Appendix 5 to Fichna JP, Borczyk M, Piechota M, et al. Genomic variants and inferred biological processes in multiplex families with Tourette syndrome. *J Psychiatry Neurosci* 2023. doi: 10.1503/jpn.220206.

Variants in genes encoding long intergenic ncRNAs

Three-hundred and fifty-five variants in 237 genes coding for long intergenic non-coding RNAs (lincRNAs) were found co-segregating with the GTS phenotype. Two ultra-rare variants (rs185426036 and a previously unreported one) in *LINC02763* were identified in three families. Ultra-rare variants were also identified in the *LNC-NR2F1* gene (in one family), in LINC00298 and in *LINC01414* (in two families each), and. Notably, *LINC01414* was also represented by uncommon variants found in four families. Rare variants in nine lncRNA genes were identified in two families each.

Long non-coding RNAs play numerous roles in gene expression, are involved in a myriad of biological processes and have been implicated in the pathogenesis of several diseases. Dysregulation of lincRNA expression can disturb cellular homeostasis, cell differentiation and development and can also deregulate the immune and nervous systems.[1] This can result in various disorders including schizophrenia, antisocial behaviors, depression, ASD, Alzheimer's disease, and Parkinson's disease.[2]

We identified GTS-associated variants in lincRNA genes previously linked to processes and structures implicated in brain functioning. For instance, an ultra-rare variant in *LINC02763* is located in the *NCAM1–TTC12–ANKK1–DRD2* gene cluster in which SNPs associated with tobacco dependence were previously identified.[3] Moreover, *NCAM1* identified in our enrichment analyses was previously linked with various psychiatric and brain developmental disorders.[4] The *NCAM1* gene encodes neural cell adhesion molecule (NCAM) an integral membrane glycoprotein that plays a key role in the regulation of cell adhesion, neural cell migration and synaptic plasticity, axonal guidance, synaptic pruning, and contact with astrocytes.[5,6] Abnormalities in NCAM signaling were reported to contribute to the etiopathogenesis of neuropsychiatric disorders (bipolar disorders, anxiety disorders, and Alzheimer's disease). It was also shown that anti-NCAM antibodies attenuate long-term potentiation.[7] As a promoter variant of *NCAM1* was shown to increase the risk of schizophrenia in the Chinese Han population[8], it could be hypothesized that the *LINC02763* variant could also act by modulating *NCAM1* transcription.

An ultra-rare variant was also identified in one family in the *lnc-NR2F1* gene. This lincRNA was recently proposed to be implicated in autism spectrum disorder/intellectual disability. The evolutionarily conserved lnc-NR2F1 functionally enhances induced neuronal cell maturation and directly occupies and regulates transcription of neuronal genes including autism-associated genes.[9] In addition, *LINC01414* and *LINC00298*, found in our study, were earlier correlated with antisocial behavior and Alzheimer's disease respectively.[10,11] *LINC00298* is associated with the enriched categories of synapse organization, cell-cell adhesion, and neuron projection morphogenesis. However, in most cases, the functional consequences of the variants identified by us, as well as the exact functions of the lincRNAs in question, are largely unknown.

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