Exploring *GRID2* Deletions in Spinocerebellar Ataxia Type 18 (SCAR18): Insights from a Pakistani Family

Background:

Spinocerebellar ataxia (SCA) is a heterogeneous group of neurodegenerative movement disorders affecting the cerebellar system, which is crucial for neuromuscular coordination. Autosomal-recessive spinocerebellar ataxia type 18 (SCAR18) is caused by bi-allelic aberrations of *GRID2* encoding Glutamate Receptor, Ionotropic, Delta-2 found in cerebellar Purkinje cells. SCAR18 is characterized by developmental delays, intellectual impairment, and cerebellar atrophy, and presents with a unique set of symptoms including gait incoordination due to cerebellar ataxia, nystagmus, and ocular abnormalities.

Methods:
Case Report

Results
A 16 years old girl born from a consanguineous union, presented with early-onset, delayed psychomotor development, severe hypotonia, binocular horizontal nystagmus, brachycephaly, and progressive gait disturbance (ataxia), alongside behavioral challenges. Head MRI showed enlarged cerebrospinal fluid spaces and reduction of cerebellar volume, suggestive of cerebellar atrophy. Whole Exome Sequencing in 2021 identified a novel homozygous *GRID2* deletion in exons 10-12, which was initially classified as a VUS, but later reclassified as likely pathogenic.

Conclusion: This is the first reported case of on exon 10-12 deletion in *GRID2* causing SCAR18, and is expected to create a premature termination codon and result in an absent or disrupted GluRD2 protein product Formerly, *GRID2* has been linked to autosomal recessive (loss-of-function) and autosomal dominant (gain-of-function) manifestations of ataxia. Both SNVs and large deletions have been previously reported. . This finding extends our understanding of *GRID2*-associated SCAR18, highlighting homozygous loss-of-function variants correlating with a severe phenotypic spectrum in SCAR18.