SNPs) in TMEM132E and TMEM98. The genes were analysed in Faroese, Danish and German PD patients and control individuals.

Methods

We selected 11 tag-SNPs covering the gene region of TMEM98 and 25 tag-SNPs covering the gene region of TMEM132E (Fig. 1). The tagging and genotyping procedure has been described previously (Gregersen \textit{et al.}, 2012). The SNPs were analysed in three PD cohorts: 36 cases and 162 control individuals from the isolated population of the Faroe Islands, 243 cases and 649 control individuals from Denmark and 232 cases and 222 control individuals from Germany. The patients were diagnosed with PD or PD with agoraphobia and have been described before (Wang \textit{et al.}, 2006; Kristensen \textit{et al.}, 2009; Koefoed \textit{et al.}, 2010; Erhardt \textit{et al.}, 2011; Gregersen \textit{et al.}, 2012). The controls were matched to the cases by country of origin.

Statistics

SNPs were tested for association with PD using the Cochran–Armitage trend test. For the three combined cohorts (Faroese–Danish, Danish–German and Faroese–Danish–German), allelic association was tested using the Cochran–Mantel–Haenszel test. Two-marker and three-marker haplotype associations were conducted using a sliding window approach as implemented in PLINK (Purcell \textit{et al.}, 2007). ACCN1 was included in the
haplotype analyses because of its location between TMEM98 and TMEM132E (Fig. 1); however, only in the analyses of the Faroese and Danish cohorts were ACCN1 genotypes available. $P$-values 0.05 or less were considered as nominally significant. Each gene was tested for association at the level of the whole gene using
COMBASSOC (Curtis et al., 2008). This program was further used to assess region-wide association by analysing the chromosome 17 region (17: 28,267,543–29,993,188) comprising TMEM98, ACCN1 and TMEM132E (only for the Faroese and Danish cohorts). SNPs within the gene region of TMEM98 and TMEM132E were imputed using MaCH 1.0 (Li and Abecasis, 2006). Fifty-six SNPs with a squared correlation above 0.3 and a quality score above 0.9 were analysed for association using PLINK.

Results
In total, 34 SNPs (11 within TMEM98 and 23 within TMEM132E) were genotyped successfully with a call rate above 0.96 and a minor allele frequency above 0.01. No deviation from Hardy–Weinberg equilibrium (P ≤ 0.0015) was observed among the controls. Thirty-eight of 1544 individuals were excluded from the analyses because of low genotyping.

No allelic or haplotype association was detected between TMEM98 and PD in any of the cohorts. One SNP (rs4795942) within TMEM132E was nominally significantly associated with PD in the Faroese cohort (Table 1). Three SNPs (rs887231, rs887230 and rs4795942) within the TMEM132E gene region showed a nominal significant association in the Danish cohort. The same three SNPs were also associated with PD when analysed in the combined samples of Faroese–Danish, Danish–German and Faroese–Danish–German cohorts (Table 1). rs887231 remained significantly associated after Bonferroni correction (correcting for 34 tests) in the combined Faroese–Danish cohort. None of the SNPs analysed showed an allelic association with PD in the German cohort. Nominally significantly associated two-marker and three-marker haplotypes were observed in all three cohorts and in the combined cohorts as shown in Table 2. Also, SNPs within the gene boundary of ACCN1 and TMEM132E were included in significant associated two-marker and three-marker haplotypes in the Danish and combined Danish–Faroese cohorts (Table 2). In the subsequent imputation analyses, several of the SNPs showed a nominal allelic association in the Faroese and Danish cohorts (P-values ranging from 0.006 to 0.037) (data not shown). None of the imputed SNPs were associated with PD in the German cohort. Neither TMEM132E nor TMEM98 showed a significant association at the level of the whole gene and no region-wise association was detected (data not shown).

Discussion
We followed up on the chromosome 17q11.2–q12 candidate region by analysing two TMEM genes (TMEM98 and TMEM132E) for association with PD in three cohorts. TMEM98 showed no association with PD. However, our data provided a trend for an association between TMEM132E and PD. Two SNPs (rs887231 and rs887230) located upstream and one SNP (rs4795942) located within TMEM132E showed both allelic and two-marker and three-marker haplotypic association in the Danish cohort. The minor allele frequencies of the three SNPs were over-represented in the control group, suggesting a protective effect of these variants. One of these SNPs (rs4795942) showed a nominal association in the Faroese cohort, with the minor allele frequency in the same direction as in the Danish cohort. The minor allele frequency of rs4795942 also indicated a protective effect in the German cohort. However, the results were not significant. After correcting for multiple comparisons, only rs887231 remained significantly associated in the combined Faroese and Danish cohort.

The two significantly associated upstream SNPs (rs887231 and rs887230) are located within the 3′ untranslated region and exon two of the predicted gene: Homo sapiens chromosome 17 open reading frame 102 (C17orf102). The C17orf102 gene encodes the hypothetical protein LOC400591 and is located 1.4 kb upstream from TMEM132E.

The involvement of TMEM132D in the aetiology of PD has been reported recently (Erhardt et al., 2011). A two-marker haplotype showed a significant association with PD in three independent German cohorts. Recently, this association has been replicated in a new independent cohort of European ancestry, in which the Danish PD cases and control individuals from our study were included (Erhardt et al., 2012). Moreover, putatively functional and rare variants within TMEM132D have also been suggested to contribute towards the risk of developing PD (Quast et al., 2012). TMEM132D and TMEM132E belong to the same gene family of five members: TMEM132A, B, C, D and E. Only two of the genes have been assigned a function. The TMEM132A gene product may play a role in cell survival by regulating stress-related genes in neuronal cells (Oh-hashi, 2010). The TMEM132D protein has been suggested to be involved in neural interconnecting and signalling (Nomoto et al., 2003). Others have shown that TMEM132D is expressed in neurons and is colocalized with actin filaments (Walser et al., 2011). As already indicated, the function of TMEM132E is unknown. However, a SNP located 38 kb downstream of TMEM132E has been associated with bipolar disorder; this association was replicated in the follow-up study (Sklar et al., 2008). The downstream SNP was, however, not in linkage disequilibrium with the SNPs analysed in this study.

The results of the current study have to be interpreted with caution, especially when considering the small sample size of the Faroese cohort, as it may have affected the P-values. However, the Faroese population is presumed to have reduced genetic heterogeneity (Jorgensen et al., 2002), which might justify the small sample size used. Furthermore, our results could be confounded
### Table 2: Significantly associated two-marker haplotypes within *TMEM132E* analysed in Faroese, Danish and German panic disorder patients and controls

<table>
<thead>
<tr>
<th>SNPs</th>
<th>Haplotype</th>
<th>FO</th>
<th>DK</th>
<th>FO + DK</th>
<th>GE</th>
<th>FO + DK + GE</th>
<th>DK + GE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>P</td>
<td>Cases</td>
<td>Controls</td>
<td>P</td>
</tr>
<tr>
<td><em>TMEM132E</em></td>
<td>OMNIBUS</td>
<td>0.161</td>
<td>0.12</td>
<td>0.012</td>
<td>0.279</td>
<td>0.198</td>
<td>0.212</td>
</tr>
<tr>
<td>rs887231</td>
<td>OMNIBUS</td>
<td>0.004</td>
<td>0.004</td>
<td>0.001</td>
<td>0.807</td>
<td>0.036</td>
<td>0.123</td>
</tr>
<tr>
<td>rs887230</td>
<td>OMNIBUS</td>
<td>0.005</td>
<td>0.006</td>
<td>0.003</td>
<td>0.112</td>
<td>0.012</td>
<td>0.012</td>
</tr>
<tr>
<td>rs4795942</td>
<td>OMNIBUS</td>
<td>0.171</td>
<td>0.039</td>
<td>0.003</td>
<td>0.171</td>
<td>0.015</td>
<td>0.171</td>
</tr>
<tr>
<td>rs788119</td>
<td>OMNIBUS</td>
<td>0.420</td>
<td>0.001</td>
<td>0.001</td>
<td>0.420</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>rs11654085</td>
<td>OMNIBUS</td>
<td>0.117</td>
<td>0.170</td>
<td>0.265</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>rs11080285</td>
<td>OMNIBUS</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>ACCN1–<em>TMEM132E</em></td>
<td>OMNIBUS</td>
<td>0.147</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Further included are the two SNPs within the gene boundary of *ACCN1* and *TMEM132E*, respectively, but only for the Faroese and Danish cohorts. SNPs with $P \leq 0.05$ (nominal significance) are given in bold. Abbreviations are the same as in Table 1.
because of population stratification. To compensate for the possible population stratification between the different cohorts, the cases and controls were matched by country of origin.

However, a clear advantage of this study is the uniform phenotypes of the patients; we only included patients with PD or PD with agoraphobia. Phenotypic heterogeneity may be one of the reasons for the difficulties of replicating the results of association studies.

In conclusion, we suggest that an additional member of the TMEM132 gene family, TMEM132E, may contribute moderately towards the risk of developing PD. However, further genetic studies are warranted.

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Conflicts of interest
There are no conflicts of interest.

References