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Dissertations-Kurzfassung

The psychiatric vulnerability genes DTNBP1 and CACNA1C and their relationships with personality traits, depressive symptoms, and cognitive function in psychiatric patients and in the general population

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Mood disorders and schizophrenia are highly heritable. Genetic factors play a major role in their development. Candidate gene studies suggest DTNBP1 as important vulnerability gene for schizophrenia. Genome-wide association studies have robustly replicated a variant in the CACNA1C gene as vulnerability factor for bipolar disorder and it has been shown that it also confers vulnerability to major depression and schizophrenia. As psychiatric disorders are clinically and genetically heterogeneous it is very unlikely however that these risk variant are associated with all symptoms of the categorical diagnoses alike. Thus the next step is to further refine genotype-phenotype correlations. One strategy to do so is to search for correlations between a certain risk variant and specific endophenotypes of mood disorders and schizophrenia. Endophenotypes, or intermediate phenotypes, which underlie a given disorder, are heritable traits themselves which are more specific and thought to more directly index part of the biology underlying the disorders. Prominent endophenotypes of mood disorders and schizophrenia are neurocognitive function and personality.

In the present work two studies are presented. In the first study the aim was to reappraise genotype-phenotype correlation findings between DTNBP1 and schizophrenia and investigating a possible association between DTNBP1 and neurocognitive function (study 1). The neurocognitive endophenotype was focused on because earlier studies suggest an influence of DTNBP1 on and neurocognitive function and DTNBP1.

The aim of the second study was to evaluate in the general population a possible influence of the CACNA1C risk variant rs1006737 on personality traits, resilience factors and depressive symptoms (study 2). The personality endophenotype was focused on because preliminary studies in healthy individuals suggest an influence of the CACNA1C risk variant rs1006737 on personality in the general population. A statistic method specifically designed to analyze previously reported sex-specific effects of CACNA1C was applied.

Study 1 investigated the association between DTNBP1 and schizophrenia in a large case-control and family sample and its association with neurocognitive function, assessed with Trail Making Test A and -B (TMT-A and –B), in a subsample of the schizophrenic cases. There was no effect of DTNBP1 on diagnosis of schizophrenia; however, the A-allele of SNP rs1047631 within DTNBP1 was nominally significantly associated with decreased processing speed on TMT-A and –B. TMT-A and -B primarily reflect working memory capacity and speed of visuoperceptual processing. The A-allele of rs1047631 has previously found to be associated with schizophrenia, decreased mRNA expression in the pre-frontal cortex of schizophrenic patients and decreased working memory performance. Further, epistatic effects of DTNBP1 and COMT, another important vulnerability gene for schizophrenia, were analysed and nominally significant effects on risk for schizophrenia were observed.

Study 2 investigated the effects of the CACNA1C variant rs100673 on personality traits, resilience factors and depressive symptoms in a large (n=3793) population-based cohort. The present data revealed a sex-specific effect of rs1006737 on personality traits, resilience factors and depressive symptoms in the general population. The A-allele was associated with emotional lability and decreased resilience in men and emotional stability and increased resilience in women. Inheritance was predominantly additive in men and recessive in women. A clear and robust effect of rs1006737 was observed for sense of coherence in women.

In summary, the results of both studies support the usefulness of the endophenotype strategy in psychiatric genetic research to refine genotype-phenotype correlations and investigate the influence of psychiatric risk variants in the general population. Study 1 supports the hypothesis that variation in DTNBP1 confers risk to schizophrenia by affecting neurocognitive function; although the power was insufficient to be able to draw a definite conclusion. Larger samples with a detailed assessment of various neurocognitive function domains are warranted to further disentangle the role of DTNBP1 in neurocognitive function. Study 2 suggests a sex-specific genotypic effect and sex-specific mode of inheritance of rs1006737 on personality traits, resilience factors and depressive symptoms in the general population and emphasizes the need in psychiatric genetic research for a detailed phenotype characterization in covering the whole continuum of risk and protective factors.