Neutral amino acid transporter (ASCT1) deficiency: a novel *SLC1A4* compound heterozygous variant causes spastic tetraplegia, thin corpus callosum, and progressive microcephaly with epilepsy

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Background

Spastic tetraplegia, thin corpus callosum, and progressive microcephaly (SPATCCM) are linked to SLC1A4 genetic variants since the first reported case in 2015. SLC1A4 encodes for the neutral amino acid transporter ASCT1 ubiquitously expressed in neuronal tissue. ASCT1 is an important serine transporter between astrocytes and neurons. Although most of the reported cases are of Ashkenazi Jewish ancestry, SPATCCM has also been reported in Irish, Italian, Czech, Palestinian, and Pakistani ethnicities.

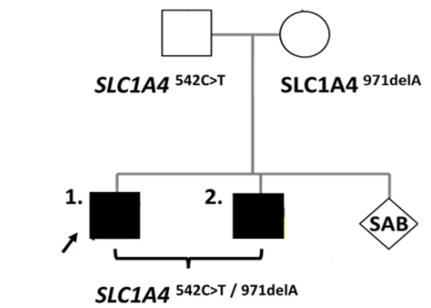


Fig1. Genetic pedigree of the affected family

Clinical Examination

we report two Pakistani male siblings from a non-consanguineous marriage presented with global developmental delay associated with spastic quadriplegia, microcephaly, and infantile spasm. Since infancy, both siblings suffered from seizure-acquired microcephaly with brain MRI demonstrating generalized atrophy of the frontal, temporal and parietal lobes with a prominence of the subarachnoid spaces, widening of the sylvian fissures and enlargement of the ventricular system not compatible with the chronological age of both patients associated with thinning of the corpus callosum.

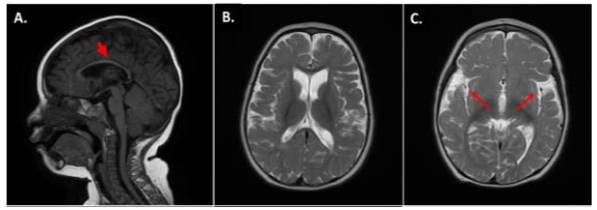
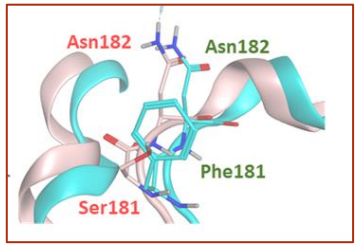


Fig2. The proband's brain MRI characteristic

Whole Exome Sequencing

WES has been performed for both patients and their parents revealing a compound heterozygous variant in the SLC1A4 gene of both patients.

c.971delA (p.N324Tfs*29)	c.542C>T (p.S181F)
Maternal	Paternal
Exon 5	Exon 2
Not reported in ExAC or 1000G	
Leads to NMD due to premature stop codon	Damaging and deleterious as predicted by: SIFT, PolyPhen2, and mutation taster



Molecular and Simulation analysis

The c.971delA (p.N324Tfs*29) deletion variant leads to the disruption of the transcript reading frame and the generation of a premature stop codon leading to its degradation by nonsense-mediated mRNA decay as confirmed by RT-PCR.

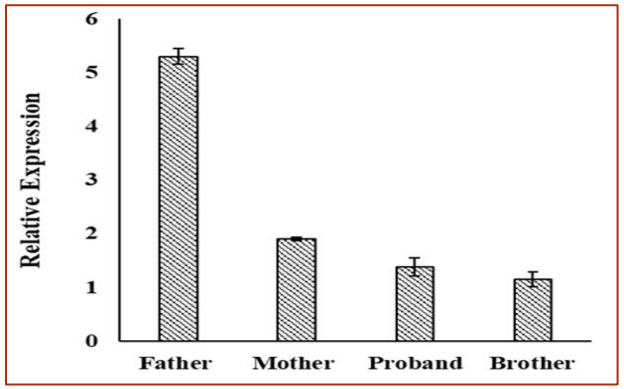


Fig3. Relative expression of the SLC1A4 gene

The c.542C>T (p.S181F) missense variant was predicted deleterious via multiple in silico prediction tools as the amino acid substitution is speculated to affect the overall ASCT1 confirmation due to the loss of an H-bond at the core of the protein at this position which might affect its function as concluded from the simulation analysis.

Conclusion: The presented cases expand the genetic and clinical spectrum of ASCT1 deficiency and support the importance of including SLC1A4 gene screening in infants with unexplained global neurodevelopmental delay regardless of ethnicity.

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