METABOLISM CLINICAL AND EXPERIMENTAL 64 (2015) 1530–1540

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) syndrome in the context of inherited lipodystrophies

Frederic Reinier[a,b], *Magdalena Zoledziewska*[c], *David Hanna*[b], *Josh D. Smith*[b], *Maria Valentini*[a], *Ilenia Zara*[a], *Riccardo Berutti*[a], *Serena Sanna*[c], *Manuela Oppo*[a,d], *Roberto Cusano*[a], *Rosanna Satta*[e], *Maria Antonietta Montesu*[e], *Chris Jones*[a], *Decio Cerimele*[e], *Deborah A. Nickerson*[b], *Andrea Angius*[a,c], *Francesco Cucca*[c,d,1], *Francesca Cottoni*[e,1], *Laura Crisponi*[c,*,1]

[a] *Centre for Advanced Studies, Research and Development in Sardinia (CRS4), Pula, Italy*
[b] *Department of Genome Sciences, University of Washington, Seattle, WA, USA*
[c] *Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale delle Ricerche (CNR), Monserrato, Italy*
[d] *Dipartimento di Scienze Biomediche, Università di Sassari, Sassari, Italy*
[e] *Dipartimento di Scienze Chirurgiche, Microchirurgiche e Mediche-Dermatologia-Università di Sassari, Italy*

ARTICLE INFO

Article history:
Received 23 December 2014
Accepted 23 July 2015

Keywords:
MDPL syndrome
Lipodystrophies
Exome sequencing
POLD1

ABSTRACT

Background. Lipodystrophies are a large heterogeneous group of genetic or acquired disorders characterized by generalized or partial fat loss, usually associated with metabolic complications such as diabetes mellitus, hypertriglyceridemia and hepatic steatosis. Many efforts have been made in the last years in identifying the genetic etiologies of several lipodystrophy forms, although some remain to be elucidated.

Methods. We report here the clinical description of a woman with a rare severe lipodystrophic and progeroid syndrome associated with hypertriglyceridemia and diabetes whose genetic bases have been clarified through whole-exome sequencing (WES) analysis.

Results. This article reports the 5th MDPL (Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome) patient with the same *de novo* p.S605del mutation in POLD1. We provided further genetic evidence that this is a disease-causing mutation along with a plausible molecular mechanism responsible for this recurring event. Moreover we overviewed the current classification of the inherited forms of lipodystrophy, along with their underlying molecular basis.

Abbreviations: CGL, Congenital generalized lipodystrophy; FPLD, familial partial lipodystrophy; T2D, type 2 diabetes; MADA, Mandibuloacral dysplasia type A; MADB, Mandibuloacral dysplasia type A; MDPL, Mandibular hypoplasia, deafness, progeroid features and lipodystrophy syndrome; HGPS, Hutchinson–Gilford progeria syndrome; WRN, Werner syndrome; PRAAS, Proteasome-associated autoinflammatory syndromes–Autoinflammatory Lipodystrophy syndrome; SHORT, Short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Reiger anomaly and teething delay syndrome; WR, Wiedemann–Rautenstrauch syndrome; MPL, Marfanoid–Progeroid–Lipodystrophy syndrome; sc, subcutaneous fat; POLD1, polymerase delta 1, catalytic subunit; SNVs, single nucleotide polymorphisms; LD, lipid droplet; ER, endoplasmic reticulum.

* *Corresponding author at:* Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle Ricerche, 09042, Monserrato (CA), Italy. Tel.: +39 070 6754620; fax: +39 070 6754652.
E-mail address: laura.crisponi@irgb.cnr.it (L. Crisponi).
[1] These authors contributed equally to the work.

http://dx.doi.org/10.1016/j.metabol.2015.07.022

Conclusions. Progress in the identification of lipodystrophy genes will help in better understanding the role of the pathways involved in the complex physiology of fat. This will lead to new targets towards develop innovative therapeutic strategies for treating the disorder and its metabolic complications, as well as more common forms of adipose tissue redistribution as observed in the metabolic syndrome and type 2 diabetes.

1. Introduction

We report here the clinical description of a woman with a rare severe lipodystrophic and progeroid syndrome associated with hypertriglyceridemia and diabetes whose genetic bases have been clarified through whole-exome sequencing analysis. This offered the starting point for discussing the main features and diagnostic difficulties of inherited lipodystrophies along with the recent progress in the dissection of their genetic bases.

The term lipodystrophy refers to a group of heterogeneous conditions characterized by selective body fat loss and predisposition to insulin resistance and its resultant complications, such as diabetes mellitus, high levels of serum triglycerides and fatty liver [1]. Adipose tissue loss can be partial or generalized to the entire body. Etiologically they can be acquired (due to various causes, usually secondary to various types of illnesses or drugs), or inherited (subclassified into autosomal recessive or dominant forms) [2]. In the literature, about 1000 patients have been reported to be affected by genetic forms of lipodystrophies and their estimated prevalence in the general population is less than 1 in a million [3]. The two most common types of genetic lipodystrophy are congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPLD) [4,5]. The other subtypes of lipodystrophies are extremely rare. Although CGL forms are easily detected clinically and are usually diagnosed by pediatricians because of the characteristic features from birth onwards, FPLD forms cause metabolic abnormalities only later in life and so are more difficult to recognize. Many of FPLD metabolic features resemble those of metabolic syndrome and/or type 2 diabetes (T2D), thus patients with FPLD are often misdiagnosed and for this reason its prevalence is probably under-estimated [6]. Lipodystrophy is also reported in several extremely rare premature aging syndromes. In the last 15 years, much progress has been made in both the characterization of the phenotypes and in unraveling the genetic basis of many subtypes of inherited lipodystrophy, although some remains to be elucidated (Table 1).

2. Case Report

A 41-year-old female, the only daughter of two-second degree cousins from Sardinia (Italy) was reported with a suspected progeroid syndrome. Paternal and maternal age at birth was respectively 40 and 31. The patient was born full-term by Cesarean section, after a difficult pregnancy preceded by three miscarriages. From the age of 3 years, she showed anomalies in weight-height parameters and was the subject of several specialist pediatric consultations. At the age of 8 years, she was diagnosed with microdactylia of the hands with associated partial rigidity of metacarpal phalanges. Widespread muscle hypotonia and hypotrophy were also found along with cutaneous scleroderma. At the age of 10 years she developed neurosensory hypoacusia. At the age of 14 years, she started her period, but had only 3–4 normal cycles before the onset of secondary amenorrhea, which continues to date. She has always been skinny and short in stature. At the age of 21 years she was diagnosed as anxio-depressive and at the age of 29, T2D appeared and was treated with insulin. Diabetic retinopathy resulted as complication. She came under our observation at the age of 32; she was 145 cm in height and weighed 33 kg, with a bird-like triangular-shaped face with a small weak chin, and beak-like nose. Her eyes are large and very prominent, with conjunctival and lid teleangiectasis. She has small thin lips with normal dentition and slightly prominent dental vaults. Her hair is normal for her age, in terms of both texture and color. Skin appears generally atrophic, yellowish in color and dyschromic over a wide area. Naso-labial folds appear accentuated. Overall, the face appears markedly older than her chronological age. Upper and lower limbs are extremely slim (wrist diameter: 11 cm; ankle diameter: 14.5 cm) due to the nearly total absence of subcutaneous (sc) tissue and to the marked muscle hypotrophy (Fig. 1). Although the external genital structure is within the norm, secondary sexual characteristics are underdeveloped: hardly any breasts and thin, sparse pubic hair. Hypogonadotrophic hypogonadism with modest drug-induced hyperprolactinemia was present but thyroid levels were in the norm. Chest X-ray is within the norm. Abdominal and pelvic ecography revealed increased liver dimensions (log max diameter: 146 mm) and non-homogeneity in ecostructure due to steatosis. Routine hematochemical tests show increase in cholesterol (214 mg/dl n.v. 0–180), triglycerides (331 mg/dl n.v. 50–170) and AST/GOT (47 U/L n.v. 10–45). Hormone tests revealed low levels of gonadotropins and estradiol (FSH 4.07 UI/l; LH 2.30 UI/l; E2 23 pg/ml) and high levels of prolactin (43.85 ng/ml n.v. 1.20–29.93). We performed whole-exome sequencing of the parent–offspring trio. Informed consent was obtained from all family members involved in the testing process. A total of 61,561 high quality SNVs and indels were called within the trio (Supplementary Table 1). Whole-exome sequencing was performed on DNA from peripheral blood, using Illumina TruSeq Exome capture and the HiSeq sequencing platform. Sequence data were aligned to the human genome reference (hg19) using the BWA (v0.6.2) alignment tool, and subjected to removal of duplicate reads with Picard (v1.7). Single nucleotide variants (SNVs) and insertion/deletions (indels) were called using the Unified Genotyper (UG) from GATK (v1.6). We performed Indel realignment with the GATK IndelRealigner,