ASH1L-Related Neurodevelopmental Disorder Presenting With Tourette Syndrome, ADHD, and Epilepsy: A Case Report and Pathophysiological Integration

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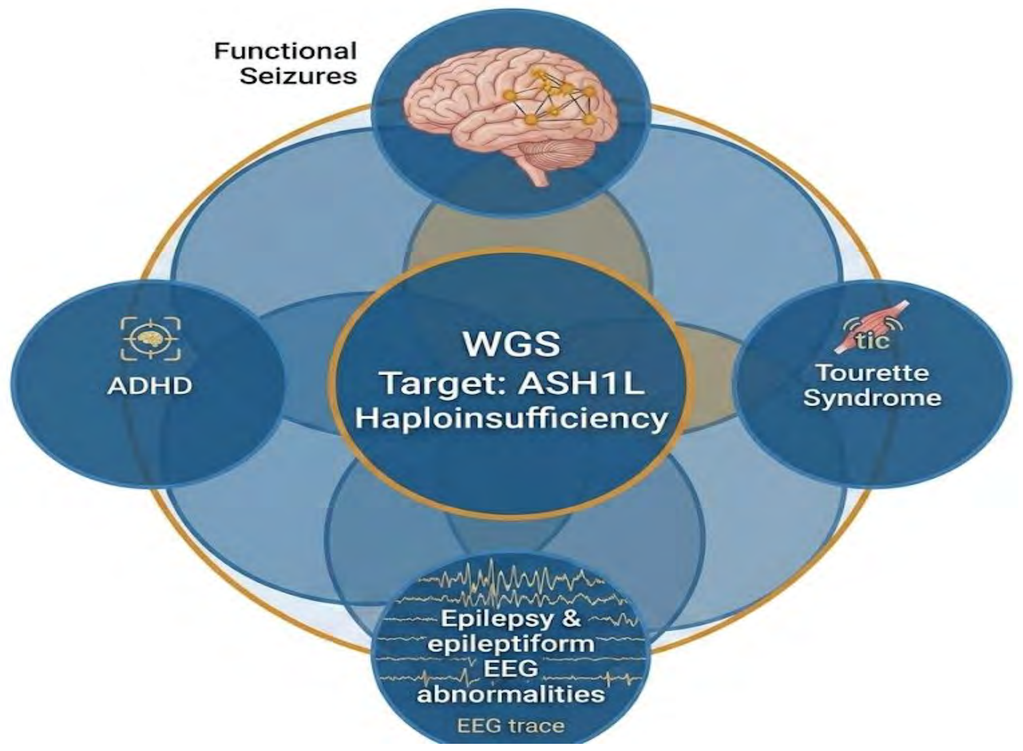
BACKGROUND

The Gene (ASH1L): Encodes a histone methyltransferase crucial for chromatin remodeling and neurodevelopment.
The Syndrome: Loss-of-function variants lead to a pleiotropic disorder (ID, ASD, epilepsy, ADHD, tics).
Experimental Models: ASH1L deficiency disrupts synaptic pruning, cortical lamination, E/I balance, and striatal dopamine pathways.
The Clinical Gap: The clinical framework and management of coexisting Tourette syndrome, epilepsy, and ADHD associated with ASH1L mutations remain poorly characterized.



Clinical Feature	Organic Focal Seizures	Functional Seizures (PNES)
Trigger	Spontaneous / Sleep activation	Emotional distress
Semiology	Focal-to-bilateral tonic movements	Prolonged motionless staring, reduced muscle tone
Duration	Short	Lasting several minutes
Ictal EEG	Right frontal epileptiform discharges	Lack of electrographic correlates
Post-ictal	Post-ictal confusion/somnolence	No post-ictal confusion
VPA Response	Sustained Control	Refractory

METHODS

Case Report: Clinical, electrophysiological, and genetic characterization of a 14-year-old male.
Clinical Presentation: TS, ADHD, focal epilepsy with secondary generalization, PNES, and severe emotional dysregulation.
Workup: neuropsychiatric follow-up, serial overnight video-EEGs, brain MRI, and drug response monitoring.
Genetics: trio WGS for pathogenic variant identification and genotype-phenotype correlation.

Results

Clinical Phenotype & History

Early Childhood: hyperactivity, impulsivity, emotional dysregulation, and IQ at the lower limits of normal.
Age 6: Onset of motor and vocal tics, progressing to complex tic phenomenology consistent with TS.
Age 7: focal-to-bilateral tonic seizure.
EEG: Right frontal epileptiform discharges with sleep activation.
MRI: Normal.
Treatment: Valproate achieved sustained organic seizure control.

The Diagnostic Twist: Non-Epileptic Events

Behavioral Arrests: subsequent episodes of loss of responsiveness were recorded.
Video-EEG Evidence: documented at least one **non-epileptic event**.
Semeiology: prolonged motionless staring and reduced muscle tone lasting several minutes, without motor automatisms or post-ictal confusion.

Genetic Characterization

Variant Identified: heterozygous *de novo* nonsense variant in ***ASH1L***.
Location: *c.3808C>T (p.Arg1270*)* in **exon 3**.
Pathogenicity: leads to a premature stop codon and protein truncation, consistent with the established haploinsufficiency mechanism.

Conclusions

Phenotypic Spectrum

This case expands the known expression of *ASH1L* haploinsufficiency across motor, attentional, and epileptic domains.

Convergent Manifestations

TS, ADHD, and epilepsy appear as convergent manifestations of altered chromatin regulation and impaired synaptic refinement.

Clinical Message

ASH1L is a strong candidate gene for complex neuropsychiatric phenotypes. Epigenetic dysregulation should be considered via WGS in patients with refractory behavioral symptoms and comorbid epilepsy.