Prevalence and Clinical Impact of Secondary Genetic Diagnosis in Children with Down Syndrome

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BACKGROUND

- Down syndrome (DS) is associated with a broad range of comorbidities
- Atypical clinical features are often attributed solely to trisomy 21, delaying recognition of additional conditions.
- Genetically distinct diagnoses may be underrecognized in this population.
- Missing diagnoses can have important implications for clinical management and patient outcomes.

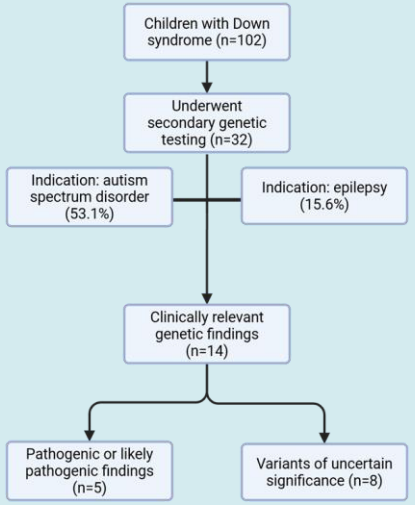
OBJECTIVE

- To determine the prevalence and clinical impact of secondary genetic diagnoses in children with trisomy 21 undergoing testing beyond chromosomal analysis.

METHODS

- Retrospective Cohort (DS, ages 0-18; 2020-2025) Neurodevelopment/peds neurology clinics UT Health Houston.
- Included CMA/WES testing.
- Analyzed indications, findings, impact on care.

RESULTS



- 31% underwent genetic testing (32/102)
- Common indications: ASD (53%), epilepsy (16%)
- 44% had clinically relevant findings Included pathogenic variants and VUS
- Diagnoses clarified atypical neurodevelopment (e.g., MELAS, CTCF)
- In DS + ASD, variants explained severity and impacted care
- VUS (e.g., SETD1A) may contribute to complex presentations

	Indication for testing	Genetic finding	Classification	Clinical interpretation/ Impact
Patient 1	ASD	16p12.2 deletion (chromosomal microarray)	Pathogenic	Associated with developmental delay, epilepsy, and neuropsychiatric features including autism. Supported additional genetic contribution to ASD; recommended parental testing and seizure monitoring.
Patient 2	ASD	19p13.11q11 duplication (11.4 Mb) involving CPAMD8 and 125 additional genes	Pathogenic	Provided a genetic explanation for severe (Level 3) ASD. Enabled access to ABA therapy, home school services, and adaptive mobility equipment.
Patient 3	ASD/Neurodevelopment concern	MT-TL1 m.3243A>G variant (7% heteroplasmy	Pathogenic	Diagnosed with MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes). Findings explained additional clinical features that may overlap with DS, including developmental concerns, hearing impairment, and short stature.
Patient 4	ASD/Neurodevelopment concern	CTCF c.1631G>C p.(R544P)	Likely Pathogenic	Diagnosed with CTCF-related neurodevelopmental disorder. Provided explanation for developmental delay, intellectual disability, feeding difficulties, GERD, and need for gastrostomy tube, features previously potentially attributed to DS.
Patient 5	Epilepsy	SETD1A c.4301 missense variant	Variant of uncertain significance (VUS), predicted deleterious	SETD1A variants are associated with neurodevelopmental disorders and seizures. Finding may contribute to epilepsy phenotype and warrants ongoing evaluation.

DISCUSSION

- Pathogenic/likely pathogenic variants found in 13.7%
- This higher yield likely reflects a specialty clinic population (neurodevelopmental/ neurology) with more targeted indications for genetic testing.
- Limitations: retrospective design, small sample, and specialty clinic recruitment limiting generalizability.
- Despite these limitations, findings highlight a notable prevalence of secondary genetic diagnoses in this population.

CONCLUSION

- Secondary genetic diagnoses are common and actionable in children with DS.
- Expanded genetic testing may improve diagnostic accuracy.
- Informs care decisions and supports appropriate interventions.