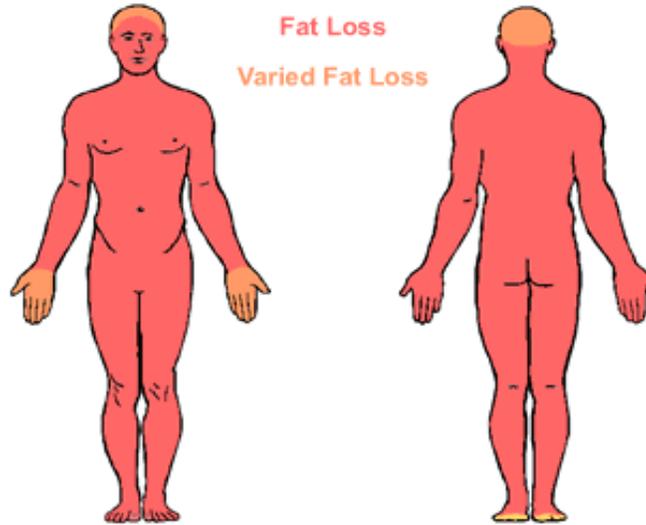


## Inherited: Congenital Generalized (CGL; Berardinelli-Seip Syndrome)



Congenital generalized lipodystrophy is a rare autosomal recessive disorder in which near total absence of the adipose tissue is evident from the birth. It was originally described by Berardinelli and Seip, and since then has been reported in approximately 500 patients of various ethnic origins. Assuming that only 1 in 4 patients is reported, the estimated worldwide prevalence is about 1 in 10 million. In an autosomal recessive disorder, parents are carriers of blips in one of their genes but are not affected. The affected patients inherit blips in both the genes inherited from the father and mother. The risk increases with consanguinity (when parents are close relatives e.g. uncle-niece, cousins etc). There is a 25% chance of transmission of both defective genes to the affected children i.e. the ratio of affected to unaffected children is 1:3.

Positional cloning and candidate gene approach have led to the identification of four genetic loci for Congenital generalized lipodystrophy: CGL1 is due to *AGPAT2* gene mutations, CGL2 is due to *BSCL2* gene alterations and CGL3 is associated with *CAV1* gene mutation and CGL4 is due to *PTRF* gene mutations.

All subtypes of CGL have near total loss of body fat. Patients also present with acanthosis nigricans (dark velvety pigmentation of the skin) in the axilla, neck, groin and sometimes even over the trunk. Metabolic complications associated with insulin resistance such as impaired glucose tolerance, diabetes, hypertriglyceridemia, and hepatic steatosis are evident at a young age and are often difficult to control. Extreme hypertriglyceridemia may result in recurrent pancreatitis. However, each variety is associated with some peculiar clinical features. Below is the table showing various problems associated with GGL.

Clinical features associated with Various Congenital Lipodystrophy	CGL1	CGL2	CGL3	CGL4
Mechanical Fat loss	+	-	+	+
Metabolic Fat loss	-	-	+	+
Bone marrow Fat loss	-	-	+	+
Bone Cysts formation	+++	+	?	?
Vitamin D problem	+	-	+	-

Muscular Dystrophy	-	-	-	+
Bone Alterations	-	-	-	+
Mental Retardation	-	+	-	-
Hypertrophic Cardiomyopathy	-	+	-	+
Metabolic Disorders	+++	++++	+	+

CGL patients with *BSCL2* mutation have more severe lipodystrophy in that there is a loss of both mechanical fat (the fat that serves supportive or protective functions and is located in the palms, soles, orbits, scalp and around the joints) and the metabolically active fat (fat that participates in the storage and release of energy and is located at most subcutaneous regions, intermuscular regions, bone marrow, intraabdominal and intrathoracic regions) when compared with other CGL patients in whom mechanical fat is preserved. This total or near absence of metabolic fat at birth or immediately afterwards is a diagnostic marker for CGL. Affected infants have a marked muscular appearance due to the absence of fat

Patients with CGL2 have earlier onset of diabetes and have higher prevalence of mild mental retardation compared to CGL1. As children, they are often noted to have a voracious appetite and accelerated linear growth. The onset of diabetes is usually during the pubertal years and requires high dose of insulin to control the blood glucose levels. Serum leptin and adiponectin levels are extremely low.

Acromegaly is quite prominent in these patients and the clinical features consist of enlarged hands, feet and prominent mandible. Enlarged spleen and liver is almost universally present in all the patients. Presence of enlarged liver may ultimately lead to cirrhosis. A high prevalence of hypertrophic cardiomyopathy (dysfunction of heart) is also seen in patients with *BSCL2* mutations.

Females present with enlarged clitoris, increased body hair, absence of or irregular menstrual cycles, and polycystic ovaries (enlarged ovaries). Only a few affected women have had successful pregnancies, whereas affected men have normal fertility. Other clinical features, which may be noted in some patients, include increased sweating, umbilical hernia and focal lytic lesions (bone appear to be eaten up on X-rays) in long bones of the upper and lower extremities. Also, nearly all patients have a prominent umbilicus or frank umbilical hernia.

### **Genetic Basis**

#### ***CGL1 locus: AGPAT2***

Our group identified the gene on the long arm of chromosome 9 (9q34), which when mutated (altered gene) causes CGL1. This gene encodes for the enzyme *AGPAT2* (1-acylglycerol-3-phosphate O-acyltransferase 2) which is responsible for the production of an important intermediate in the synthesis of triglycerides or fat. Mutations (alterations) in this gene may result in lipodystrophy either due to lack of triglyceride synthesis or due to abnormal adipocyte (fat cell) function. Interestingly, almost all patients of African origin have a splice-site mutation (IVS4-2A>G) on the same haplotype, suggesting that the mutation has a common ancestral origin.

#### ***CGL2 locus: BSCL2***

Mutations in another gene located on the long arm of chromosome 11 (11q13) called *BSCL2* (Berardinelli-Seip Congenital Lipodystrophy 2) causes CGL2. The gene product of *BSCL2* is a protein, *Seipin* whose function remains unknown. Therefore how *BSCL2* mutations cause CGL

remains to be elucidated. Patients with *seipin* mutations have a higher prevalence of mild mental retardation and hypertrophic cardiomyopathy than do those with *AGPAT2* mutations.

#### **CGL3 locus: *CAV1***

Recently, it was found that mutation in gene located on chromosome 7q31 which encodes caveolin -1(*CAV1*) causes CGL3. To date only one patient have been reported and she had clinical features similar to those reported in patients with CGL1 and CGL2.

#### **CGL4 locus: *PTRF***

Polymerase 1 and transcript release factor (*PTRF*; also known as cavin) is a protein which in humans is encoded by *PTRF* gene. The gene is located on chromosome 17. It is a highly abundant caveolae component and is suggested to have an essential role in caveolar formation. Recently, it has been reported that mutations in *PTRF* gene in 5 nonconsanguineous patients caused a disorder presenting as generalized lipodystrophy and muscular dystrophy. Muscle hypertrophy, muscle mounding, mild metabolic complications, and elevated serum creatine kinase levels were also observed in these patients.

#### **Other Types of Congenital Generalized Lipodystrophy**

Some patients with congenital generalized lipodystrophy (less than 20 percent) have neither *AGPAT2* or *BSCL2* mutations, nor linkage to either gene locus, suggesting that additional loci and other distinct pathways are involved.

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