The Autism- and Schizophrenia-Associated 3q29 CNV Deletion Elicits a Transient Increase in Proliferation in Embryonic Mouse Cortical Development

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Neurodevelopmental disorders impact an individual's behaviors, emotions, and learning, and are the consequence of both genetic and environmental factors. Abnormal development in the prefrontal cortex contributes to disorders such as autism spectrum disorder (ASD), intellectual disability, and schizophrenia (SZ). A heterozygous deletion of the 3q29 copy number variant (CNV) induces intellectual disability and increases risk for ASD and SZ, and in the mouse model, produces reduced forebrain weight soon after birth, indicating that abnormalities begin in the embryonic period. We characterized the course of embryonic cortical neurogenesis, the process of generating neurons from precursors, and we hypothesize that the 3q29 CNV deletion disrupts cortical neurogenesis. We found that the 3q29 deletion elicits increased proliferation at embryonic days (E) 14.5 and E15.5 selectively, with no differences before or after, as revealed by immunohistochemistry for proliferation markers including Edu (cells in S phase), P-H3 (M phase), Pax6 (ventricular zone, VZ), and Ki67 (stem cells, VZ and sub-VZ). At E15.5, the deletion increases cells entering S phase by 37% (p=0.0008), mitotic cells by 25% (p=0.03), and proliferative precursors in the VZ and SVZ, reflected by heights of 15% (p=0.045) and 19% (p=0.039), respectively. In future studies we will examine roles of apoptosis and characterize consequences for cortical layer formation. Changes in cortical neuron numbers, distribution, and types may underlie neurodevelopmental disorder phenotypes (ASD, SZ) and severity. These insights may improve the accuracy and efficiency of diagnosis and treatment of these conditions. Supported by the Rutgers School of Graduate Studies and NIH R25ES020721.