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AAV9-IGHMBP2 gene therapy ameliorates the severity of the SMARD1 mouse model

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Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a rare infantile motor neuron disease with the primary clinical symptom being respiratory distress due to diaphragmatic paralysis. SMARD1 is caused by loss of function mutations in immunoglobulin helicase μ DNA binding protein 2 (IGHMBP2). Defects in IGHMBP2 lead to increased vulnerability to motor neuron death, leading to downstream effects including reduced muscle fiber size and innervation deficiencies. Currently there is no treatment for SMARD1, and patients rely on palliative care measures such as mechanical respiratory ventilators. Recently, we developed a mouse model on the FVB background that represents the first patient-derived missense mutation D564N (*Ighmbp2*$^{D564N/D564N}$). The homozygous D564N mutant mice display severe phenotypic and cellular pathology defects such as reduced lifespan, motor deficits, selective muscle vulnerability to denervation, and respiratory defects.

Objective: Our goal is to determine if gene replacement therapy is an effective means to rescue the D564N homozygous mice. We utilized a single stranded adeno-associated viral vector carrying human full-length IGHMBP2 administered through an intracerebroventricular injection at postnatal day 2. Treated D564N mice show a significant correction in phenotypic defects including an extension in lifespan, increased weight, and regained motor function through behavioral tests such as Rotorod and grip strength. Additionally, AAV9 has shown protective effects in cell pathology including motor neuron restoration, innervation improvement, and increased myofiber size. Analysis of whole-body plethysmography was conducted and showed that treatment significantly improved the respiratory rate and tidal volume. These results are preliminary and my work will focus upon quantitatively determining the phenotype of the gene therapy-rescued SMARD1 mice. This work should provide the first insight into the viability of gene therapy in a patient-based model of SMARD1 and provide a foundation for additional pre-clinical studies.