More than an extra chromosome: Unexpected multiple diagnoses in individuals with Down syndrome

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P297

The **phenotype** observed in individuals with **Down syndrome** (DS) due to trisomy 21 can be **highly variable in terms of severity and types of additional features beyond the classic hallmarks** (congenital hypotonia, dysmorphic features and cognitive impairment). Various factors may lead to this variability (e.g., specific gene expression level differences on chromosome 21), but the **possibility of a dual diagnosis** should be considered. For the majority of patients with DS, however, genetic testing is concluded once the DS confirmatory result is obtained from chromosomal microarray analysis or karyotyping, and any potential phenotypic deviations are not investigated further. We describe four patients from the in-patient service with a cytogenetically-confirmed diagnosis of Down syndrome for whom additional (rapid) trio exome sequencing was performed due to the presence of more severe neurological features than expected to be associated with DS.

Patient 1
Newborn male

Presenting with:
- Extreme tonic-clonic seizure burden & status epilepticus
- Thrombocytopenia (concern for transient abnormal myelopoiesis)
- Electrolyte abnormalities (including hypocalcemia)

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

Patient 2
14 y/o female

Presenting with:
- Worsening seizure burden (diagnosis of Lennox-Gastaut syndrome since childhood)

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

Patient 3
Newborn male

Presenting with:
- Seizures
- Overgrowth
- Structural brain abnormalities including hemimegalencephaly and hypoplasia of the cerebellar vermis

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

Patient 4
9 y/o male

Presenting with:
- Progressively worsening seizures (but less severe neurological involvement compared to patients 1, 2, and 3)
- Failure to thrive

No additional diagnosis was made by molecular testing

CONCLUSIONS

Additional diagnoses were made in three out of four cases, which illustrates that additional molecular genetic testing may be a valuable complementary tool for the care of individuals with Down syndrome; it may be considered specifically when the severity of the neurological presentation exceeds the expected manifestations associated with Down syndrome.

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Additional dual diagnosis cases described on P682: "Phenotype expansion or multilocus variants? Additional molecular findings in patients with well-known chromosomal disorders"