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Abstract Title

Examining cell-type specific contribution of the 16p11.2 locus to neurodevelopmental disorders

Authors

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Background

Neurodevelopmental disorders are heterogeneous conditions that affect children's lives by altering their cognitive, social communication, and behavioral phenotypes. Both genetic and non-genetic factors influence the penetrance of these conditions. Among genetic factors, copy number variation (CNV) is common and can be a duplication or deletion. The 16p11.2 region is highly prone to deletions and duplications due to low-copy repeats or paralogous sequences. The penetrance and expressivity of the 16p11.2 deletion are higher than those of the duplication, suggesting greater severity of cortical malformation in children. Our current research investigates the impact of 16p11.2 gene dosage on diverse neuronal populations in the developing mouse cortex.

Objective

The objective of our research is to investigate the impact of 16p11.2 gene dosage on diverse neuronal populations in the developing mouse cortex.

Methods

The 16p11.2 locus is highly conserved in the 7qf3 locus of the mouse genome. Mosaic Analysis with Double Markers (MADM) was used to investigate the impact of 16p11.2 deletion on neuronal subtypes in the mouse model. MADM is a lineage-tracing approach that generates cells with different genotypes within the same tissue. Each genotype is labeled with a different fluorescent marker (red: wild type, green:

heterozygous, yellow: homozygous), allowing precise identification and comparison at the single-cell level. To test our hypothesis that 16p11.2 is required in a cell-type-specific manner, MADM-based mouse models were combined with tissue-specific Cre drivers and the 16p11.2 deletion allele. Nkx2.1 and Emx1-Cre drivers targeted inhibitory interneurons and cortical excitatory projection neurons, respectively. Thus, 16p11-MADM mosaic mice were successfully generated. Brains were dissected at P0, P21, and P90, followed by immunohistochemistry to assess alterations in cortical structures and cell types.

Results

Our lab-generated 16p11-MADM mouse shows a reduction in body-brain weight ratio compared to control mice. Homozygous deletion of the 16p11.2 locus reduced the number of inhibitory and excitatory neurons at both P0, P21 and P90. Heterozygous deletion (more common clinical situation) reduced the inhibitory neuron population but increased the excitatory neuron number. This indicates a probable excitatory-inhibitory imbalance due to 16p11.2 deletion. Also, there are certain type of neuron population, which are affected by 16p11.2 deletion and some neurons are resilient to 16p11.2 locus as they can survive till mature adulthood (P90) without 16p11.2 locus.

Conclusion

Our data show that a single copy of the 16p11.2 locus is required for neuron production, but two copies are essential for maintaining the neural population.