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Clinical presentations, metabolic abnormalities and end-organ complications in patients with familial partial lipodystrophy

Baris Akinci[a,*], Huseyin Onay[b], Tevfik Demir[a], Şenay Savas-Erdeve[c], Ramazan Gen[d], Ilgin Yildirim Simsir[e], Fatma Ela Keskin[f], Mehmet Sercan Erturk[g], Ayse Kubat Uzum[h], Guzin Fidan Yaylali[i], Nilufer Kutbay Ozdemir[j], Tahir Atik[k], Samim Ozen[l], Banu Sarer Yurekli[e], Tugce Apaydin[f], Canan Altay[m], Gulcin Akinci[n], Leyla Demir[o], Abdurrahman Comlekci[a], Mustafa Secil[m], Elif Arioglu Oral[p]

[a] Division of Endocrinology, Dokuz Eylul University, Izmir, Turkey
[b] Department of Medical Genetics, Ege University, Izmir, Turkey
[c] Division of Pediatric Endocrinology, Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Disease Training and Research Hospital, Ankara, Turkey
[d] Division of Endocrinology, Mersin University, Mersin, Turkey
[e] Division of Endocrinology, Ege University, Izmir, Turkey
[f] Division of Endocrinology, Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey
[g] Mus Public Hospital, Mus, Turkey
[h] Division of Endocrinology, Capa Faculty of Medicine, Istanbul University, Istanbul, Turkey
[i] Pamukkale University, Denizli, Turkey
[j] Diyarbakir Training Hospital, Diyarbakir, Turkey
[k] Division of Pediatric Genetics, Ege University, Izmir, Turkey
[l] Division of Pediatric Endocrinology, Ege University, Izmir, Turkey
[m] Department of Radiology, Dokuz Eylul University, Izmir, Turkey
[n] Division of Pediatric Neurology, Dr.Behcet Uz Children's Hospital, Izmir, Turkey
[o] Department of Biochemistry, Ataturk Training Hospital, Izmir, Turkey
[p] Division of Endocrinology and Metabolism, Brehm Center for Diabetes Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

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ABSTRACT

Objective. Familial partial lipodystrophy (FPLD) is a rare genetic disorder characterized by partial lack of subcutaneous fat.

Methods. This multicenter prospective observational study included data from 56 subjects with FPLD (18 independent Turkish families). Thirty healthy controls were enrolled for comparison.

Abbreviations: FPLD, familial partial lipodystrophy; TuLip, Turkish Lipodystrophy Study Group; WB-MRI, whole body magnetic resonance imaging; *LMNA*, lamin A/C; *LMNB2*, lamin B2; *PPARG*, peroxisome proliferator activated receptor gamma; *PLIN1*, perilipin; *AKT2*, v-akt murine thymoma viral oncogene homolog 2; *CIDEC*, cell death inducing DFFA like effector C; *LIPE*, hormone sensitive lipase; *AGPAT2*, 1-acylglycerol-3-phosphate O-acyltransferase 2; *BSCL2*, Berardinelli–Seip congenital lipodystrophy 2 (seipin); *CAV1*, caveolin-1; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel; HDL, high density lipoprotein; LDL, low density lipoprotein; ADA, American Diabetes Association; US, ultrasound; MRS, magnetic resonance spectroscopy; PCOS, polycystic ovary syndrome; PCO, polycystic ovaries; ELISA, enzyme-linked immunosorbant assay; OGTT, oral glucose tolerance test.

* *Corresponding author at:* Division of Endocrinology, Dokuz Eylul University, Izmir, Turkey. Tel.: +90 232 4123747; fax: +90 232 2792267.
E-mail address: barisakincimd@gmail.com (B. Akinci).

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Results. Pathogenic variants of the *LMNA* gene were determined in nine families. Of those, typical exon 8 codon 482 pathogenic variants were identified in four families. Analysis of the *LMNA* gene also revealed exon 1 codon 47, exon 5 codon 306, exon 6 codon 349, exon 9 codon 528, and exon 11 codon 582 pathogenic variants. Analysis of the *PPARG* gene revealed exon 3 p.Y151C pathogenic variant in two families and exon 7 p.H477L pathogenic variant in one family. A non-pathogenic exon 5 p.R215Q variant of the *LMNB2* gene was detected in another family. Five other families harbored no mutation in any of the genes sequenced. MRI studies showed slightly different fat distribution patterns among subjects with different point mutations, though it was strikingly different in subjects with *LMNA* p.R349W pathogenic variant. Subjects with pathogenic variants of the *PPARG* gene were associated with less prominent fat loss and relatively higher levels of leptin compared to those with pathogenic variants in the *LMNA* gene. Various metabolic abnormalities associated with insulin resistance were detected in all subjects. End-organ complications were observed.

Conclusion. We have identified various pathogenic variants scattered throughout the *LMNA* and *PPARG* genes in Turkish patients with FPLD. Phenotypic heterogeneity is remarkable in patients with *LMNA* pathogenic variants related to the site of missense mutations. FPLD, caused by pathogenic variants either in *LMNA* or *PPARG* is associated with metabolic abnormalities associated with insulin resistance that lead to increased morbidity.

1. Introduction

Familial partial lipodystrophy (FPLD) is a rare genetic disorder characterized by partial loss of fat which primarily affects the limbs, trunk and gluteal areas [1]. Fat loss is typically observed in the arms and legs while subcutaneous fat may accumulate in other areas of the body such as face and neck [2]. FPLD is associated with insulin resistant diabetes, hypertriglyceridemia, low HDL cholesterol, hepatic steatosis, and an increased risk of cardiovascular disorders [3,4]. Previous studies have suggested that hypertriglyceridemia precedes the plasma glucose abnormalities in subjects with FPLD, and that hyperinsulinemia can be detected at early stages of the disease [3–5].

FPLD has been reported to be caused by pathogenic variants in several genes, most of which are inherited as autosomal dominant traits that include lamin A/C (*LMNA*) [6], peroxisome proliferator-activated receptor gamma (*PPARG*) [7], perilipin 1 (*PLIN1*) [8], Vakt murine thymoma viral oncogene homolog 2 (*AKT2*) [9], and hormone-sensitive lipase (*LIPE*) [10]. Pathogenic variants in the cell death-inducing DFFA-like effector C (*CIDEC*) gene cause autosomal recessive FPLD [11]. The Dunnigan variety, caused by heterozygous mutations in the *LMNA* gene, is the most common subtype of FPLD [1]. No disease-causing mutation could be identified in some patients; suggesting that there are additional genes associated with FPLD to be discovered.

In this multicenter prospective observational study, we report the clinical characteristics, metabolic abnormalities and end-organ complications of 18 Turkish families with FPLD who are registered in the Turkish Lipodystrophy Study Group (TuLip) database. Given that there are new drug targets in development for these rare diseases, it is very important to document the natural history of the drug naïve state. We believe that these data will add to the literature by providing crucial natural history data.

2. Materials and Methods

FPLD was clinically diagnosed based on fat loss in selected areas and the diagnosis was supported by documenting fat distribution using whole body magnetic resonance imaging (WB-MRI). The WB-MRI was acquired by using a 1.5-T MR imaging system with a 6 multichannel body coil (Gyroscan Intera, release 8.1; Philips Medical Systems, Best, the Netherlands). Analyses of the genes *LMNA*, *LMNB2*, *PPARG*, *PLIN1*, *AKT2*, *CIDEC*, *LIPE*, *AGPAT2*, *BSCL2*, and *CAV1* were carried out by direct automated DNA sequencing from the patients' genomic DNA by sequencing the coding exons and the exon-intron boundaries of the genes. Genomic DNA was isolated from peripheral blood cells using standard techniques. Sequencing was performed by using a Miseq platform (Illumina California). PolyPhen-2 [12], SIFT [13], MutationTaster-2 [14] and Human Splicing Finder [15] were used in order to classify the novel variants.

Prospective follow-up data were collected by the members of the TuLip in several centers. After reviewing the registry retrospectively, the affected subjects with FPLD were invited for a final visit. Blood was taken from the cannulated antecubital vein between 8:00 a.m. and 9:00 a.m. after 8-h overnight fasting. 75-g OGTT was performed in order to evaluate carbohydrate intolerance in patients without known diabetes. Glucose, HbA1c, alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT) levels were measured by standardized methods with appropriate quality control and quality assurance procedures. Diabetes was defined according to the recommendations of American Diabetes Association (ADA) [16]. Hypertriglyceridemia and low level of high density lipoprotein-cholesterol (HDL) were defined according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines [17]. Age specific thresholds were used for adolescents [18,19]. Leptin levels were measured with enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Boster, Pleasanton, CA).