Bipolar disorder is a highly heritable psychiatric disorder but the aetiology of the disease is complex, involving multiple genetic and environmental influences. Identifying genetic variants associated with bipolar disorder will increase the understanding of disease mechanisms and may lead to development of targeted therapeutics. Several genome-wide association studies have been conducted that together suggest that the genetic susceptibility of bipolar disorder is clearly polygenic in nature.1

One identified single nucleotide polymorphism (SNP) that has been linked to bipolar disorder is of particular interest: rs1006737, situated within intron 3 of the gene CACNA1C at chromosome 12, with the A allele associated with an increased risk.2 This gene codes the alpha 1C subunit (Cav1.2) of the L-type voltage-gated calcium channel, with bipolar disorder and other psychiatric disorders. However, the causal pathway linking genetic variants in CACNA1C with increased risk for developing brain disorders remains unclear. Here, we explored the association between the rs1006737 SNP and cerebrospinal fluid (CSF) markers. We found a significant association between the risk allele in rs1006737 and a decreased CSF hyperphosphorylated tau/total tau ratio in patients with bipolar disorder, thus linking variation in the CACNA1C gene to a neurochemical marker of neuroaxonal plasticity in those with this disorder.

\[ \text{Declaration of interest} \]
None.

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\[ \text{Results} \]
The CACNA1C rs1006737 SNP was genotyped with the KASPar PCR SNP genotyping system (KBioscience, Hoddesdon, UK; www.kcggenomics.com). SPSS Statistics version 20 was used for all statistical analyses. Analysis of covariance (ANCOVA) with age and gender as covariates was used to analyse effects of rs1006737 on CSF marker concentrations. All \( P \)-values are presented as two-tailed. Bonferroni correction was used to correct for multiple comparisons (\( \alpha = 0.05/15 = 0.00333 \)).
medications, previous episodes of psychosis, Global Assessment of Functioning score, Clinical Global Impression score, diagnosis, duration of illness or number of episodes. A low P-tau/T-tau ratio was significantly associated with the A allele group \((F(1,128) = 13.484, P < 0.001, \chi^2 = 0.00333)\) (online Fig. D81), whereas the rs1006737 genotype had no effect on any of the other biomarkers (online Table DS2). We also found a significant association between the P-tau/T-tau ratio and the A allele under an additive model \((\beta = -0.260, P = 0.002, \text{age and gender as covariates})\). We next analysed whether this association was specific to bipolar disorder by analysing healthy controls \((n = 54)\). The frequency for the A allele of rs1006737 in the control group was 0.30 with the genotypes distributed according to Hardy–Weinberg equilibrium \((\chi^2 = 0.675, P = 0.411)\). In the control group, the rs1006737 SNP was not associated with the P-tau/T-tau ratio \((F(1,50) = 0.275, P = 0.602)\) or with any of the other CSF biomarkers (online Table DS3).

Discussion

Variations in CACNA1C has previously been linked to various brain functions but it is unclear how these variations affect the brain on a chemical level. Here, we found a significant association between the rs1006737 SNP and the CSF P-tau/T-tau ratio in patients with bipolar disorder. No association was found in healthy controls, implying that the association is not a general physiological phenomenon but occurs in patients with a psychiatric illness.

\(\text{Ca}_{1.2}\) is primarily regulated through an interaction with \(\text{Ca}^{2+}\)-bound calmodulin (CaM), which also mediates the downstream effects of \(\text{Ca}_{1.2}\).\(^{11}\) Downstream effectors of CaM include the proline-directed protein kinase (CaMK) pathway.\(^{9}\) Interestingly, phosphorylation of tau is regulated by a range of proline-directed and non-proline-directed kinases, including CaMK and MAPK,\(^{12}\) linking calcium signalling with phosphorylation of tau. Phosphorylation of tau reduces its binding to microtubules leading to destabilisation of microtubules and promoting cytoskeletal flexibility, which have been suggested to be important for axonal and synaptic growth/development and thus neurodevelopment and synaptic plasticity.\(^{12}\) In addition, tau phosphorylation is markedly increased in brain tissue in pathological conditions (i.e. tauopathies), and in CSF in Alzheimer’s disease (for a review see Blennow et al.\(^{13}\)). There are, however, no differences between patients with bipolar disorder and controls in either P-tau or T-tau concentrations.\(^{7}\) Thus, the difference in P-tau/T-tau between rs1006737 risk allele carriers and non-risk allele carriers probably reflects alterations in the regulation of tau phosphorylation.

Importantly, this study links variations in the CACNA1C gene to neuroaxonal plasticity at the neurochemical level in people with bipolar disorder. Further studies are, however, needed to sort out the biological and clinical significance of altered tau phosphorylation in relation to CACNA1C polymorphism in bipolar disorder and other psychiatric disorders.

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