Next-Generation Sequencing test within a neurologic region of interest leads to diagnosis of *RYR1*-related disorder for 36-year-old female after three decades

Pamela D. Gerrol, MS, CGC[1]; Natalie A. Vena, MS, CGC[1]; Anne Rutkowski, MD[2,3]
1) Claritas Genomics, Cambridge, MA; 2) Cure Congenital Muscular Dystrophy, cureCMD.org;
3) Kaiser SCPMG, Los Angeles, CA

CLARITAS GENOMICS

Synopsis

We report on a 36yo female with a progressive neuromuscular disorder who has remained without a definitive molecular diagnosis, thus lacking the benefit of prognostic and familial risk information. She initially presented to Neurology at age 3 with motor delay and lumbar lordosis. She experienced gradual progression of muscle weakness in all extremities, facial diplegia, and ophthalmoplegia and is now wheelchair-dependent. Muscle biopsy performed at age 3 was consistent with type I fiber predominance and centronuclear myopathy. Prior testing included *MTM1* sequencing and deletion/duplication studies which were negative. Testing performed at Claritas Genomics revealed two *RYR1* variants, confirmed by parental studies to appear *in trans*. Though neither variant was conclusively classified as pathogenic using the ACMG standards and guidelines for interpretation of sequence variants, the molecular results identified, suggestive of autosomal recessive *RYR1*-centronuclear myopathy, are consistent with the patient's clinical phenotype, thus providing her with a molecular diagnosis after 30 years of uncertainty.

Clinical information

The patient was born at 42 weeks to a G3 SAB2 mother. Both feet were reportedly "turned in" which was treated with serial casting. She initially presented to Neurology at age 3 with motor delay and lumbar lordosis. Initial exam showed upper and lower facial weakness, no ophthalmoplegia, neck flexor weakness, proximal weakness, and the use of a Gower maneuver. After a relatively stable disease course in childhood, there was gradual progression of muscle weakness, proximal greater than distal, in upper and lower extremities. She developed ophthalmoplegia (bilateral restricted upward gaze) and facial diplegia in the second decade and is now wheelchair-dependent. Disease progression was noted by the patient during and after both pregnancies. Currently, she experiences daily muscle spasms, restless leg syndrome, and a feeling of breathlessness without hypoventilation or hypercapnea on polysomnography. Evaluations have included EMG consistent with myopathy; normal nerve conduction studies;and muscle biopsy performed at age 3 consistent with type I fiber predominance and centronuclear myopathy--no cores or ultrastructural changes. No cardiac involvement was detected by echocardiogram and Holter monitor. There is no personal or family history of malignant hyperthermia. *MTM1*(MIM 300415) sequencing and deletion/duplication studies were negative.

Test Information

We performed the Claritas Pediatric Neurology Exome, which employs two next-generation sequencing (NGS) technologies to detect and orthogonally confirm variants in 614 neurology-related genes. This approach focuses on genes with known clinical relevance and reduces the number of variants requiring confirmation[++], thus reducing turnaround time. Using HPO codes relating to the patient's phenotype to filter the 614 genes*, NGS identified 11 potentially clinically-relevant variants, including two in *RYR1* (MIM 180901): a novel frameshift variant and a previously reported missense variant. The maternally-inherited c.14662_14663delAT (p.Met4888Valfs*20) frameshift variant predicted to result in a premature stop codon was classified as likely pathogenic. The paternally-inherited c.10622C>T (p.Ala3541Val) missense variant had been previously reported, but no conclusive evidence was provided to determine pathogenicity; it was classified as a variant of uncertain significance.

++Sanger sequencing performed for single-platform-detected variants and low-coverage areas
*Myopathy (HP:0003198) • Muscle weakness (HP:0001324) • Muscular hypotonia (HP:0001252)

Conclusion

The molecular results identified using our orthogonal approach in next-generation sequencing of a pediatric neurology-related region of interest are suggestive of an autosomal recessive *RYR1*-centronuclear myopathy, consistent with the patient's clinical phenotype, and have provided this 36 year old woman with a molecular diagnosis after over 30 years of uncertainty.

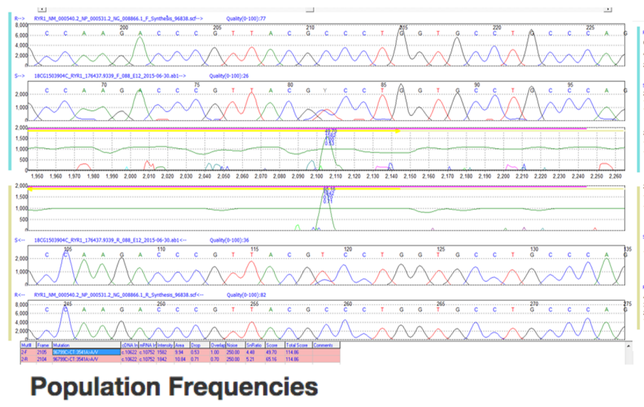
The following photo and quote appeared in an article featuring our patient in the BloombergBusinessweek magazine's Technology section on 09/10/15, reprinted here with permission:

"...Smith is participating in research that may one day lead to treatments or more supportive care. 'Just being connected feels good. I felt alone for a long time,' she says. 'And I want to do it for the bigger picture, too. Not just for myself, but so I can be counted.'..."

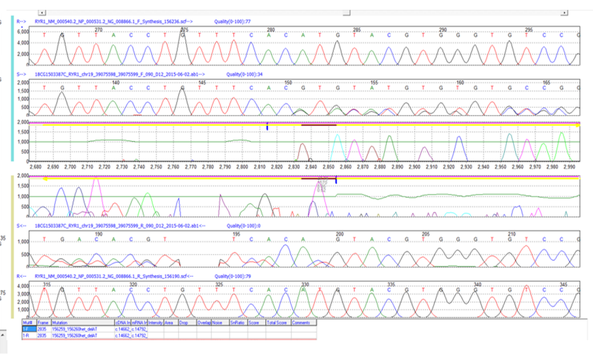
Photo credit Lindsay Beckwith, reprinted with permission

http://www.bloomberg.com/news/articles/2015-09-10/genetic-analysts-can-now-more-quickly-identify-rare-illnesses

RYR1: c.10622C>T p.Ala3541Val



RYR1: c.14662_14663delAT p.Met4888Val fs*20



delAT not previously reported

Population Frequencies

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
South Asian	1	16128	0	6.2e-05
European (Non-Finnish)	2	63722	0	3.139e-05
African	0	9678	0	0
East Asian	0	8326	0	0
European (Finnish)	0	5816	0	0
Latino	0	10932	0	0
Other	0	850	0	0
Total	**3**	**115452**	**0**	**2.598e-05**

Frequencies from: http://exac.broadinstitute.org/gene/ENSG00000196218

See other Claritas Genomics posters:
1619, 1933, 1981, 2071, 2085

CLARITAS GENOMICS INC.
99 Erie Street | Cambridge, MA 02139

clientservices@claritasgenomics.com
p: 617.553.5880 p: 855.373.9003 f: 617.553.5842