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Review

Lipodystrophies: Disorders of adipose tissue biology

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ABSTRACT

The adipocytes synthesize and store triglycerides as lipid droplets surrounded by various proteins and phospholipids at its surface. Recently, the molecular basis of some of the genetic syndromes of lipodystrophies has been elucidated and some of these genetic loci have been found to contribute to lipid droplet formation in adipocytes. The two main types of genetic lipodystrophies are congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPL). So far, three CGL loci: 1-acylglycerol-3-phosphate-O-acyltransferase 2 (*AGPAT2*), Berardinelli–Seip Congenital Lipodystrophy 2 (*BSCL2*) and caveolin 1 (CAV1) and four FPL loci: lamin A/C (*LMNA*), peroxisome proliferator-activated receptor γ (*PPARG*), v-AKT murine thymoma oncogene homolog 2 (*AKT2*) and zinc metalloprotease (*ZMPSTE24*), have been identified. AGPAT2 plays a critical role in the synthesis of glycerophospholipids and triglycerides required for lipid droplet formation. Another protein, seipin (encoded by *BSCL2* gene), has been found to induce lipid droplet fusion. CAV1 is an integral component of caveolae and might contribute towards lipid droplet formation. PPARγ and AKT2 play important role in adipogenesis and lipid synthesis. In this review, we discuss and speculate about the contribution of various lipodystrophy genes and their products in the lipid droplet formation.

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The disorders of lipodystrophies have been known for more than a century. The first one was initially known as lipodystrophia progressiva or Barraquer–Simons syndrome (now called acquired partial lipodystrophy) [1,2]. Since then many other acquired and genetic syndromes of lipodystrophy have been reported, the most recent being the one induced by protease-inhibitors based highly active antiretroviral therapy in patients infected with human immunodeficiency virus [3]. All the disorders are characterized by selective loss of body fat although the extent of fat loss varies. If the fat loss is significant, patients develop insulin resistance and its complications such as, diabetes, dyslipidemia, hepatic steatosis, acanthosis nigricans, polycystic ovarian disease and hypertension [1,4]. A substantial progress has been made recently in understanding the molecular defects in patients with genetic forms of lipodystrophies, which will be reviewed in brief here. Readers are referred to more detailed recent reviews on the subject [5,6]. Acquired lipodystrophies have been reviewed recently in several other publications [2,4,7–9]. In this review, we will speculate about the role of some of the lipodystrophy loci in the formation of lipid droplets (also called lipid bodies) in the cells.

The two most common phenotypes observed among patients with genetic lipodystrophies are: a. generalized loss of body fat occurring at birth which is called congenital generalized lipodystrophy (CGL, Berardinelli–Seip syndrome) or partial loss of body fat generally occurring later in life either during childhood or puberty called familial partial lipodystrophy (FPL) (Fig. 1). So far, three genetic loci have been reported for CGL, whereas for FPL, four loci have been discovered. Besides these, there are some other uncommon phenotypes for which the genetic basis remains to be elucidated.

1. Congenital generalized lipodystrophy (CGL)

This rare autosomal recessive disorder is usually recognized at birth or shortly thereafter because of near total lack of body fat and increased muscular appearance of neonates. The children with this disorder undergo rapid growth and have markedly increased appetite. Acanthosis nigricans manifests later. Liver enlargement due to fatty deposition can be seen early in life and can lead to cirrhosis later. Women with CGL may have hirsutism, clitoromegaly, oligo-amenorrhea and polycystic ovaries. After pubertal development, some patients develop focal lytic lesions in the long bones. Hypertrophic cardiomyopathy and mild mental retardation are seen in some patients [10–12]. Metabolic complications can be seen early and hypertriglyceridemia and diabetes are difficult to manage.

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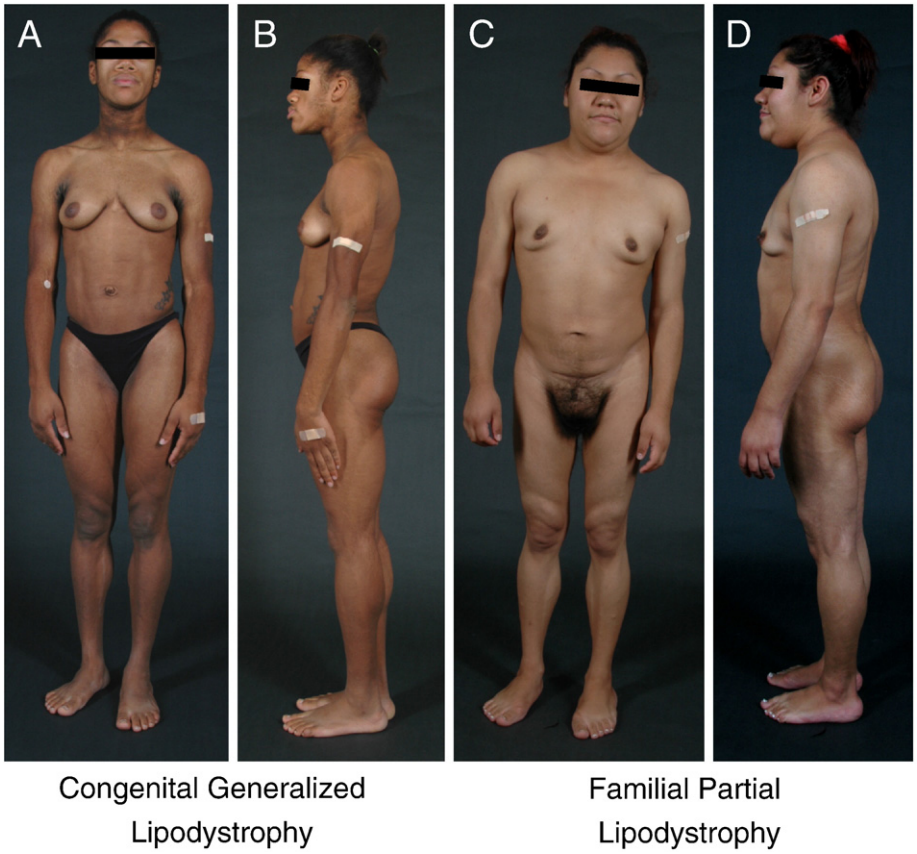

Fig. 1. Phenotypes of Congenital generalized lipodystrophy and familial partial lipodystrophy of the Dunnigan variety. A. and B. Front and lateral views of a 19-year-old female of African-American origin with congenital generalized lipodystrophy, type 1 due to 1-acylglycerol-3-phosphate acyltransferase 2 (*AGPAT2*) homozygous mutation. She has generalized lack of body fat, marked muscularity, acanthosis nigricans in the neck and axillae and acromegaloid features and umbilical prominence. She developed diabetes at the age of 14 years and severe hypertriglyceridemia was noted 15 years of age. C and D. Front and lateral views of a 24-year-old Hispanic woman with familial partial lipodystrophy of the Dunnigan variety due to heterozygous missense mutation in the Lamin A/C (*LMNA*) gene. She had fat loss the upper and lower extremities and trunk at puberty and also accumulated excess fat in the face, submental, supraclavicular and vulvar regions. She had mild acanthosis nigricans in the neck and axillae.

Patients typically have markedly low serum levels of leptin and adiponectin [13].

To understand the molecular basis of this disorder, two groups independently pursued positional cloning approach that led to identification of two loci: 1-acylglycerol-3-phosphate-O-acyltransferase 2 (*AGPAT2*) gene on chromosome 9q34 for CGL, type 1 [14,15] and Berardinelli–Seip Congenital Lipodystrophy 2 (*BSCL2*) gene on chromosome 11q13 for CGL, type 2 [16] Cardiomyopathy and mild mental retardation is more prevalent in CGL, type 2 patients,[11,12,15] whereas focal lytic lesions in long bones are more prevalent in those with CGL, type 1 [17]. Patients with CGL type 1 lose all metabolically active adipose tissue present in most subcutaneous areas, intraabdominal and intrathoracic regions, and bone marrow but have well-preserved mechanical adipose tissue depots located in the palms, soles, under the scalp, retro-orbital and peri-articular regions. On the other hand, patients with CGL type 2 lose both types of adipose tissue [17–19].

Only recently, a single patient from Brazil with a complex phenotype was reported to harbor homozygous null mutation in caveolin 1 (*CAV1*) gene. This patient had some distinct clinical features such as well-preserved bone marrow fat, and lack of lytic lesions in the long bones [20]. She had preservation of "mechanical" adipose tissue in the retro-orbital region, peri-articular region and in the palms and soles; but the scalp fat was decreased. She had short stature, primary amenorrhea, hypocalcemia and hypomagnesemia, which were attributed to vitamin D resistance [20].

Still there is a possibility of cloning additional loci for CGL as some affected patients do not reveal mutations in any of these genes and their pedigrees do not show linkage to these loci [11,21].In one of our pedigrees, two siblings with CGL also have congenital muscular dystrophy, not reported previously [22].

2. CGL1 locus*: AGPAT2*

The AGPATs are acyltransferases which catalyze esterification of a fatty acid to lysophosphatidic acid (LPA or 1-acylglycerol-3-phosphate) in order to covert it to phosphatidic acid (PA or 1,2 diacylglycerol-3-phosphate). This is a key intermediate step during biosynthesis of glycerophospholipids and triglycerides [23] (Fig. 2). Based on structural homology to the major isoforms, AGPAT1 and AGPAT2, at least seven other proteins have been designated as AGPATs. However, documentation of AGPAT activity, i.e., conversion of LPA to PA, has not been performed for many of these isoforms. Furthermore, some AGPAT isoforms have been found to have other enzymatic activities and have been reannotated as glycerol phosphate acyltransferase 4 (GPAT4 instead of AGPAT6) or acyl-CoA: lysophosphatidylethanolamine acyltransferase 2 (LPEAT2 instead of AGPAT7) [24–26]. All the isoforms studied until now localize to the ER, where the formation of lipid droplet is initiated. It remains unclear if all of these or only a few are involved in the formation of lipid droplet. *AGPAT2* mRNA has been shown to be highly expressed in the mouse fibroblast, 3T3-L1 cells and the human omental adipose tissue. AGPAT2 protein has 278 amino acids and has two highly conserved domains, NHXXXXD and EGTR, required for the enzymatic activity [27,28] However, study of a few naturally occurring AGPAT2 mutants reveals important role of the carboxy-terminus for