

Congenital Generalized Lipodystrophy Types 1 and 2 via *AGPAT2* and *BSCL2* Gene Sequencing (Test #463)

Brief Description of Clinical Features: Congenital generalized lipodystrophy (CGL) is a group of disorders characterized by altered body fat distribution and insulin resistance. CGL type 1 (CGL1, OMIM #608954) and type 2 (CGL2, OMIM #269700), known also as Berardinelli-Seip congenital lipodystrophy types 1 and 2, demonstrate near absence of body fat at birth or in early infancy and severe insulin resistance leading to diabetes mellitus. Patients have hypertriglyceridemia and low levels of HDL cholesterol. Absence of adipose tissue results in a hypermuscular appearance. Bone age is advanced in early childhood and patients have an accelerated growth rate and a voracious appetite (Argawal et al. *J Clin Endocrinol Metab* 88:4840-4847, 2003). Fatty infiltration of the liver may lead to hepatic disease including cirrhosis. Other complications include acanthosis nigricans and hypertrophic cardiomyopathy (Van Maldergem et al. *J Med Genet* 39:722-733, 2002). When compared with CGL1, CGL2 may have a higher incidence of premature death and a lower incidence of partial or delayed onset of lipodystrophy (Van Maldergem et al. 2002).

Genetics: Congenital generalized lipodystrophy types 1 and 2 are inherited as autosomal recessive disorders. Mutations in the seipin gene (*BSCL2*, OMIM 606158) are responsible for CGL2 (Magré et al *Nat Genet* 28:365-370, 2001), whereas mutation in the *AGPAT2* gene (OMIM #603100) are responsible for CGL1 (Argawal et al. *Nat Genet* 31:21-23, 2002). Mutations that result in null alleles are the most frequent pathogenic changes in the *AGPAT2* and *BSCL2* genes, although missense mutations have also been reported in both genes.

Description of This Particular Test: Seipin is encoded by the *BSCL2* gene located on chr 11q13 and 1-acyl-glycerol-3-phosphate acetyltransferase is encoded by the *AGPAT2* gene located on chr 9q34. Testing is accomplished by amplifying the coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. Testing of the two genes is carried out in the order specified by the client.

Reference Sequences:

Gene:	Genomic: NC_	mRNA: NM_	Protein: NP_	CCDS:
<i>AGPAT2</i>	000009.11	006412.3	006403.2	7003.1
<i>BSCL2</i>	000011.8	001130702.1	001124174.1	44627.1

Indication for Testing: 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, 26 were found to have *AGPAT2* gene mutations and 11 to have *BSCL2* gene mutations (Agarwal et al. *J Clin Endocrin Metab* 88:4840-4847, 2003). Linkage to the *AGPAT2* and *BSCL2* loci was ruled-out in three of the remaining patients suggesting further genetic heterogeneity exists.

Among a cohort of 94 CGL patients, Magré et al. (*Diabetes* 52:1573-1578, 2003) found *BSCL2* mutations in 62 patients and *AGPAT2* mutations in 30 of the remaining 32 unrelated subjects.

Turnaround Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequential Sequencing of: *AGPAT2*, *BSCL2*

Gene	CPT Codes						Totals
	83890	83891	83898	83904	83894	83912	
<i>AGPAT2</i>	\$ 30 x1	\$ 40 x1	\$ 170 x9	\$ 260 x9	\$ 60 x1	\$ 80 x1	\$ 640
<i>BSCL2</i>	\$ 30 x1	\$ 40 x1	\$ 210 x12...	\$ 320 x12	\$ 60 x1	\$ 80 x1	\$ 740
Panel	\$ 30 x1	\$ 40 x1	\$ 380 x21	\$ 580 x21	\$ 120 x1	\$ 160 x1	\$1,310*

*When both genes on this panel are sequentially tested, a 15 % discount will apply to the total cost.

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

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