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Short communication

# Generalized lipodystrophies: Clinical characterization and physiopathology



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## 1. Introduction

Congenital generalized lipodystrophy (CGL), also known as Berardinelli-Seip congenital lipodystrophy (BSCL), represents the most extreme phenotype of lipodystrophies with almost complete loss of body fat observed at birth or during the first months of life and early development of metabolic complications during childhood. This disease was first reported in the 1950s in Brazil by Dr. Waldemar Berardinelli and in Norway by Dr. Martin Seip. BSCL is a genetically transmitted disease classified into four subtypes based on the genes involved, with BSCL1 and BSCL2 being the most prevalent.

## 2. Clinical features

BSCL1 is caused by mutations in the *AGPAT2* gene, encoding the 1-acyl-sn-glycerol-3-phosphate acyltransferase, involved in triglyceride (TG) synthesis. BSCL2 is associated with mutations in the *BSCL2* gene that encodes the protein named seipin. Less common subtypes, BSCL3 and BSCL4, result from mutations in genes encoding proteins associated with caveolae, specifically Caveolin-1 and PTRF (also known as Cavin-1). BSCL is characterized by a near absence of adipose tissue, resulting in prominent veins, muscle hypertrophy, and a gaunt appearance. Diagnosis typically involves anthropometric measurements and imaging techniques such as MRI or DXA.

Patients with BSCL exhibit severe metabolic complications such as those seen in obesity, including insulin resistance, hyperinsulinemia, and glucose intolerance. The condition is often referred to as lipodystrophic diabetes due to these metabolic disturbances. Complications such as retinopathy, nephropathy, and neuropathy may arise due to difficulty in glycaemic control.

BSCL is associated with severe hypertriglyceridemia and ectopic lipid deposition, particularly in the liver. This can progress to non-alcoholic steatohepatitis (NASH) and cirrhosis. The disorder also leads to reduced levels of adipokines such as leptin and adiponectin, contributing to hyperphagia and further metabolic complications.

Cardiovascular complications are frequent in BSCL patients, with hypertrophic cardiomyopathy being a common feature. Other cardiac abnormalities include diastolic dysfunction and QT prolongation.

Hyperandrogenism is frequently observed in both male and female patients, leading to genital enlargement, hirsutism, and menstrual irregularities. Polycystic ovary syndrome (PCOS) is common in affected females, likely due to insulin resistance and hyperandrogenism.

Finally, neurological manifestations and skeletal abnormalities are present in some patients but are less frequent than the other clinical manifestations.

## 3. Physiopathology of BSCL

Lipodystrophies represent a group of rare disorders and studying these conditions is challenging due to their rarity and complex clinical manifestations. However, advances in animal and cellular models have shed light on their pathophysiology.

### 3.1. The TG synthesis key player, *AGPAT2*, controls adipocyte maintenance

1-acyl-sn-glycerol-3-phosphate acyltransferase (AGPAT) are key enzymes involved in lipid synthesis. The isoform AGPAT2, highly expressed in the adipose tissue, catalyses the acylation of the lyso-phosphatidic acid (LysoPA) to produce the PA that will subsequently enter the triglyceride or phospholipid synthesis. In humans, AGPAT2 mutations are the cause of BSCL1. Total AGPAT2 KO mice present with virtually no white and brown adipose tissue. The AGPAT2 deficient mice are hyperglycaemic, hyperinsulinemic, insulin-resistant and display liver steatosis. Indirect calorimetry studies revealed that these mice have a constant respiratory quotient along the day suggesting that these animals are metabolically inflexible and unable to switch from one substrate to another according to the nutritional status. Mechanistic studies revealed that AGPAT2 deficiency induced autophagy and adipocytes cell death due to abnormal lipid accumulation leading to cellular stress activation.

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### 3.2. *BSCL2* encodes the mysterious protein seipin

Mutation in the gene *BSCL2* has been the first genetic cause for generalized lipodystrophy in humans. Cellular studies reported that seipin is involved in lipid droplet (LD) homeostasis and in ER contact sites with the LD and the mitochondria. Seipin deficient (SKO) displayed a near-complete lack of white adipose tissue (90% reduction), insulin resistance, and hepatic steatosis. SKO mice also display renal function alteration associated with elevated glycation and TG levels in SKO glomerular area. Studies have also reported the rapid development of diabetic cardiomyopathy characterized by left ventricular hypertrophy, cardiac insulin resistance, and diastolic dysfunction.

In order to address the question of the central role of adipocytes seipin deficiency and subsequent lipodystrophy in the pathophysiology of *BSCL2*, several genetic animal models have been created. For example, inducible adipo-specific seipin deletion led to progressive adipocyte loss and the development of metabolic complications supporting a key role for seipin in maintaining full mature adipocyte phenotype.

### 3.3. *The unexpected involvement of caveolae*

Caveolin-1 null mice display progressive lipodystrophy, characterized by the loss of hypodermal fat layer and generalized reduction of all WAT depots, hypertriglyceridemia but very mild insulin resistance. Cavin-1 invalidation reproduced typical BSCL phenotype with significant fat loss, glucose intolerance, hepatic and muscular insulin resistance and hypertriglyceridaemia.

Caveolae deficient adipocytes have to face with a metabolic situation characterized by defective fatty acid mobilization and an altered insulin-dependent nutrient supply which both likely converge to induce autophagy. These metabolic stresses could have an additional impact on WAT remodeling processes and the development of an inflammatory state, that, altogether, may favor and contribute to the development of lipodystrophy.

## 4. Conclusion

Congenital generalized lipodystrophies are extreme manifestations of adipocyte dysfunction characterized by nearly total absence of white adipose tissue. The study of the 4 genes causing BSCL brought key insight into the pathways controlling adipocytes good health.

Clinical manifestations are early and severe, and currently, recombinant leptin is the most validated therapeutic option for improving metabolic complications of Berardinelli-Seip congenital lipodystrophy (BSCL). Cellular therapy could represent a longer-term hope, but preclinical proof of concepts still needs to be established.

### Animal rights

All the animal experiments have performed according to ethical regulations.

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### Disclosure of interest

The author declares that he has no competing interest.

### Further reading

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