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Integrated Genomic and Functional Evidence for Channelopathy-Like Mechanisms in Neurodevelopmental Delay With GST Deletions as Redox Modifiers

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BACKGROUND

- Ion channel dysfunction is a recognised cause of neurodevelopmental disorders.
- Many patients remain genomically unresolved despite CMA and exome sequencing.
- GST deletions may modify redox vulnerability and mitochondrial stress.
- Functional convergence may reveal channelopathy-like mechanisms beyond diagnostic genomic yield.

AIM

- To evaluate whether children with neurodevelopmental delay and excitability-related phenotypes show a reproducible channelopathy-compatible functional profile.
- To assess whether GST deletions act as redox susceptibility modifiers.

METHODS

Retrospective cohort, 2025

N = 61 children

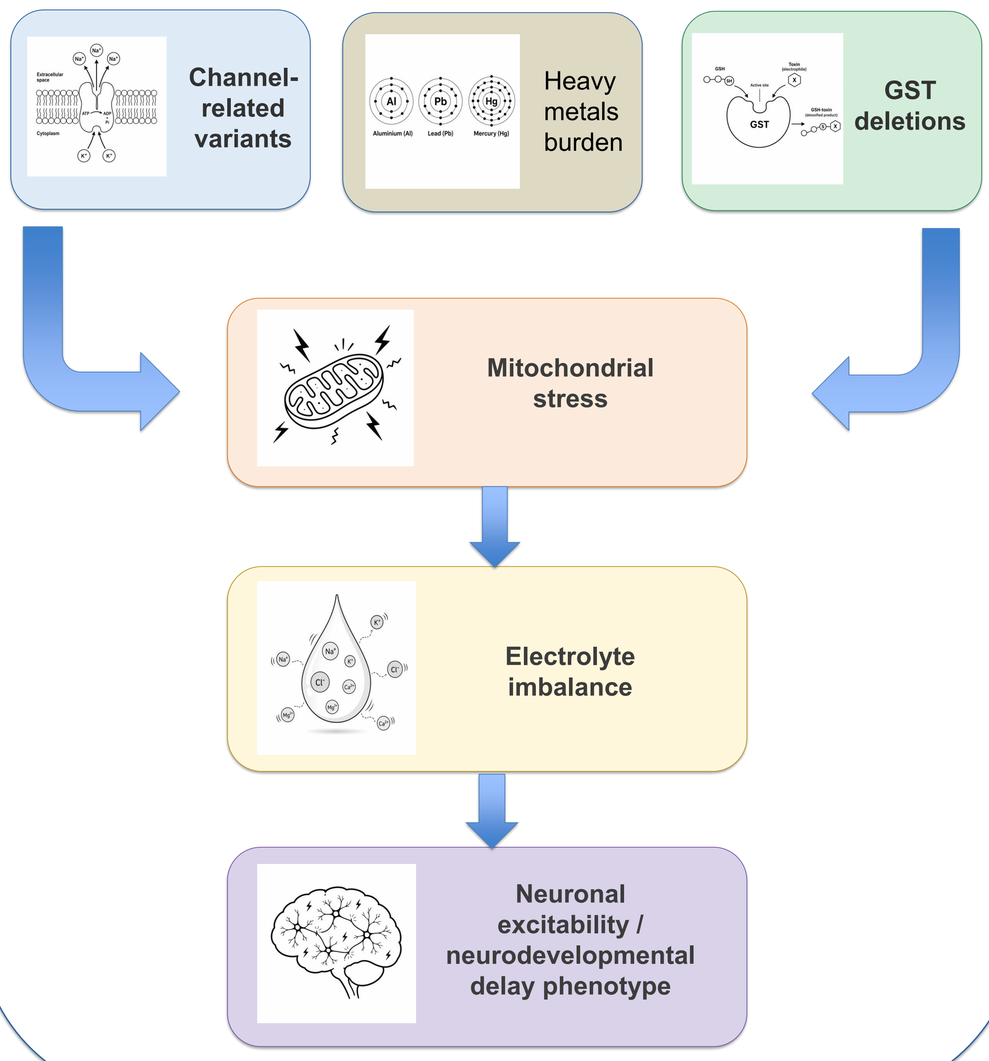
Developmental delay with excitability-related features

Genomic testing: chromosomal microarray and exome sequencing

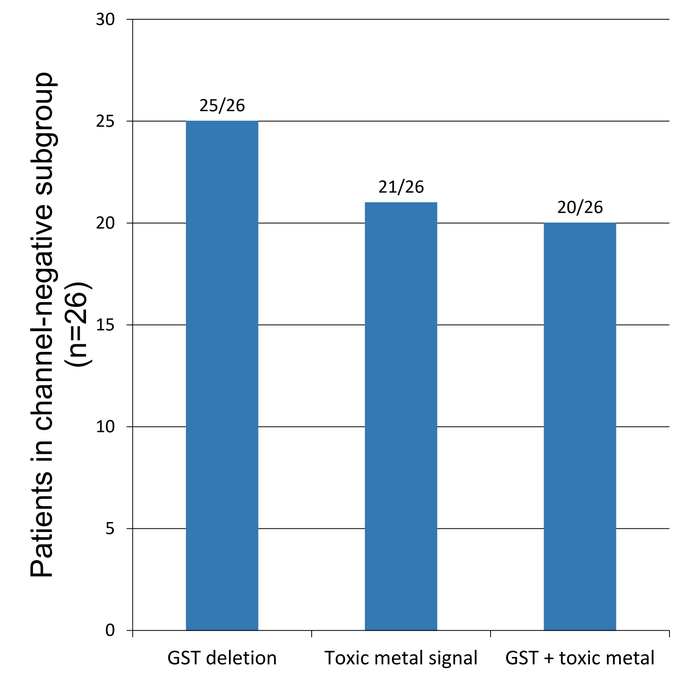
Functional assessment: systemic electrolytes; mitochondrial stress defined by elevated lactate, elevated pyruvate, or increased lactate:pyruvate ratio; toxic metal signals

Stratification: channel-related variants and GST deletion status

INTEGRATED MECHANISTIC MODEL

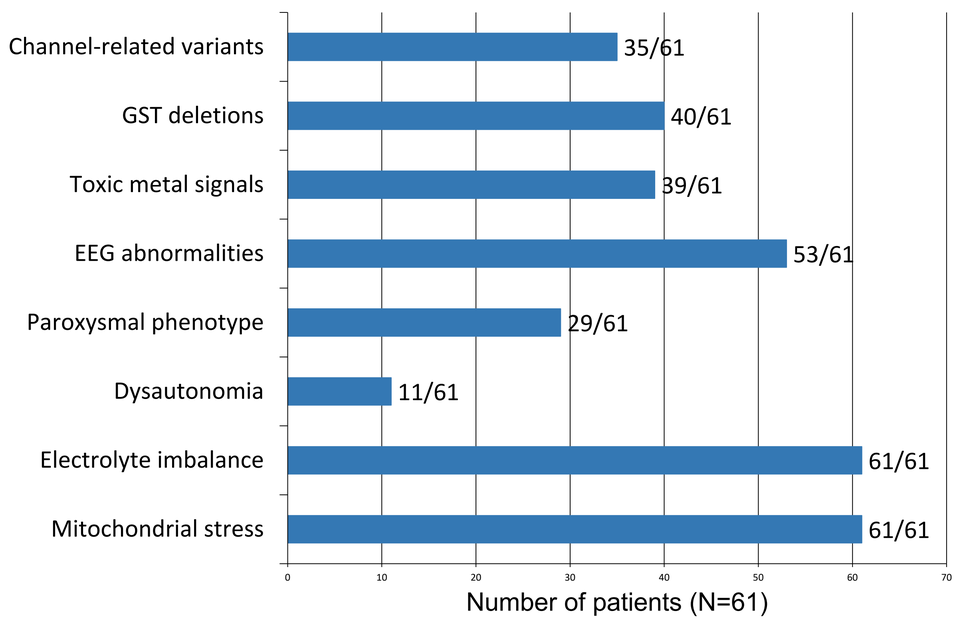


KEY FINDINGS IN CHANNEL-NEGATIVE SUBGROUP

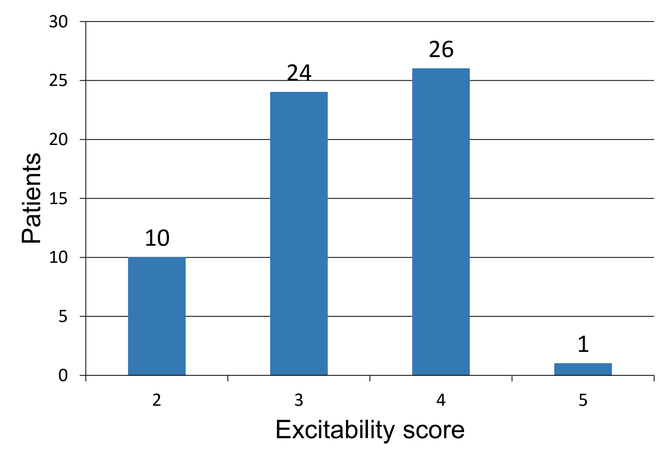


Most channel-negative cases retained a strong GST/toxic-metal signal, supporting a modifier-based pathway toward excitability.

COHORT SUMMARY



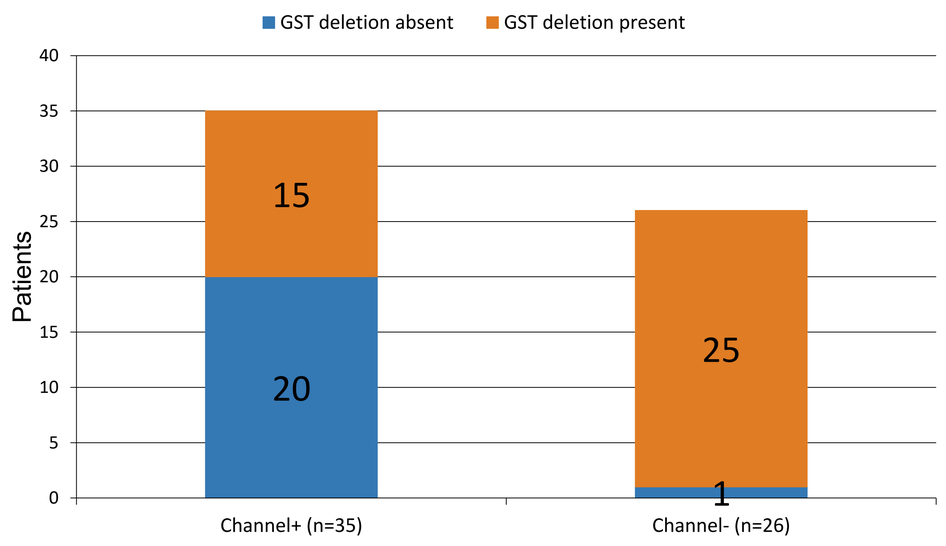
EXCITABILITY SCORE DISTRIBUTION (mean = 3.3)



ELECTROLYTE PROFILE

- K+ — Dominant: elevated potassium
- Na+ — Frequent: altered sodium-potassium balance
- Ca^{2+} — Less frequent: elevated calcium
- Mg^{2+} — Rare: elevated sodium or magnesium

GST DELETIONS BY CHANNEL STATUS



GST GENOMIC DISTRIBUTION

Dominant: chromosome 22 GST gene cluster

Additional: chromosome 1

Rare: chromosomes 6, 11 and 14

CONCLUSION

1. A channelopathy-compatible functional phenotype was observed across the cohort.
2. GST deletions may act as redox susceptibility modifiers, particularly in genomically unresolved cases.
3. Integrating genomic and functional profiling may improve interpretation of unresolved neurodevelopmental disorders.

Conflict of interest: None declared.

No patient-identifiable data are shown.

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