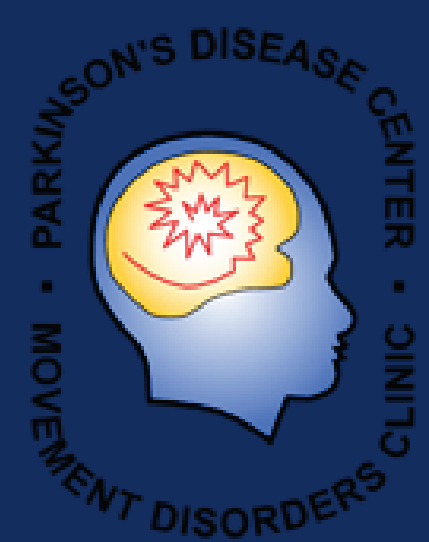


# Dystonia-spasticity in a patient with a novel *SLC25A12* mutation

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## Objective

To describe a unique case of psychomotor regression, dystonia and spasticity in a patient with a compound heterozygous mutation in *SLC25A12*.

## Background

- Global cerebral hypomyelination is a recently-described autosomal recessive disorder.
- Cardinal features include developmental arrest, hypotonia, and seizures.
- It is caused by deficiency of the neuronal mitochondrial aspartate-glutamate carrier, ACG1 (Aralar), encoded by the *SLC25A12* gene.
- Studies in the aralar/AGC1 knockout mouse show a decrease in brain N-acetylaspartate levels and global hypomyelination, attributed to the lack of neuron-produced NAA used by oligodendrocytes for myelin lipid synthesis.
- Animal model data also suggest effects on the nigrostriatal dopaminergic system, with decreased expression of vesicular monoamine transporter-2 (VMAT2) and associated catabolism of dopamine in the striatum.
- Dystonia and spasticity have not previously been reported in patients with mutations in this gene.

## Methods

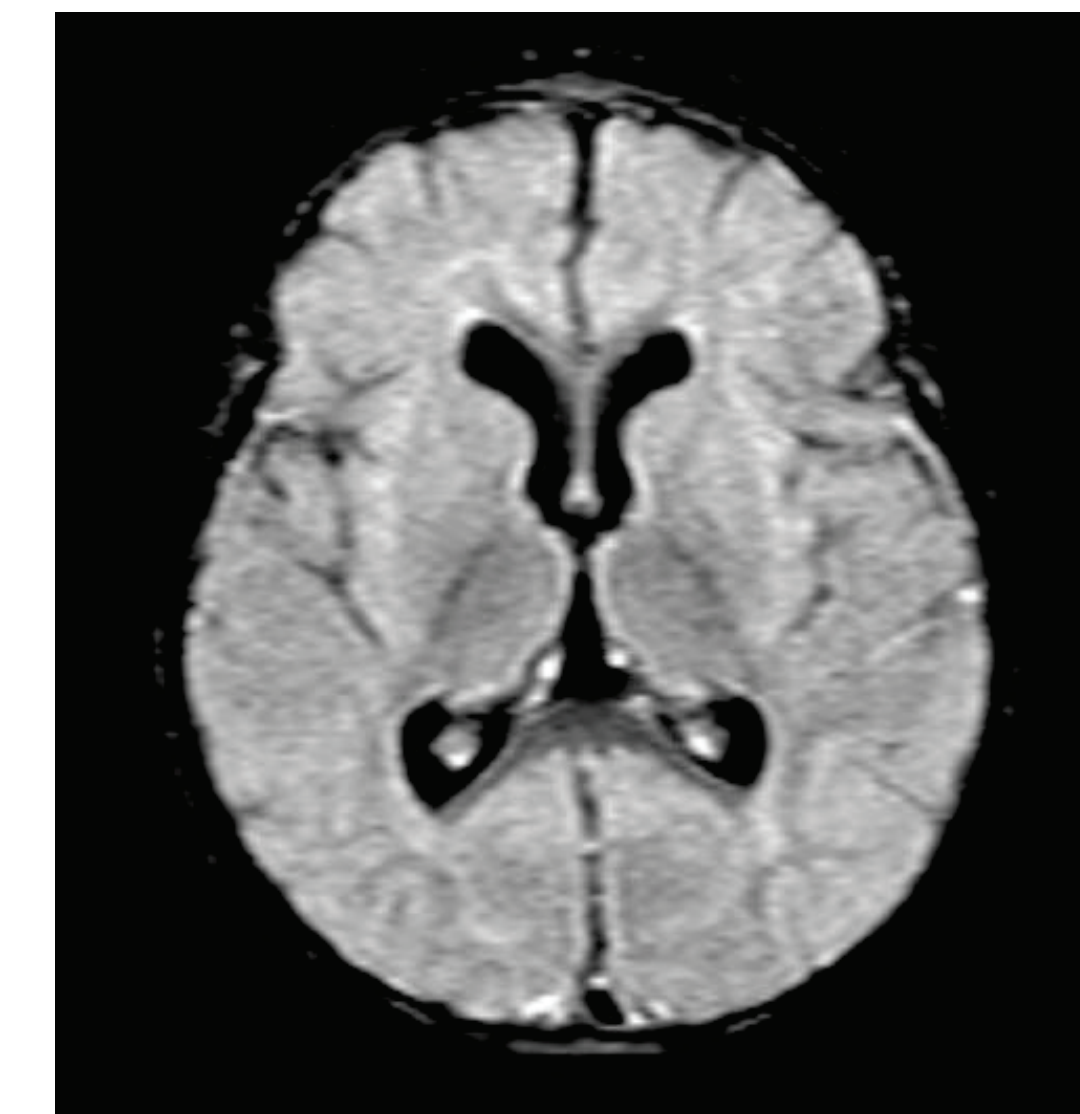
- We describe a 3 year-old Hispanic female who presented for evaluation of dystonia with psychomotor regression and epilepsy.
- Full-term, uncomplicated delivery with normal development through 11 months of age (walked at 11 months, used “mama” specifically and one other word).
- At 12 months of age, she began to have episodes of status epilepticus with lateral eye deviation and hemi-body tonic stiffening.
- Onset of seizures correlated with abrupt cognitive and motor regression (no language, hypotonia, able to roll but not sit).
- There is no family history of cognitive or motor impairment, regression, or epilepsy.
- Examination was notable for ability to crawl but not walk, equinovarus deformity of the feet, decreased axial tone with spasticity of the extremities, brisk reflexes, and intermittent dystonic posturing of the left arm (elbow, wrist, and MCP flexion with finger posturing).
- Brain MRIs revealed hypomyelination and progressive nonspecific atrophy, and MR spectroscopy showed a decreased NAA:choline ratio.

## Results

- Whole exome sequencing revealed two novel mutations in *SLC25A12 in trans*; a deleterious frameshift mutation in exon 4 (c.2956C>T, p.K100fs) and a c.215T>C (p.I72T) mutation in the conserved calcium-binding region predicted to be deleterious by 2 of 3 protein prediction programs.
- This case likely represents two novel pathogenic mutations, with additional symptoms not previously described in this condition.

## Conclusions

- Whole exome sequencing has become a powerful tool to accelerate genetic diagnosis in Mendelian disorders, as well as for phenotypic expansion of associated clinical manifestations.
- Future studies of ACG1 malate-aspartate shuttle activity may provide further insight into dopamine regulation in dystonia and other movement disorders.



## References

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