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Genetic variant analysis of the putative regulatory regions of the LRRC7 gene in bipolar disorder

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Keywords

LRRC7; Bipolar disorder; allelic association study; regulatory regions

The leucine rich repeat containing 7 (LRRC7) gene encodes the LRRC7 or densin-180 protein, one of the major components of the post-synaptic density (PSD) of excitatory synapses. It is required for normal synaptic spine architecture and function. Studies indicate that densin-180 influences the function of mGluRs and CaMKII at synapses and contributes to localization of mGluR5 and DISC1 in the PSD fraction (Izawa et al. 2002, Carlisle et al. 2011). Homozygous LRRC7 knock-out mice display a wide variety of abnormal behaviours that are often considered endophenotypes of schizophrenia and autism spectrum disorders. These results support the hypothesis that variants that disrupt the organization and/or dynamics of postsynaptic signalling complexes in excitatory synapses can cause behavioural endophenotypes of mental illness (Carlisle et al. 2011). Furthermore repeated variable prenatal stress has been shown to alter the expression of postsynaptic genes including densin-180 in the rat frontal pole and some of these gene expression changes are analogous to those observed in people living with BP and schizophrenia (Kinnunen et al. 2003). Together, the important role of this gene in the synapse and mental illness endophenotypes observed in animal models suggest that LRRC7 may have a role in susceptibility to BP. The biphasic nature of BP makes a compelling argument for the existence of genetically determined pathological switch mechanisms that may manifest themselves in the loss of control of gene expression. 877bp of the 5'UTR, the first exon and putative regulatory regions upstream the first exon (hg19 chr1:70225232-70226109) of the LRRC7 gene were screened for variants using high resolution melting in 1099 people with BP. BP and control subjects were recruited to the study as previously described (Fiorentino et al. 2014). Six variants were detected in the LRRC7 gene: rs145644109, rs185432613, rs372648197, rs17397812, rs1340770, rs17397812. Two variants, rs185432613 and rs372648197, whose allele frequencies had not previously been reported, were selected for genotyping in 1099 BD and 937 control samples using previously described methods (Fiorentino et al. 2014).

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rs185432613 was successfully genotyped in 1052 BP subjects and 909 controls. Seven BP cases and 9 controls were found to be heterozygous for this variant. rs185432613 is located 349bp upstream from the first exon of LRRC7. Bioinformatics analysis of the variant allele using TESS (http://www.cbil.upenn.edu/cgi-bin/tess/tess) predicted that this allele destroyed a binding site for one transcription factor (Zta) and created four binding sites for transcription factors (POU1F1a, POU3F2, Cdx-1, Cad).

Only one of 1065 BP subjects and none of 926 control subjects were found to be heterozygous for rs372648197. This variant is located 557bp upstream from the first exon of LRRC7 and was predicted by TESS to destroy a binding site for transcription factor POU1F1a and to create 12 transcription factor binding sites (Sin, HSF1, GR, GR/PR, GR AR,PR A, PR B, PR, GR alpha, GR beta, PR A, LVa). TESS prediction highlights the possibility of a functionally important role for this variant. Because of its rarity, large sample sizes would be needed to confirm these results. Biochemical studies of the role of this variant could provide a basis for further functional and therapeutic studies of LRRC7.

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