Gemin 5, an RNA-binding protein is essential for assembly of the SMN complex. It facilitates the formation of small nuclear ribonucleoproteins (snRNPs), the building blocks of spliceosomes. It is also involved in regulating the splicing of pre-mRNAs and has been shown to bind snRNA-binding protein of the SMN complex. There are no pathogenic variants in Gemin5 identified to date in publicly available databases.

We identified autosomal recessive variants in the Gemin5 gene in four unrelated patient families with total 5 affected individuals. These variants have not been reported in any publicly available databases. The probands presented with developmental delay, central hypotonia and ataxia. MRI scanning of the patient brain showed cerebellar atrophy among all of the affected individuals. There were no obvious neurological symptoms among the heterozygous parents or siblings. In addition to this, we found novel compound heterozygote variants including deletions and frameshift mutations in 14 additional patients with overlapping clinical symptoms. To understand the mechanisms of Gemin5 variants, we have generated induced pluripotent stem cells (iPSC) lines and differentiated them into the neurons. We found that neurons expressing homozygous variants in Gemin5 drastically reduced the expression of snRNP components (SMN, Gemin2, Gemin4 and Gemin6) as compared to controls and heterozygotes suggesting a potential disruption in snRNP complex. Gemin5 protein formed nuclear aggregates in patient neurons as compared to unaffected siblings. Loss of either Gemin5 or SMN protein are sufficient to perturb snRNP complex. Furthermore, we found that RNAi-mediated knock down of endogenous rigor mortis gene (fly homologue of human Gemin5) caused developmental delay, motor dysfunction and premature lethality suggesting that loss-of-function of Gemin5 is deleterious. Here, we provide the first evidence that, patients carrying autosomal recessive mutations in Gemin5 display neurological symptoms. Our data suggests that pathogenic mutations in Gemin5 perturb the physiological functions by potential loss-of-function of Gemin5.