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Impact of Spliceosomal Defects on Early Brain Development

The human genome contains the code necessary to produce all the proteins that make up the living organism. But first, the genomic DNA must be converted into an intermediary RNA molecule, which in turn needs to undergo extensive modifications before it can be translated into a protein. One of the most important aspects of RNA processing is called splicing, where long segments of RNA are removed and a much more compact version – the messenger (m)RNA – is produced. Alternative splicing of these regions allows for a large number of diverse mRNAs and proteins to be created. This process is thought to be particularly important in the normal developing brain. Mutations in at least 8 genes that are involved in splicing cause developmental disorders that include microcephaly, autism, sensorineural hearing loss, eye anomalies, psychomotor delay and intellectual disability. Our team was involved in identifying several of those mutations in human patients: Mandibulofacial dysostosis and microcephaly syndrome (caused by mutations in the gene EFTUD2), Nager syndrome (mutations in SF3B4), and cerebrocostal mandibular syndrome (mutations in SNRPB). Now, we are poised to study the downstream effects of those mutations in a mouse model system. We have used CRISPR-Cas9 genome editing to generate mouse models of the above three diseases. In this proposal, we will focus on the effect of the spliceosomal mutations on the developing brain. We will identify both differences and similarities across the three distinct disorders. Focusing on the similarities, we will aim to understand common splicing defects that are likely to be universally important to neurodevelopment and hence pertinent to a wider range of neurodevelopmental disorders. In addition to classical experimental approaches, we will use RNA-sequencing and single-cell RNA sequencing to profile splicing defects in the structures of interest and identify changes in specific sub-populations of cells. The long-term goal of this research program is to identify molecular pathways that can be used as therapeutic targets in neurodevelopmental disorders.