M57. DISC1 GENE NETWORK MUTATIONS IN MAJOR MENTAL ILLNESS

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Background The genetic etiology of schizophrenia (SCZ) has been studied in a familial Finnish cohort since the late 1980s. Over the years, linkage and association studies of these families have continually identified the 1q42 region, and the Disrupted in Schizophrenia 1 (DISC1) gene in particular, as being a key locus of interest. Haplotypes and variants in the DISC1 gene have also been noted to associate with the risk to other mental illnesses in the Finnish population, including bipolar disorder and autism spectrum disorders, as well as to variations in phenotypes such as visual working memory, anhedonia, and gray matter volume in the dorsal lateral prefrontal cortex. Furthermore, studies in the SCZ family cohort have also observed association at genes for DISC1 interacting partners, the DISC1 network, including NDE1, PDE4D, PDE4B, and NDEL1. Despite this consistent line of evidence for these loci in the Finnish population, any true causal variants have yet to be identified.

Methods To identify any potential mutations a subset of SCZ families (n=20 families, 96 individuals) were sequenced at 24 genes from the extended DISC1 network. All identified variants were then prioritized using association analysis (p<0.05) combined with bioinformatic prediction of function, focusing on exonic and regulatory variants. These selected 67 variants were then genotyped in a larger sub-cohort of the SCZ families (n=1415 individuals in 420 families), alongside population based controls (n=359 individuals), in order to verify the observations in the small discovery sample. Verification of both the variants existence and association (p<0.05) to SCZ, or alternative phenotypes available in these families, led to the selection of those variants to be genotyped across a combined Finnish cohort featuring individual data sets for different major mental illnesses. This includes the rest of the SCZ cohort (n= 2,289), a family cohort for bipolar disorder (n=683), twin pairs concordant and discordant for SCZ (n=307), a selection of a population cohort based on anxiety (n=974), three small cohorts for psychosis (n=825) and population based controls (n=1,406).

Results With the aid of the three step sequencing and genotyping approach, we identified 12,795 variants in the DISC1 gene network, of which 67 variants from 9 genes were identified as associated (p<0.05) and genotyped in the verification stage. This additional genotyping step validated association (p<0.05) findings for 26 variants in 8 genes, which have been genotyped across the combined cohort with major mental illness in Finland. Preliminary results from the validation stage highlight a specific exonic variant in DISC1 (p = 0.0000051), a regulatory variant in NDE1 (p = 0.011), and an exonic variant in PDE4D as being the main variants of interest at these loci.

Discussion This research aims to identify the potential mutations within the DISC1 network which have been alluded to through our previous studies of Finnish cohorts for major mental illness. Our initial findings confirm the observation of association at a number of DISC1 network genes, including DISC1 itself, while focusing on the specific variants at these loci that have potential functional consequences. Thus, the
variants we are observing may represent the principal mutations at these loci in the Finnish population, and predispose to psychiatric disorders beyond schizophrenia. 

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