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Case Report

Familial partial lipodystrophy with gene mutation in both *LMNA* and *PPARG*: report of a case and review of literature

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Abstract: Lipodystrophies are a group of rare diseases characterized by the loss of adipose tissue. Familial partial lipodystrophy (FPLD) is often associated with fat accumulation in nonatrophic depots. FPLD is linked to a single mutation in the lamin A/C *(LMNA)* or peroxisome proliferator-activated receptorgenes (*PPARG*). We reportan FPLD case with a gene mutation in both *LMNA* and *PPARG*. Analysis of the coding region of *LMNA* revealed a heterozygous C-to-T mutation at nucleotide 1698 in exon 15. Similarly, analysis of the coding region of *PPARG* revealed a heterozygous C-to-T mutation at nucleotide 1431 in exon 8. The patient presents a loss of subcutaneous fat in the face and extremities, but increased subcutaneous fat in the neck, shoulder, and vulva. The patient also presents severe aortic and main pulmonary artery stenosis. Conclusion: An interaction between the two mutations may worsen the clinical symptoms, and/or lead to atypical clinical symptoms.

Keywords: Lipodystrophies, familial partial lipodystrophy, *LMNA* mutation, *PPARG* mutation

Introduction

Lipodystrophies area group of rare diseases characterized by the loss of adipose tissue, which can be classified into localized (partial lipodystrophy) or generalized by the extent of fat loss [1]. They are classed asgenetic or acquired according tothe etiology [2, 3]. Familial partial lipodystrophy (FPLD) is often associated with fataccumulation innonatrophic depots. Affected people show complications such as diabetes mellitus, insulin resistance, hypertriglyceridemia, acanthosisnigricans, hepatic steatosis, cardiac hypertrophy and hypertension. FPLD is broadly subdivided into three types: FPLD1 (Kobberling type), FPLD2 (Dunnigan type) and FPLD3 [1]. FPLD2 is linked to a mutation in the lamin A/C gene (*LMNA*), which encodes the A-type lamins (lamin A and lamin C). Mutations in *LMNA cause several diseases called "laminopathies" including progeroid syndromeand lipodystrophies* with metabolic alterations and cardiovascular complications [4, 5]. FPLD3 is associated with a mutation in the *PPARG* encoding the peroxisome proliferator-activated receptorγ (PPARγ). PPARγ plays an important role in adipose tissue metabolism [6]. Patients with FPLD3 mayexhibit disorders of metabolism, such as insulin resistance, dyslipidemia, and hypertension. Mutations in *PPARG* are also associated with several cardiovascular diseases [7].

FPLD appears to always result from a single gene mutation such as *LMNA* mutation in FPLD2 or *PPARG* mutation in FPLD3. We were unable to find any published description of a double or multi-gene mutation in a single type of FPLD. Here, we report a case of FPLD with a mutation in both *LMNA* and *PPARG*.

Case report

A 13-year-old female Chinese patient was referred to Tianjin Medical University General Hospital with impaired glucosemetabolism. She had a history ofvoracious appetite, polydipsia, and polyuriaover 2 months, with more severe symptoms after she caught a cold 1 week previously. She was born by cesarean delivery after

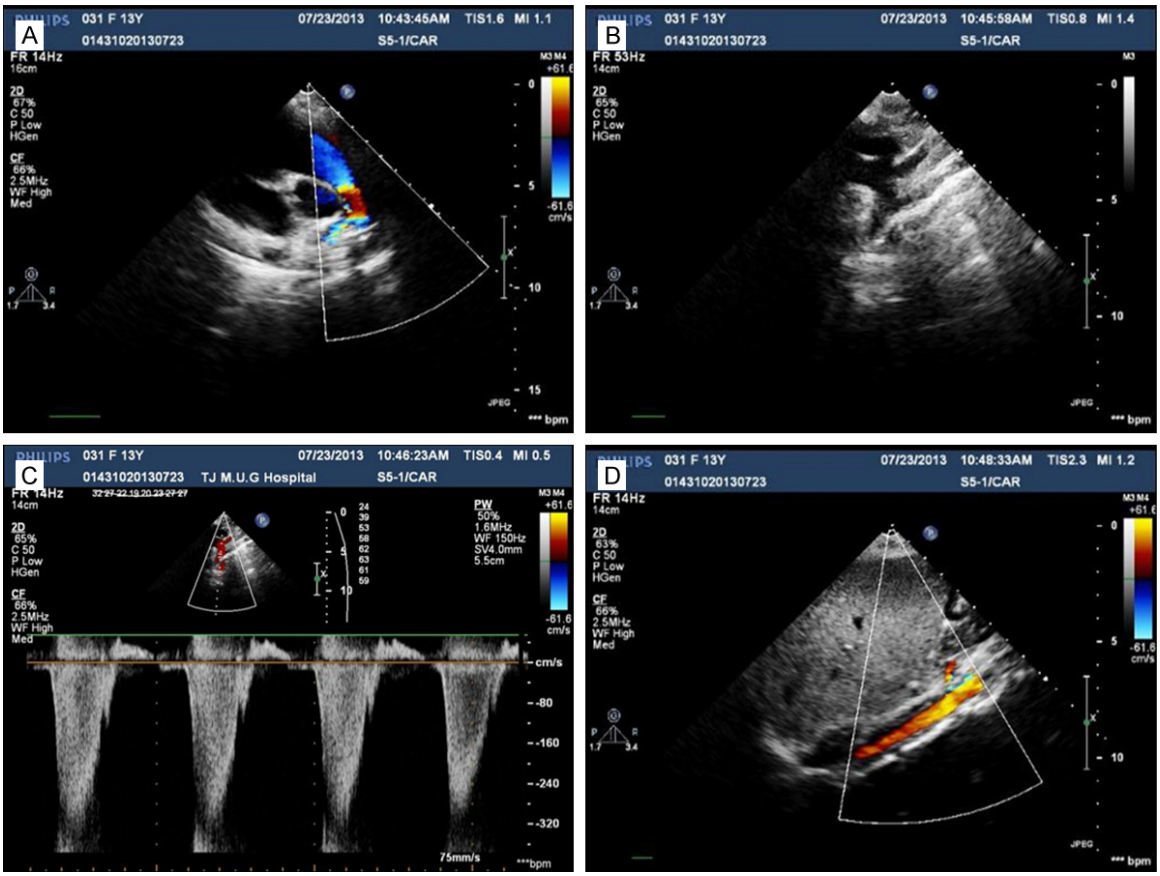

Figure 1. Two-dimensionalechocardiographic examination, the echocardiogram presenting the main pulmonary artery and aortic stenosis and increased blood velocity. A: Color Doppler flow imaging showing the main pulmonary artery stenosis where the blood velocity was raised; B: Aortic arch view showing the aortic stenosis; C: Pulsed-wave Doppler imaging showing that the velocity of the aortic stenosis was increased to 3.03 m/s; D: Color Doppler flow imaging showing the thickness and stenosis of the aorta and the blood flow velocity clearly raised.

Table 1. The results of genetic analysis

Name of gene	Exon	Nucleotide site of variant	Amino acid site of variant
LMNA	Exon 15	C1698C/T	His566His
PPARG	Exon 8	C1431C/T	His477His
LMNB2	-	-	-
AGPAT2	-	-	-
BSCL2	-	-	-
AKT2	-	-	-

a full-term pregnancy. At 2 years of age, she was diagnosed with rickets. Over the third year of life, she developed unusual facial features with a triangular chinbut abnormal fat accumulation on the neck and shoulders. At 5 years of age, she under went surgical excision of the excess fat. She also had fat accumulation on hervulva since 3 months of age.

Physical examination revealed reduced fatin the face, upper and lower extremities. Excess fat was noted on theneck and vulva. No prominent muscles were noted. Her hair was thick, black, and curly. She had mild acanthosisnigricansin the inguen. There were surgical scars in the middle of the scapular area, and on the right and left scapula. Cardiac auscultation showed amurmurat the apex. The rest of the physicalexamination was unremarkable.

Biochemical evaluations showed hyperglycemia and dyslipidemia. The fasting blood glucose was raisedat 20.9 mmol/L (normal upper limit = 6.4 mmol/L) and 120 min blood glucose after a meal was raised at 26.7 mmol/L. Glycosylated hemoglobin was 5.5%. Triglycerides were raised at 13 mmol/L (normal upper limit = 1.7 mmol/L). Glucose in the urine was 'three plus'. Renalfunction and FT3, FT4, TSH, FSH,

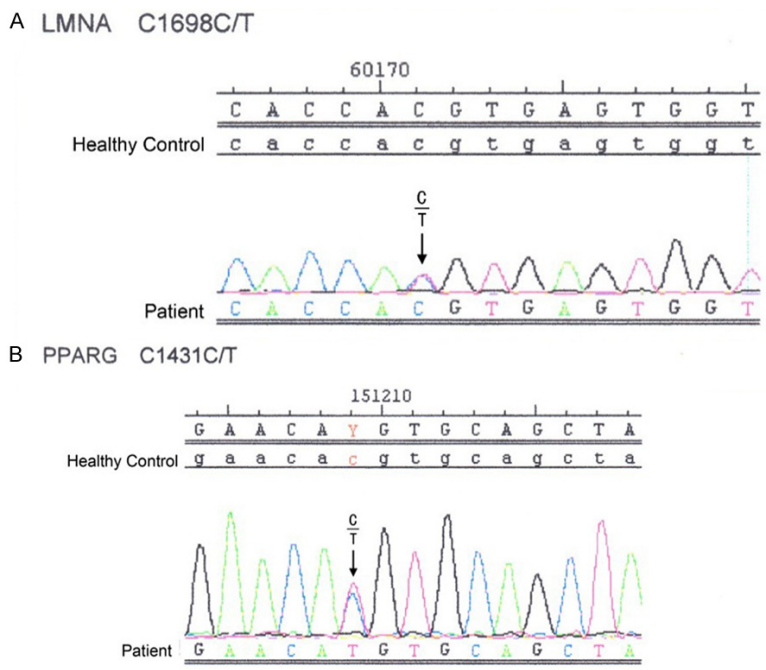

Figure 2. Sequence analysis of the *LMNA* and *PPARG* gene. A: A heterozygous c.1698C>T variant in exon 15 of *LMNA*; B: A heterozygous c.1431C>T variant in exon 8 of *PPARG*.

and LH levels were normal. The patient had a normal 46XX karyotype.

Two-dimensionalechocardiographic examination showed homogeneous and mild left ventricular hypertrophy. Left-ventricle systolicfunction was normal, with an ejection fraction of 67%. Themitral valve was mildly thickened with the anterior leaflet mildlyprolapsing to the left atriumduring systole. The main pulmonary arterydiameter was 14 mm (**Figure 1A**), the ascending aorta diameter 11 mm, aortic arch diameter 10 mm, and thoracic aorta diameter 7.5 mm (**Figure 1B**). The posterior pericardium showed 2-4 mm of fluid-filled darkspace. Doppler echocardiography showed that themitral valve had mild-to-moderate regurgitation. The peak flow velocity of the thoracic aorta was 3.03 m/s (**Figure 1C**). Pulmonary valve systolicvelocity was 1.38 m/s and maximum systolic pressure ofthe pulmonary artery was 29 mmHg. Abdominal ultrasound revealed that the abdominal aorta diameter was 7.4 mm (**Figure 1D**).

We performed molecular analysis of multiple genes: *LMNA*, *PPARG*, *LMNB2*, *AGPAT2*, *BSCL2*, and *AKT2*. We found that the patient carried an *LMNA* mutation in exon 15 and a *PPARG* mutation in exon 8 (**Table 1**). Clinical diagnosis of FPLD was confirmedby the identification of mutations in *LMNA* and *PPARG*.

Discussion

FPLD, first described in the 1970 s [8, 9], shows autosomal dominant inheritance. FPLD is characterized by fat loss in theextremities, followed by fat hypertrophy at truncal sites during childhood, puberty or early adulthood [2, 3, 10]. FPLD canbe subdivided into three types according to the type of genetic mutation. FPLD1 (Kobberling type) is rarely reported in the literature [11]. FPLD2 results from mutations in the *LMNA* gene; mutations in this genecause several diseases including progeroidsyndrome, lipodystrophies (insulin resistance, hypertriglyceridemia, depressed high-density lipoprotein cholesterol, mild acanthosisnigricans, hirsutism, polycystic ovarian syndrome, and menstrual irregularities) and cardiovascular complications [4, 5]. FPLD3 results from mutations in the PPARG gene, which encodes the adipose transcription factor PPARγ. Mutations in *PPARG* lead to less severe forms of lipodystrophy than do mutations in *LMNA*, affecting the extremities and the buttocks, but more severe hypertension and other metabolicabnormalities [12].

Our case carried a novel double genetic mutation: aheterozygous c.1698C>T variantin exon 15 of *LMNA* and a heterozygous c.1431C>T variantin exon 8 of *PPARG* (**Figure 2**). Different mutations in *LMNA* can affect the resulting phenotype. Aheterozygous p.R842W (c.1444 C>T) variantin exon 8 is the most commonmutation in *LMNA* [13]. Patricia et al. reported that some patients with FPLD2 harbored aheterozygous p.R482Q (c.1445G>A) or p.N466D (c.1396A>G) mutation in exon 8, or were homozygous for a p.R584H (c.1751G>A) mutation in exon 11. In addition, anovel variant p.R582C (c.1744C>T) in exon 11 and a p.R349W (c.1045>T) variant in exon 6 have been

described [14, 15]. The heterozygous c.1698 C>T mutation in exon 15 in our case is the first description of this mutation in FPLD.

The mutational spectrum of *PPARG* and the resulting phenotypes are diverse. Visser et al. found aheterozygous p.R194W and p.Y151C mutation in FPLD patients with diabetes [16]. Angelik et al. studied a novel change at nucleotide 1270 in *PPARG* exon 5 (p.D424N) [12]. A heterozygous p.R425C (c.1273C>T) mutation has also been reported [17]. In our case, the patient harbored a heterozygous C-to-T change at nucleotide 1431 in exon 8. Anil et al. also reported a c.1431C>T change, but the mutation was in exon 6, not in exon 8 [17].

We assume that the double genetic mutation in our patient caused a unique combination of symptoms and physical signs. Our patient presented with anunusualfat distribution: fat losson her face but fat accumulation on her neck, shoulders, and vulva. This fat distribution has not been described in previous studies. FPLD patients with *LMNA* mutation always show typical lipoatrophyon the limbs and trunk, and excess subcutaneous fat inthe chin and supraclavicular area. However, patients with *PPARG* mutation display loss of subcutaneous fatinthe face and neck. It is reported that an increase in subcutaneous fat on the abdomen is the best way to discriminate patients with FPLD due to *PPARG* or *LMNA* mutation [12]. However, our patient did not show abdominalaccumulation of subcutaneous fat. In our case, the patient had normal blood pressure, although hypertension has been reported to be associated with PPARG and *LMNA* mutations. Interestingly, our case presented a rare aortic and main pulmonary artery stenosis. Although cardiomegaly, left ventricular hypertrophy, valvular disease and atherosclerosishave been reported inlipodystrophies [18-21], only Araújo-Vilar et al. have reported an FPLD patient with aortic stenosis, left ventricular hypertrophy, and severecalcification of the aorta extending to a mitral annulus [22]; the aortic stenosiswas not as severe as theaortic and main pulmonary artery stenosis in our case. In addition, our patient presented thick, black, curly hair, mild acanthosisnigricans, hyperglycemiaand hypertriglyceridemia, which have not been reported in previous research related toeither *PPARG* or *LMNA* mutations.

The mechanisms by which the double genetic mutation leads to the symptoms and physical signsin this patient arestill unclear. Lamin A and lamin C polymerize with the B-type lamins to form a constituent of the nuclear lamina that exists in most differentiated somatic cells. The *LMNA* gene plays a role in DNA replication, chromatin anchoring, and spatialorientation in the nuclearpore complex, and forms a complex with nuclear envelope proteins [1, 15]. Meanwhile, PPARγ, which induces nuclear transcription factors, plays an important role in the regulation of adipose tissue and glucose metabolism [23-25]. Aninteraction between the mutations in LMNA and PPARG may worsen the clinical symptoms, and/or result in atypical clinical symptoms. This phenotype needs further investigation.

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Disclosure of conflict of interest

None.

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