

Abstract Title: Interventional genomics in rare neurological diseases

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Abstract: GEMIN5 is essential for core assembly of small nuclear Ribonucleoproteins (snRNPs), the building blocks of spliceosome formation. We identified biallelic mutations in GEMIN5 among patients presenting with developmental delay, motor dysfunction and cerebellar atrophy. We found that these GEMIN5 variants perturb snRNP complex protein expression and assembly. While doing a genetic screen, we identified SMN as a genetic suppressor of GEMIN5-mediated neurotoxicity in vivo. We discovered that an increase in SMN expression by either genetically or the antisense oligonucleotide (ASO) Nusinersen, significantly upregulated the expression of GEMIN5 in mammalian cells and mutant GEMIN5 derived iPSC neurons. Furthermore, we identified a strong functional association between the expression patterns of SMN and GEMIN5 in patient Spinal Muscular Atrophy (SMA) derived motor neurons harboring loss of function mutations in the SMN gene. Interestingly, SMN binds to the C-terminus of GEMIN5 and regulates GEMIN5 expression through the Tudor domain. Lastly, we observed that SMN upregulation ameliorates defective snRNP biogenesis and alternative splicing defects caused by loss of GEMIN5 in iPSC neurons and in vivo. Collectively, these studies indicate that SMN is a potent regulator of GEMIN5 expression and neuropathologies.

Area of expertise: Neurogenetics, neurodegenerative diseases, animal models, induced pluripotent stem cells