PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

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Progressive Bulbar Palsy With or Without Sensorineural Deafness (Brown-Vialetto-Van Laere Syndrome and Fazio-Londe Disease) via *C20orf54* Gene Sequencing (Test #417)

Brief Description of Clinical Features: Brown-Vialetto-van Laere syndrome and Fazio-Londe disease are rare neurologic disorders caused by mutations in the *C20orf54* gene (OMIM 613350). Progressive bulbar palsy with sensorineural deafness, also called Brown-Vialetto-van Laere syndrome (BVVLS, OMIM 211530), is a disorder with clinical findings of bulbar palsy, neurological deterioration, muscle weakness, respiratory insufficiency, and early death. Onset of symptoms has been reported in the first decade of life (Green et al. *Am J Hum Genet* 86:485-489, 2010). Sensorineural deafness was also found to be a common feature, but more often in patients with later onset. Fazio-Londe disease (OMIM 211500) is a progressive bulbar palsy with onset in childhood that presents with hypotonia and respiratory insufficiency due to diaphragmatic paralysis (Bosch et al. *J Inherit Metab Dis* 34:159-164, 2011). The Fazio-Londe disease patients described by Bosch et al. (2011) displayed plasma acylcarnitine and urine organic acid profiles suggestive of a mild form of the multiple acylCoA dehydrogenation defect (MADD). However, further biochemical testing revealed a profound flavin deficiency in spite of a normal dietary riboflavin intake. Brown-Vialetto-van Laere syndrome and Fazio-Londe disease are believed to represent variable presentations of a single disorder (Dipti et al. *Brain Dev* 27:443–446, 2005).

Genetics: BVVLS and Fazio-Londe disease are inherited as autosomal recessive disorders. By two different approaches, the *C20orf54* gene (OMIM 613350) was identified as the cause of Brown-Vialetto-van Laere syndrome (Johnson et al. *Am J Hum Genet* 87:567-569, 2010; Green et al. *Am J Hum Genet* 86:485-489, 2010). The *C20orf54* gene encodes a human homolog of the rat riboflavin transporter and it is thought to play a role in riboflavin transport in humans as well (Green et al. *Am J Hum Genet* 86:485-489, 2010; Bosch et al. *J Inherit Metab Dis* 34:159-164, 2011). A small number of patients worldwide have thus far been documented. *C20orf54 m*utations types reported in patients include missense, nonsense, splicing, and frame-shifting.

Description of This Particular Test: The *C20orf54* gene is composed of 4 coding exons encoding a protein of 469 amino acids. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. As indicated, we will also sequence one (Test #100, $190) or two (Test #200, $340) exons in family members of patients with known mutations or to confirm research results.

Reference Sequences: **Genomic: NC_**000020.10 **mRNA: NM_**033409.3
Protein: NP_212134.3 **mRNA and Protein: CCDS** 13007.1

Indication for Testing: Patients with clinical features consistent with Brown-Vialetto-van Laere syndrome or Fazio-Londe disease and demonstrated autosomal recessive inheritance.

Sensitivity of test: Brown-Vialetto-van Laere syndrome and Fazio-Londe disease are both rare disorders, and clinical sensitivity cannot yet be estimated. Analytical sensitivity should be high because all mutations thus far reported are expected to be detected by sequencing genomic DNA.

Turnaround Time: Maximum of 40 days, although many tests are completed in 2 – 3 weeks.
Specimen Requirements: See page 4 of Requisition Form.

Price: **Sequencing of *C20ORF54* Gene** **Exons 2-5** **$ 540**

CPT Codes:

Sample Ascertainment x1	83890	$ 30	DNA Isolation x1	83891	$ 40
Amplification x6	83898	$140	Sequencing x6	83904	$210
Separation x1	83894	$ 30	Interpretation/Report x1	83912	$ 90

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