More than an extra chromosome: Multiple diagnoses in patients with Down syndrome and severe neurological burden

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BACKGROUND

Individuals with Down syndrome (DS) can exhibit a wide spectrum of clinical features with varying degrees of severity.

- The prevalence of seizures is higher in this population compared to the general population
  - 8-26% of patients with DS have seizures[1]
- Congenital heart disease (CHD) is the most common cardiovascular condition in individuals with DS
  - ~ 50% of infants with DS have CHD[2]

The possibility of a dual diagnosis should be explored when the phenotype is more severe than anticipated for DS.

METHODS

Five patients were diagnosed with Down syndrome by standard cytogenetic techniques. They subsequently underwent **trio exome sequencing** (ES) due to their severe clinical presentation.

RESULTS

Trio ES identified a pathogenic or likely pathogenic variant in genes associated with their respective phenotypes for 3 of the 5 patients. These 3 had a more severe neurological presentation.

PRACTICE IMPLICATIONS

The variants identified had clinical utility for patients as well as their family members. The findings were either relevant for reproductive decision-making or provided diagnostic insight into familial conditions. This further highlights the need for updated, comprehensive risk assessment and genetic testing for patients with unexpectedly severe phenotypes.

Patient 1: Newborn male

- Extreme tonic-clonic seizures
- Status epilepticus
- Thrombocytopenia (concern for transient abnormal myelopoiesis)
- Electrolyte abnormalities (+ hypocalcemia)

- ***UFSP2*:** Homozygous pathogenic c.344T>A (p.V115E), Developmental and epileptic encephalopathy, 106 [AR]
- ***GATA1*:** De novo likely pathogenic c.159_160delinsAGTG (p.T54Vfs*84), Various hematological abnormalities [XLR]

Patient 2: 14 y/o female

- Worsening seizure burden
- Diagnosis of Lennox-Gastaut syndrome since childhood

- ***NBEA*:** *De novo* pathogenic c.3911dup (p.D1304Efs*11), Neurodevelopmental disorder with or without early-onset generalized epilepsy [AD]

Patient 3: Newborn male

- Seizures
- Overgrowth
- Hemimegalencephaly and hypoplasia of the cerebellar vermis
- Family history of seizures in father

- ***NPRL3*:** Paternally inherited pathogenic c.189-1G>A, Epilepsy, familial focal, with variable foci 3 [AD]
- Incomplete penetrance has been described for *NPRL3* phenotypes

Patient 4: 9 y/o male

- Progressively worsening seizures
- Failure to thrive

Patient 5: 6-week-old male

- Extensive cardiac anomalies
- Possible pulmonary hypertension
- Family history of consanguinity

- Less severe neurological involvement compared to patients 1, 2, and 3
- No additional diagnosis made by molecular testing

Conclusions: Additional molecular genetic testing may complement cytogenetic testing for patients with Down syndrome, especially when the neurological presentation is unexpectedly severe.

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References: (1) Altuna M, Giménez S, Fortea J. Epilepsy in Down Syndrome: A Highly Prevalent Comorbidity. J Clin Med. 2021;10(13):2776. Published 2021 Jun 24. doi:10.3390/jcm10132776 (2) Dimopoulos K, Constantine A, Clift P, et al. Cardiovascular Complications of Down Syndrome: Scoping Review and Expert Consensus. Circulation. 2023;147(5):425-441. doi:10.1161/CIRCULATIONAHA.122.059706