DISC1 EXPRESSION AND FUNCTION IN THE HIPPOCAMPUS

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Disrupted In Schizophrenia-1 (DISC1) is a highly promising schizophrenia susceptibility gene which is involved in several processes important to neurodevelopment, such as neurite outgrowth and neuronal migration. DISC1 is expressed in several brain areas implicated in schizophrenia, with particularly strong expression in the hippocampus. Immunohistochemical analysis of Disc1 expression in the mouse hippocampus reveals strong expression in areas CA1-CA3 and the dentate gyrus throughout development, with expression becoming more well-defined as these structures mature. We have also discovered that Disc1 is expressed by precursors migrating toward the dentate gyrus in early development. Given that functional and anatomical abnormalities in the hippocampus are consistently observed in the schizophrenic brain, there is an intriguing possibility that DISC1 abnormalities confer an increased risk for schizophrenia by disrupting the development of the hippocampus. To investigate this possibility, we have performed functional studies in the mouse hippocampus that indicate a role for Disc1 in its development.
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ALTERNATIVE SPLICING OF A NOVEL CASSETTE EXON IN THE DOPAMINE TRANSPORTER IS ASSOCIATED WITH SCHIZOPHRENIA

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We aimed to refine previously detected, replicable associations and epistatic interactions between intronic variations within the dopamine transporter (SLC6A3, "DAT") and schizophrenia. In fine-mapping analyses, we obtained near complete common variation information within these regions. To date, 375 variations have been catalogued, including 164 common variants which we captured at r2 < 0.95 using 88 'tag' SNPs. Significant associations with schizophrenia were replicated with several linkage disequilibrium (LD) clusters spanning introns 3 and 4 of the gene between two Caucasian cohorts (494 cases / 540 controls from the U.S., 659 trios from Bulgaria). A primate-specific computational model predicted a novel 108 base pair cassette exon defined by a potential recursive splice site and a standard 5' splice site motif within intron 3. The predicted exon was flanked within 600 nucleotides by schizophrenia-associated SNPs which fell within predicted splicing regulatory signals. Alternative transcripts have not been previously identified at DAT. We detected alternative splicing of the cassette exon (E3b) in cell transfection experiments and verified the inclusion of E3b in endogenous DAT transcripts in human substantia nigra tissue using RT-PCR assays. Differential inclusion of E3b was observed between constructs bearing schizophrenia risk alleles in this region and a construct with non-risk alleles. Using tag SNPs to represent all plausible risk alleles spanning the cassette exon and predicted regulatory sequences, we detected a significant association between schizophrenia and a common haplotype in both cohorts. E3b introduces multiple in-frame stop codons into the mRNA which truncates the DAT open reading frame and may serve as a mechanism to negatively regulate DAT production. Exon E3b is conserved among primates and many other placental mammals but appears to have been lost in the Glires clade. We conclude that alternative splicing of a novel cassette exon could alter DAT function in the human brain and confer risk for schizophrenia.
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SCHIZOPHRENIA GENETICS: NUMBER OF GENES, ENVIRONMENTAL INFLUENCES AND DISEASE PENETRANCE UNDER EPISTATIC MODELS

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Schizophrenia is a complex disease with a prevalence of about 1% in the general population. Little is known about the genetics underlying schizophrenia, the number of genes and the interplay between genes. We aim to get insight into the genetics of schizophrenia by investigating a range of genetic models and their fit to empirical data. In particular, we consider additive, multiplicative and network models as well as combinations of additive and network models. These models are evaluated by calculating a likelihood-based score of how well they fit observed prevalences from pooled epidemiological studies of families where at least one member suffers from schizophrenia. (1) Our models are functions of number of genes, allele frequencies and environmental influence where the disease penetrance is determined as a function of the particular genetic model and environmental influence. The data are best explained by models containing few genes in epistasis, and furthermore, models with recessive genes are generally superior. Particularly, best fits are obtained under a one-gene additive model combined with network models with recessive genes, which is in keeping with recent findings on a de novo copy number variant expressing a rare chromosomal deletion. (2) Another striking result is that the percentage of individuals in the general population predisposed to schizophrenia is between 5% and 7% in the best fit model. Compared to a prevalence of 1%, this indicates that the environment has an important influence on the development of schizophrenia: only one in six (five to seven) predisposed individuals develops schizophrenia.

References

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CONVERGING EVIDENCE FOR *DPYSL2* AS A RISK FACTOR FOR SCHIZOPHRENIA

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The genetic basis of schizophrenia is not clearly understood and no causative mutations have been definitively identified. It is highly heritable and involves the interaction of multiple genes of small effect and their interplay with the environment. Understanding the number of genes and their role and interaction in the pathophysiology, susceptibility to the disease or particular clinical symptoms and antipsychotic metabolism remains a crucial