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LARGE-SCALE MUTATION SCREENING OF THE PUTATIVE AUTISM SUSCEPTIBILITY GENE SCN2A IN SCHIZOPHRENIA

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Introduction: Recent genetic findings suggest shared genetic risk between autism, epilepsy and schizophrenia. A sodium channel subunit gene, SCN2A, exhibits de novo stop-codon mutations in individuals with autism and a stop-codon mutation in an individual with a seizure disorder. Our recent exome-sequencing study of schizophrenia cases identified a de novo splice-site mutation at SCN2A and further mutations may exist.
Objectives: To examine a role for rare, protein damaging mutations at SCN2A in the aetiology of schizophrenia.
Aims: We aim to show an excess of coding sequence mutations in schizophrenia cases when compared to controls.
Methods: Mutation screening of the coding sequence of SCN2A in 993 Caucasian individuals with DSM-IV schizophrenia. We employed High-Resolution Melt Analysis(LightScanner™), followed by dye- terminator sequencing to confirm allele carriers. We compared our results to an exome-sequencing dataset of 4300 Caucasian individuals (NHLBI Exome Sequencing Project).
Results: 34 variants were identified; 15 intronic, 13 synonymous and 7 non-synonymous. One of the non-synonymous variants introduces a stop codon at amino acid 169 (169 E>X). No stop-codon variants were identified in the control dataset. Burden analysis did not show an excess of protein damaging changes in the UK dataset when compared to controls.
Conclusions: A total of 4 stop-codon mutations have been identified at SCN2A; all in individuals with a neuropsychiatric disorder. Our data do not suggest a general role for protein coding mutations at SCN2A in the pathogenesis of schizophrenia; however there may be a role for very damaging alleles at SCN2A in several neuropsychiatric disorders.