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Abstract

Hemizygosity of the 16p11.2 ~600 kb BP4-BP5 region (29.5 to 30.1Mb) is one of the most frequent known genetic etiology of autism spectrum disorder (ASD). It is also associated with a highly penetrant form of obesity and a significant increase in head circumference. Mirror phenotypes are observed in carriers of the reciprocal duplication, who present a high risk of being underweight, microcephalic and/or developing schizophrenia. We profiled the transcriptome of individuals carrying reciprocal CNVs in 16p11.2 and analyzed the data using a gene dosage model. The genome-wide transcript perturbations correlated with clinical endophenotypes of this CNV and were enriched for genes associated with ASD. We also uncovered a significant correlation between 16p11.2 copy number changes and expression levels of genes mutated in ciliopathies. This result was replicated in orthologous mouse models, raising the possibility that ciliary dysfunction might contribute to 16p11.2 pathologies.

We then cataloged the long-range chromosomal contacts of genes located within the 600kb CNV and identified complex chromatin looping with genes mapping to the syntenic distal 220kb BP2-BP3 interval positioned ~1Mb away. We show that deletions and duplications of the 220kb locus display strikingly overlapping phenotypic manifestations with the 600kb CNVs, *i.e.* mirror impacts on weight and head circumference and associations with ASD, supporting the view that *cis*-acting chromosomal contacts intervene in the crosstalk between co-regulated genes. Consistent with this hypothesis, chromatin targets contacted by 16p11.2 600kb BP4-BP5 gene promoters are enriched for genes associated with ASD and/or genes that encode known interacting proteins, suggesting that disruption of chromatin interplays participates in the observed phenotypes.