A GENOME-WIDE ASSOCIATION STUDY IDENTIFIES A GENE NETWORK ASSOCIATED WITH PARANOID SCHIZOPHRENIA AND ANTIPSYCHOTICS-INDUCED TARDIVE DYSKINESIA

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Background: Schizophrenia (SCZ) is a devastating psychiatric disorder, while the use of antipsychotics is plagued by significant side-effects. For instance, tardive dyskinesia (TD) is an abnormal involuntary movement disorder associated with a long-term treatment with antipsychotics. The abnormal movements affect the face, mouth (including tongue), extremities, and trunk, allowing distinguishing two types of TD: orofacial and limbtruncal. SCZ and TD could share pathogenic mechanisms and TD could be an exacerbation brought about by antipsychotics in individuals with an innate tendency to spontaneous dyskinesia.
Methods: 505 patients with paranoid SCZ, of which 95 had TD, were recruited from acute care or chronic care settings in the Siberian regions of Tomsk, Kemerovo and Novosibirsk. 503 volunteers without psychiatric disorders from the same geographic area were used as a negative control. The Illumina iScan System and the Infinium Global Screening Array-24 v1.0 BeadChip were used for the genotyping. Next, a genome-wide association study was conducted, in which 29 clinical phenotypes were analyzed, using a mixed-linear model version implemented in the software package rMVP. Bonferroni correction for multiple testing indicated a genome-wide significance level of $p \leq 1.81 \times 10^{-7}$. Tentatively associated variants with $p \leq 5 \times 10^{-6}$ were selected for the downstream analysis only if they fell under either of the two categories: (1) one variant associated with two or more different phenotypes; (2) two or more variants in linkage disequilibrium (LD) associated with the same phenotype. A bioinformatic functional annotation of the associated variants followed (**Figure 1**). Data generated by the PsychENCODE Consortium (PEC) and other bioinformatic databases were used to reveal regulatory elements in LD blocks that contain associated SNPs. Genes regulated by these elements were characterized with Network Data Exchange-NDEx Integrated Query and PEC co-expression Network Modules.
Results and Discussion: Eleven genomic regions (LD blocks), associated with paranoid SCZ and TD (including a number of elements in the clinical picture of these disorders), were revealed (**Figure 2**). Paranoid SCZ and abnormal involuntary movements that indicate the orofacial type of TD are associated with the same genomic loci on chromosomes 3p22.2, 8q21.13, and 13q14.2. The limbtruncal type of TD is associated with a locus on chromosome 3p13 where the best functional candidate is *FOXP1*, a high-confidence SCZ gene (the PEC study, Wang et al., 2018). The regions contain multiple regulatory elements that regulate 44 genes. Among them, 11 were identified as top interacting genes that form a single network with 11 additional interacting partners (**Figure 3**). The genes in this network are implicated in brain development and function (selected top Gene Ontology categories: CNS development, neuron development, axon ensheathment, synapse, synaptic vesicle cycle, and signaling receptor activity) and in inflammatory response. They are found in PEC network modules that are altered in SCZ, bipolar disorder and autism spectrum disorders.

Figure 1: A schematic of the functional annotation

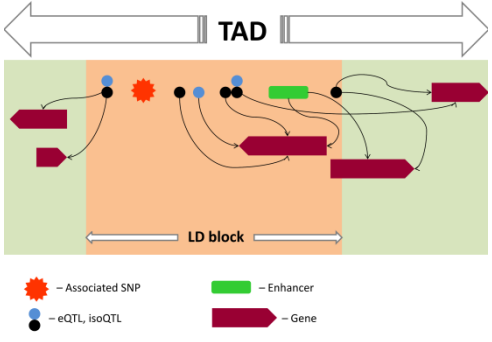


Figure 3: The network of 11 top genes (orange) and 11 new interacting partners (blue)

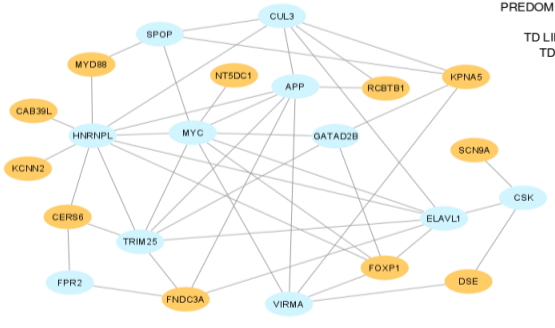
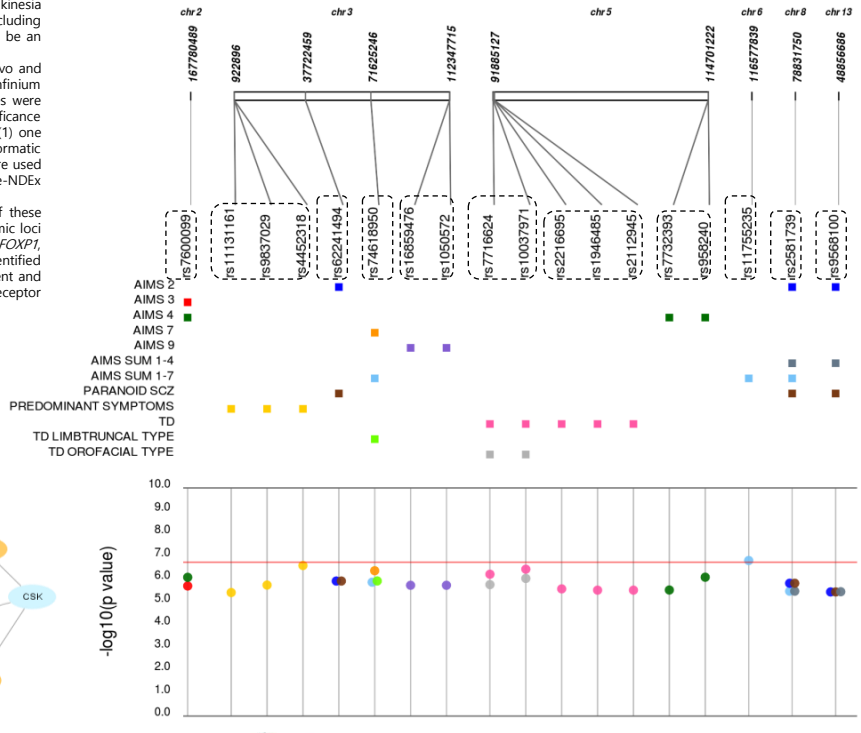


Figure 2: GWAS results for the top selected SNPs



Conclusions: Results of the present study suggest that orofacial and limbtruncal types of TD share the molecular network with paranoid SCZ. This may indicate common pathogenic mechanisms for SCZ and TD, driven by interacting genes implicated in neurodevelopment.

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