

Seipin-Related Disorders via *BSCL2* Gene Sequencing (Test #461)
Distal Hereditary Motor Neuropathy, Type V
Congenital Generalized Lipodystrophy, Type 2
Spastic Paraplegia 17

Brief Description of Clinical Features: Seipin-related neurologic disorders include distal hereditary motor neuropathy type V (HMSN_V; OMIM #600794) and spastic paraplegia 17 (SPG17, Silver syndrome; OMIM #270685). The distal hereditary motor neuropathies represent a phenotypic continuum of distal neuropathy with weakness and wasting starting in the distal limbs, predominately the hands. Onset of the *BSCL2* related neuropathies is between the first and seventh decades of life and progression is slow. Motor neuron involvement includes amyotrophy of the peroneal and hand muscles, gait disturbances, and mild to severe spasticity (Wagner and Auer-Grumbach, *GeneReviews*, 2005). Remarkable variability of phenotypic expression, even within families, has been described (Auer-Grumbach et al. *Ann Neurol* 57:415-424, 2005). Mutations in the seipin gene are also the cause of congenital generalized lipodystrophy (CGL2, Berardinelli-Seip congenital lipodystrophy; OMIM #269700), a congenital or early infancy onset disorder characterized by near absence of adipose tissue and insulin resistance (Magré et al *Nature Genetics* 28:365-370, 2001). Patients affected with CGL2 exhibit accelerated growth and maturation in early childhood, muscle hypertrophy, hyperpigmented and coarse skin, hirsutism, hepatomegaly, hyperlipidemia, and insulin resistant diabetes mellitus.

Genetics: Distal hereditary motor neuropathy type V and Silver syndrome are inherited as autosomal dominant disorders. Missense mutations in the gene encoding seipin (*BSCL2*; OMIM #606158) are the cause of both neuropathies (Windpassinger et al. *Nature Genetics* 36:271-276, 2004). Mutations in the *GARS* gene are another cause of HMSN_V (Antonellis et al. *Am J Hum Genet* 72:1293-1299, 2003). Congenital generalized lipodystrophy type 2 is inherited as an autosomal recessive disorder and almost all reported causative *BSCL2* mutations for this disorder predict null alleles.

Description of This Particular Test: Seipin is encoded by the *BSCL2* gene located on chr 11q13. Testing for CGL2 is accomplished by amplifying the 11 coding exons (exons 2-12) and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. In distal neuropathy patients, exon 3 is tested initially.

Reference Sequences: **Genomic:** NC_000011.8 **mRNA:** NM_001130702.1

Indication for Testing: Individuals with clinical and electrophysiological signs consistent with a distal neuropathy with or without spasticity and autosomal dominant inheritance. Individuals with clinical features of a generalized lipodystrophy with congenital or early infancy onset and insulin resistance.

Sensitivity of Test: Among a cohort of 45 congenital generalized lipodystrophy patients Agarwal et al. (*J Clin Endocrinol Metab* 88:4840-4847, 2003) found 11 with *BSCL2* mutations and 26 with *AGPAT2* gene mutations. Two *BSCL2* mutations (p.Asn88Ser and p.Ser90Leu) have been found in a small number of patients with neurological disorders. Analytical sensitivity should be high because all *BSCL2* mutations reported to date are of the type expected to be detected by DNA sequencing of genomic DNA.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of *BSCL2*** **exon 3: \$ 190** **exons 2-12: \$ 740**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x12	83898	\$210	Sequencing x12	83904	\$320
Separation x1	83894	\$ 60	Interpretation/Report x1	83912	\$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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