A common risk variant in CACNA1C supports a sex-dependent effect on longitudinal functioning and functional recovery from episodes of schizophrenia-spectrum but not bipolar disorder

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4377209
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Year 2015
Title A common risk variant in CACNA1C supports a sex-dependent effect on longitudinal functioning and functional recovery from episodes of schizophrenia-spectrum but not bipolar disorder
Journal European Neuropsychopharmacology
Volume 25
Number 12
Pages / **Article-Number** 2262-2270
Keywords Adolescent; Adult; Aged; Aged, 80 and over; Bipolar Disorder/*genetics; Calcium Channels, L-Type/*genetics; Female; Genetic Predisposition to Disease; Humans; Longitudinal Studies; Male; Middle Aged; Phenotype; Polymorphism, Single Nucleotide/*genetics; Psychiatric Status Rating Scales; Schizophrenia/*genetics; Sex Factors; Young Adult; Calcium channel; Gaf; Gas; Global assessment of functioning; Recovery; Schizoaffective
Sex is a powerful modulator of disease susceptibility, course and outcome. The gene CACNA1C is among the best replicated vulnerability genes of bipolar disorder and schizophrenia. The aim of the present study was to investigate whether sex and a variant in CACNA1C (rs10774035 as a proxy for the well-acknowledged risk variant rs1006737) influence psychosocial adaptation in a large German patient sample with schizophrenia-spectrum (n=297) and bipolar (n=516) disorders. We analyzed Global Assessment of Functioning (GAF) scores, retrospectively collected for different time points during disease course. We investigated whether CACNA1C sex-dependently modulates longitudinal GAF scores and recovery from episodes of psychiatric disturbance in the above mentioned disorders. Psychosocial recovery was measured as difference score between the current GAF score (assessing the last remission) and the worst GAF score ever during an illness episode. Covariate- adjusted association analyses revealed a sex x rs10774035 genotype interaction on longitudinal GAF and recovery from illness episodes only in schizophrenia-spectrum but not in bipolar disorders. In schizophrenia-spectrum affected males, rs10774035 minor allele (T) carriers had higher GAF scores at three time points (premorbid, worst ever, current). In contrast, females carrying rs10774035 minor alleles had impaired recovery from schizophrenia-spectrum episodes. These results encourage further investigations of gene x sex interactions and longitudinal quantitative phenotypes to unravel the rich variety of behavioral consequences of genetic individuality.
Publisher ELSEVIER SCIENCE BV
ISSN/ISBN 1873-7862 (Electronic) 0924-977X (Linking)
URL https://www.ncbi.nlm.nih.gov/pubmed/26475575
edoc-URL https://edoc.unibas.ch/61551/
Full Text on edoc No;
Digital Object Identifier DOI 10.1016/j.euroneuro.2015.09.012

PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/26475575
ISI-Number WOS:000366947300008
Document type (ISI) Article