

# Novel Homozygous Mutation in the *AGPAT2* Gene in a Child With Berardinelli-Seip Congenital Lipodystrophy Syndrome

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**Abstract-** Berardinelli-Seip congenital lipodystrophy (BSCL) is an autosomal recessive disorder, characterized by the generalized absence of subcutaneous fat and muscular hypertrophy. Meanwhile other signs and symptoms have already been reported with this genetic disorder. Herein, we report an infant with BSCL, who was referred to our center because of acromegaloid and muscular appearance from the age of three months. He had dark skin, hypertrichosis prominent subcutaneous vessels and organomegaly in physical examination. Genetic study showed novel homozygous mutations in the *AGPAT2* gene, which confirmed diagnosis of BSCL in this patient. Although clinical suspicious could help us to make diagnosis of congenital disorders, definite diagnosis relies on genetic studies.

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## Introduction

Berardinelli-Seip congenital lipodystrophy (BSCL) (1), also named as congenital generalized lipodystrophy (CGL) (2) or congenital generalized lipodystrophy (3) is an autosomal recessive disorder, characterized by the generalized absence of subcutaneous fat and muscular hypertrophy (4). This syndrome was originally described by Seip and Berardinelli. This syndrome is a very rare autosomal recessive disorder with an incidence of one per ten million people. It seems that only more than hundred patients have been reported from various ethnic and racial backgrounds so far (5). Patients with BSCL usually present with acanthosis nigricans in the flexural area of the body, representing insulin resistance. Main characteristics of the patients are hypertriglyceridemia, the high serum level of insulin and glucose, resulting in diabetes mellitus, hyperhidrosis, umbilical hernia lytic lesions in long bones, hepatomegaly, due to the fatty liver that may lead to liver cirrhosis, as well as

splenomegaly. Females have clitoromegaly hypertrichosis, menstrual problems, polycystic ovaries, and mostly infertility, while fertility in the affected male is usually normal.

## Case Report

A 13-month-boy is presented here, who was born from second degree consanguineous marriage. He was referred to the Children's Medical Center, the Pediatrics Center of Excellence in Iran, because of extraordinary muscular appearance plus large feet and hands from three months of age. Inguinal herniorrhaphy was done for him twice because of recurrent inguinal hernia. He was a product of cesarean section with normal birth scales.

On examination, -weight: 12 kg, -height: 85 cm, -head circumference: 48 cm, -blood pressure: 110/70 mmHg (90 and 95<sup>th</sup> percentile, considering his age and sex). He had a coarse face, hyperpigmented skin, hypertrichosis, prominent subcutaneous vessels,

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particularly in abdominal wall and extremities. Acanthosis nigricans, hyperpigmented velvety patches were obvious on posterior cervical and axillary regions. Liver and spleen were palpable 7 cm and 1 cm below the costal margin, respectively. Genitalia was normal considering his age and sex. Feet and hands were larger than usual (Figure 1). Cognitive and neuromuscular developmental milestones were appropriate.



**Figure 1.** The clinical phenotype of the patient with Berardinelli-Seip Congenital Lipodystrophy Syndrome

Thyroid and renal function tests were normal. Through liver function, he has SGOT: 53 mg/dl; SGPT: 124 mg/dl; that was higher than normal. Abdominal ultrasonography revealed 12 cm liver span plus grade II-III of fatty change of liver. The spleen was larger than normal; 96×37.5 cm with heterogeneous echogenicity. Ascetic fluid was seen in the abdominal cavity.

He has been referred to our center again about one year later when he was 27 months of age. At the last presentation his physical examination was as follow: - weight: 16 kg (SDS<sup>1</sup>=2.5), -height: 100 cm (SDS=3.6). He had also developed hyperlordotic posture.

Laboratory data were as follow: -Serum insulin level: 23 IU/L, -FBS: 85 mg/dl, -HOMA-IR: 4.82, - Triglyceride: 500 mg/dl, -Cholesterol: 151 mg/dl.

Echocardiography was in favor of early stage of hypertrophic cardiomegaly.

The genetic study was done for him, and different exons and splice junctions of BSCL1 (*AGPAT2*) gene were sequenced. Reference sequences used: NM\_006412.1.3. The patient had novel homozygous mutation in the *AGPAT2* gene (C.662-2A>C). The parents were heterozygote for the same mutation. This mutation is localized in the highly conserved intron 5' splice site of the gene. It is expected to induce abnormal splicing of exon 6 and can hence be considered causal. It confirms the clinical diagnosis of Seip-Berardinelli

congenital lipodystrophy.

## Discussion

Lipodystrophies are characterized by loss of adipose tissue in some anatomical areas, frequently with fat deposition in non-atrophic sites and usually ectopic sites (6). CGL is usually diagnosed at birth or soon thereafter (1). This syndrome is characterized by profound deficiency of adipose tissue, severe insulin resistance, and diabetes mellitus approximately in 25-35 percent during teenage, hypertriglyceridemia, and fatty liver (7). As a consequence of decreased adipose mass, affected individuals develop Leptin deficiency (7). The presence of three major criteria or two major and two or more minor criteria make a diagnosis of CGL very likely.

Major criteria are -Lipoatrophy affecting trunk limbs and face, -Acromegaloid features, -Hepatomegaly, -Hypertriglyceridemia, and -Insulin resistance, where minor criteria are -Hypertrophic cardiomyopathy, -Psychomotor retardation or mild (IQ: 50-70) to moderate (IQ: 35-50) mental retardation, -hirsutism, -precocious puberty in female cases, -Bone cysts, and -phlebomegaly.

Two genes are known to be associated with CGL: *AGPAT2* in CGL type 1; and *BSCL2*, in CGL type 2 (6). One another gene Caveolin-1 (*CAV-1*) has been reported as a critical gene in human adipocyte function that was mutated in one patient with CGL, but with no mutation in *AGPAT2* or *BSCL2* (9).

Although genitomegaly may be apparent at birth, it would not be persistent after puberty and acanthosis nigricans can get diminished or even disappeared with progression to puberty in spite of acromegalic gigantism. Advanced dentition and hepatosplenomegaly are early and also constant features.

The increased growth rate is most marked during the first 4 years, and these children may attain 90 percent of their adult height up to 10 years of age. Growth subsequently slows, and adults are normal and even short stature. Diabetes mellitus usually begins in teenage years, but despite poor control, ketoacidosis is absent. Patients survive into young adulthood or early middle age. Treatment is supportive, etretinate and dietary fish oil for acanthosis nigricans. Restriction of easily digestible carbohydrates, avoidance of large meal and following a rigid special diet with regular size meal are other essentials of management in this complex disorder (5).

According to mentioned criteria, our patient was a Seip-Berardinelli case, because of involvement with all major criteria and at least two minor criteria. Based on

## Berardinelli-seip syndrome

the genetic study, he was homozygous for C.662-2A>C mutation of *AGPAT2* gene.

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