Generation and Phenotypic Characterization of a Transgenic Mouse Model for a Neurodevelopmental Rare Genetic Disorder

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During a whole exome sequence (WES) screen aiming to identify novel candidate genetic mutations that cause neurodevelopmental disorders in pediatric patients, we detected an 11 bp deletion mutation in the ATG9B gene. The patients, children of a consanguineous marriage, displayed mental retardation, facial dysmorphia, obesity, and behavioral abnormalities. The deletion mutation resulted in frameshift and addition of a premature STOP codon, truncating the ATG9B protein. This is a novel autosomal recessive genetic disorder, also the first genetic disease linked with ATG9B. ATG9B is a homolog of ATG9A, a ubiquitously expressed autophagy mediator that acts as intracellular membrane carrier towards phagophore assembly sites. There is plenty of literature on ATG9A and its roles in autophagy. However, ATG9B, whose expression is restricted to placenta and pituitary gland, has not been investigated. We hypothesized; the clinical anomalies observed in patients resulted from abnormal placental development due to ATG9B truncation. When expressed in mammalian cells, the mutant ATG9B aggregates and sequesters in a perinuclear compartment while WT protein displays a distribution similar to ATG9A and localizes as perinuclear and cytosolic puncta. We generated ATG9B knockin mice by inserting a STOP codon at the mutation site, and constitutive ATG9B KO mice by exon deletion. Homozygous knockin and knockout mice were viable. Currently, we are phenotyping the mouse models by analyzing the development, autophagy and apoptosis in placental histological sections. Behavioral tests are in progress. In summary, we identified a novel rare genetic disease, generated transgenic knockin and knockout mouse models, and we expect to accumulate additional data on the disease etiology and ATG9B's functions during placental development by FEBS 2023. This project is completely novel, aims to present a novel genetic disease with in depth characterization, ready to start strategizing potential remedies.