Whole Exome Sequencing in a Myopathic Child: Where Does a Parent Go from Here?

Leslie Jackson, MSN,CRNA; Mary C. Theroux, MD
Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE

Clinical History

- 3.5-year-old white female
- Static encephalopathy
- Global developmental delay
- Seizure disorder
- Hypotonia
- Cortical visual impairment
- Nystagmus
- Intermittent esotropia
- High palate
- Epicanthal folds
- Mild hirsutism

Clinical Work Up

- Normal acylcarnitine profile
- Normal palsma amino acid profile
- Normal creatine kinase
- Normal urine organic acids
- Normal urine MPS screen
- Screen for San Filippo syndrome
- Plasma N-acetyl-alpha-D-glucosaminidase activity is within normal range
- Transferrin electrophoresis to rule out disorders of glycosylation
- **Fatty Acid Profile**: concentrations of C26:0, pristanic acid and phytanic acid were elevated.

Consistent with peroxisomal disorders, the patient was thought to have infantile refsum disease.

Genetic Work Up

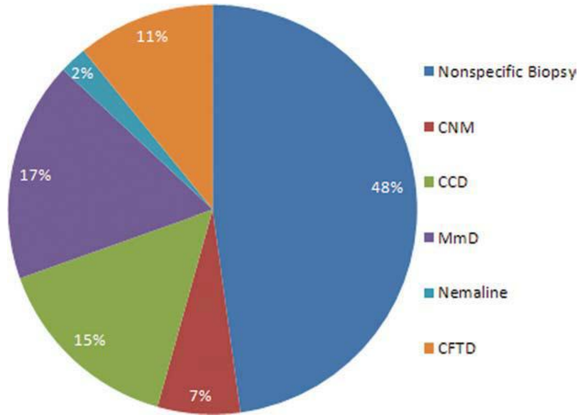
- Normal female karyotype
- SNP microarray: No demonstrable regions of genomic imbalance and no increased homozygosity was observed
- Rett: MECP2 sequencing: normal
- XLMR: CASK analysis: normal
- Rubinstein-Taypi: CREBBP sequencing-normal
- Prader-Willi Syndrome: methylation analysis of AS/PWS critical region: normal
- PMD/PMD-like testing:
  - PLP1 Duplication: not detected
  - LMNB1 duplication: not detected
- Mutation analysis: none detected
- GJC2 (formerly GJA12) mutation analysis: none detected
- Mutation analysis of the PEX genes which are associated with peroxisomal disorders: normal
- **Diagnosis of peroxisomal disorder now in question**

Anesthetics and Surgeries

- Sevo/Propofol/Roc
- Sevo/Nitrous
- Sevo/Nitrous (Laryngospasm)
- Sevo/Nitrous
- Sevo/Nitrous
- Sevo/Nitrous
- Sevo/Nitrous
- EGD with Biopsy
- PEG
- PEG to MIC
- Tympanostomy/ABR
- Tympanostomy
- Tympanostomy
- Strabismus Correction

Whole Exome Sequencing (WES)

Figure 1



Prevalence of myopathies in a sub population of USA[1]

- Mutations in disease genes related to clinical phenotype: none
- *RYR1* variant: A variant of unknown clinical significance in a disease gene related to clinical phenotype on chromosome 19: on exon 36, nucleotide c.G5861A, amino acid p.R1954H.A heterozygous c.5861G>A (p.R1954H).
- Comment: mother is also heterozygote, and father is negative for the same variant

Discussion

RYR1-related myopathies are one of the most common forms of congenital myopathy.[1]

Distribution of the muscle histology of a subpopulation (Fig 1) representative of North America. Causative mutation was found in 16/44 patients and 13/16 such mutations were in *RYR1*.[1] *RYR1* (variants) is listed in the reportable genetic variants recommended by ACMG in their 2013 consensus document.[2]

Questions from parents

1. Does discovery of RYR1 help diagnose the patient?.
2. History of seizures: How does it fit in with presence of *RYR1 variant*?
3. Should Patient be subjected to CHCT?
4. Should her mother be tested first since she is also positive for the same variant?

References

1. Amburgy et al: Prevalence of congenital myopathies from a representative pediatric united states population: Annals of neurology 2011.
2. Greenet al: ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genetics in Medicine 2013