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

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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.

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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,

Table 1 – Classification and molecular basis of genetic lipodystrophies.

Lipodystrophy subtype	Transmission Pattern	Chromosome position	Gene	Protein	Role in lipodystrophies
CGL1	AR	9q34.3	*AGPAT2*	1-acylglycerol-3-phosphate o-acyltransferase 2	Adipogenesis; Lipid synthesis or storage
CGL2	AR	11q13	*BSCL2*	Seipin	Adipogenesis; LD synthesis and maintenance
CGL3	AR	7q31.1	*CAV1*	Caveolin 1	LD synthesis and maintenance; Lipid synthesis or storage
CGL4	AR	17q21.2	*PTRF*	Cavin 1	LD synthesis and maintenance; Lipid synthesis or storage
FPLD1/Kobberling type	NK	NK	*NK*		
FPLD2/Dunnigan type	AD	1q22	*LMNA*	Lamin A/C	LD synthesis and maintenance; Lipid synthesis or storage
FPLD3	AD	3p25.2	*PPARG*	PPAR gamma	Adipogenesis
FPLD4	AD	15q26.1	*PLIN1*	Perilipin	LD synthesis and maintenance
FPLD5	AR	3p25.3	*CIDEC*	Cell death-inducing dffa-like effector c	LD synthesis and maintenance
FPLD6	AR	19q13.2	*LIPE*	Lipase hormone sensitive	Mobilization of free fatty acids from adipose tissue
FPLD7	AR	19q13.2	*AKT2*	Y-akt murine thymoma viral oncogene homolog 2	Intermediate in insulin signaling
HGPS	AD	1q22	*LMNA*	Lamin A/C	LD synthesis and maintenance; Lipid synthesis or storage
MADA	AR	1q22	*LMNA*	Lamin A/C	LD synthesis and maintenance; Lipid synthesis or storage
MADB	AR	1p34.2	*ZMPSTE24*	Zinc metalloproteinase STE24	Involved in the maturation of Lamin A
MDPL	AD	19q13.33	*POLD1*	Polymerase (DNA directed), delta 1, catalytic subunit	Critical role in DNA replication and repair
MPL	AD	15q21.1	*FBN1*	Fibrillin 1	NK
PRAAS	AR	6p21.32	*PSMB8*	Proteasome subunit beta type 8	Required for the differentiation of pre-adipocytes into adipocytes
SHORT	AD	5q13.1	*PIK3R1*	Phosphatidylinositol 3 kinase regulatory subunit 1	Role in the metabolic actions of insulin
WR	AR	NK	*NK*		
WRN	AR	8p12	*WRN*	Werner Syndrome ATP-Dependent Helicase	Critical role in DNA replication and repair

AR = autosomal recessive, AD = autosomal dominant, NK = Not Known.

and base quality recalibration with GATK Recalibration. We filtered the Variant Call Format file (VCFv4.1) by lower quality and potential false positives variants using the GATK Variant Filtration [quality by depth (QD) < 5.0, quality score (QUAL) <= 50, allelic imbalance (AB) >= 0.75, Homopolymer runs (HRun) > 4.0]. Because the parents were second cousins, the variants were initially filtered to identify homozygous variants likely to have an impact in the proband. No candidate gene was identified under this model or with a compound heterozygotes model in the proband. Since neither of the parents was affected, the variants were then filtered for *de novo* occurrences in the proband; one variant was identified in *POLD1* (c.1812_1814delCTC; p.S605del) recently reported causal for Mandibular hypoplasia, Deafness, Progeroid features associated lipodystrophy syndrome (MDPL) syndrome [7]. The mutation was then confirmed by traditional Sanger sequencing and was absent in the parents (Fig. 1). A critical revaluation of the clinical phenotype of the proband was consistent with the previously reported MDPL phenotype (Supplementary Table 2), although considering its very recent description and complex phenotype, the clinical diagnosis of MDPL has been and is quite challenging.

3. Molecular Basis of Lipodystrophies

The growing literature on various phenotypes and molecular mechanisms of genetic lipodystrophies has led to increased recognition of these syndromes. Here, we comprehensively review the progress, concerning the molecular and physiological aspects of lipodystrophies starting from MDPL.

3.1. *Mandibular hypoplasia, Deafness, Progeroid Features Associated Lipodystrophy Syndrome (MDPL)*

MDPL (MIM #615381) is a recently described autosomal dominant systemic disorder with only 11 patients thus far reported worldwide [7–9; this report]. Here we describe the 11th affected individual (Fig. 1 and Supplementary Table 2). Our patient has classical phenotypic features of MDPL:

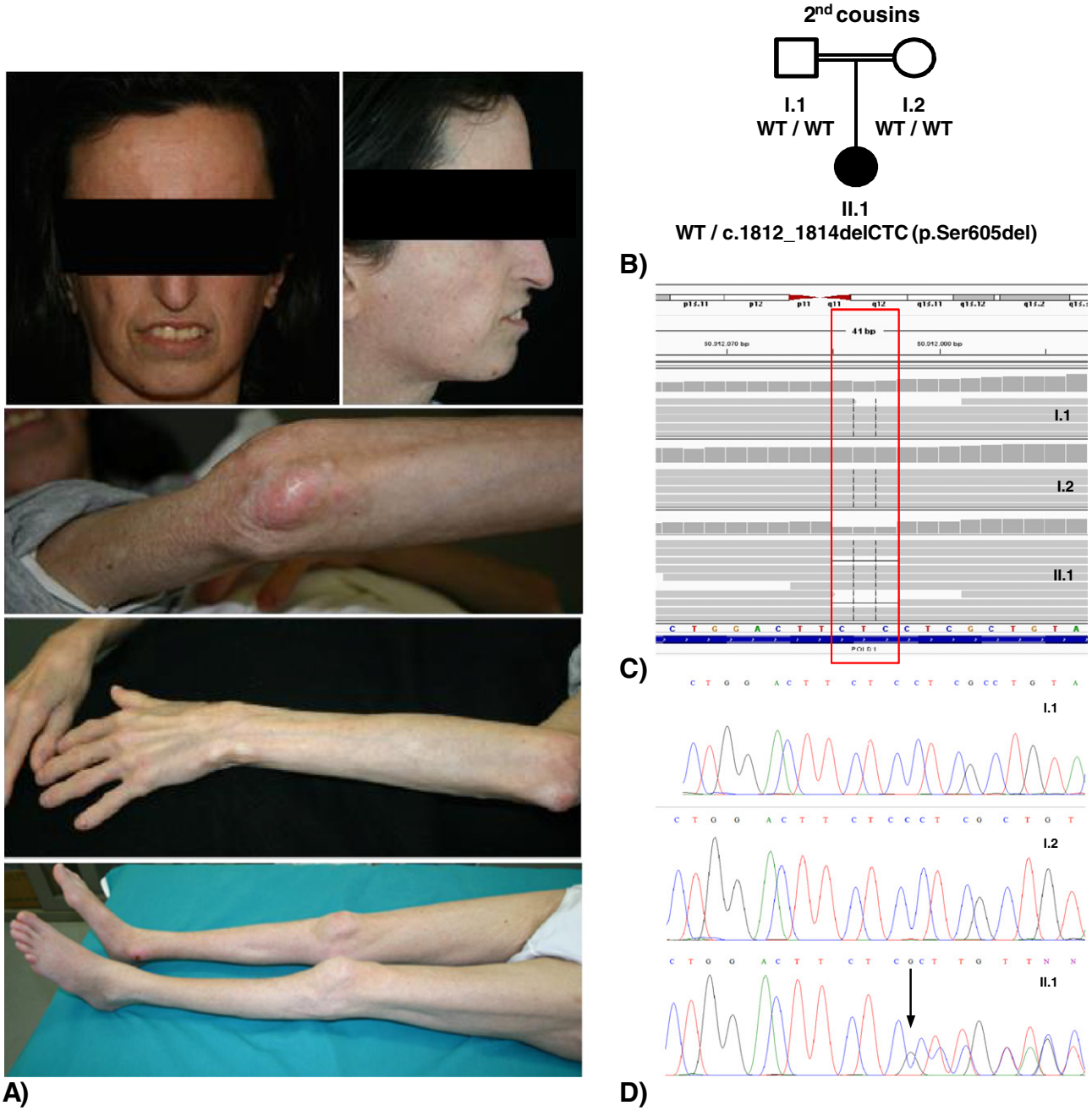

Fig. 1 – Clinical and genetic characterization of the patient described. A: Pictures of the 41-year-old patient affected by MDPL syndrome showing lipodystrophy affecting nearly the upper and lower limbs and typical facial characteristics. B: Family pedigree. Mutation status of POLD1 c.1812_1814delCTC (p.Ser605del) is indicated beneath symbols for each subject. WT indicates wild-type. C: Schematic representation of the mapped exome sequencing reads visualized using the Integrative Genomics Viewer (IGV) browser for patient and parents. The upper part shows the per-base coverage, with coverage represented in gray indicating the WT base, whereas colored bases indicate the detection of variants and black lines indicate the deletion. D: Sanger sequencing of three individuals in family over the c.1812_1814 position in *POLD1*. Father and mother panels show WT c.1812_1814 position and the daughter panel shows the c.1812_1814delCTC *de novo* variant. Arrow indicates the frameshift start.

noticeable loss of sc fat, a distinguishing facial appearance with prominent eyes, metabolic abnormalities comprising insulin resistance and diabetes mellitus and sensorineural deafness with onset between 6 and 18 years of age. Distinct facial features include mandibular hypoplasia, dental overcrowding, beaked nose, prominent eyes, and a high-pitched voice. MDPL patients often present with metabolic abnormalities such as insulin resistance and hypertriglyceridemia, despite their reduced values of body mass index (BMI). Males showed hypogonadism and cryptorchidism; of

the 3 females reported so far, 2 had normal menstrual periods and 1 (reported here) presented with secondary amenorrhea at the age of 14. All had high educational achievement. Of the 11 MDPL patients reported so far, 6 are carriers of a *de novo* heterozygous mutation in *POLD1*; 5 had a single codon deletion (p.S605del) and 1 a missense mutation (p.R507C) (Supplementary Table 2) [7,8]. The *POLD1* gene encodes the catalytic and proofreading subunit of DNA polymerase-delta, which is responsible for DNA synthesis of the lagging strand during DNA replication. POLD1 cooperates with WRN to maintain genome stability. The mutation p.S605del occurs in a highly conserved region of the catalytic subunit of the polymerase. *In vitro* functional expression studies in *E. coli* showed that the catalytic activity of the enzyme was dramatically reduced by this mutation while its proofreading activity was only partially altered [7]. The identification of this recurrent p.S605del mutation found so far in 5 MDPL patients and the discovery of a *de novo* event in all of them suggest that this is a deletion hot spot. It is highly suggestive that the CTCCT motif within the two CTC triplets corresponds to the complementary strand of the consensus sequence – TG(A/G)(A/G)(T/T)(A/C) – identified by Krawczak and Cooper as common to deletion hotspots found in different human genes [9,10]. Furthermore this consensus sequence fits perfectly with the DNA polymerase arrest site WGGAG where W = A or T. Thus the arrest of DNA synthesis at the replication fork may have increased the probability of either a slipped-mispairing event or the formation of secondary-structure intermediates leading to the deduplication found so far in MDPL patients.

MDPL patients share some clinical features with Mandibuloacral Dysplasia (MAD) associated Lipodystrophy but reveal many distinct features such as progressive general lipodystrophy, no acro-osteolysis and clavicular hypoplasia, male hypogonadism and undescended testis, sensorineural hearing loss during childhood, no alopecia, and better long-term survival [11].

3.2. *Mandibuloacral Dysplasia Associated Lipodystrophy (MAD)*

MAD is a rare autosomal recessive disorder, characterized by growth retardation, skeletal abnormality with progressive osteolysis of the distal phalanges and clavicles, craniofacial anomalies with mandibular hypoplasia, lipodystrophy and mottled cutaneous pigmentation. Some patients may show progeroid features. Patients with MAD either have partial loss of sc fat from the extremities (MAD type A; MIM #248370) or more generalized loss of sc fat involving the face, trunk and extremities (MAD type B; MIM #608612). The most common MADA defect is a homozygous missense mutation (p.R527H) in the C-terminal domain of lamins A/C [12–14], but different homozygous or compound heterozygous patients have been reported [15–22]. MADB patients present heterozygous compound mutations in the zinc metalloproteinase (*ZMPSTE24*) gene [23–31]. ZMPSTE24 cleaves farnesylated prelamin A into mature lamin, pointing out the farnesylated prelamin A in the underlying physiopathological mechanism, suggesting that accumulation of prelamin A and/or lack of mature lamin A in the cell may lead to cellular senescence. These patients do not develop diabetes.

3.3. *Other Types of MAD*

Some MAD patients have no mutations in either the *LMNA* or *ZMPSTE24* gene, suggesting that other genes/pathways could be involved.

3.4. *Hutchinson–Gilford Progeria Syndrome (HGPS)*

One of the best known progeroid syndromes is HGPS (MIM #176670), a rare autosomal dominant disorder characterized by short stature, low body weight, early loss of hair, lipodystrophy, scleroderma, decreased joint mobility, osteolysis, and facial features that resemble aged persons. Cardiovascular compromise leads to early death. Cognitive development is normal. Onset is usually within the first year of life. MADA and Hutchinson–Gilford progeria syndrome are caused by the same gene, and may represent a single disorder with varying degrees of severity, although the majority of patients with HGPS have *de novo* heterozygous dominant mutations in the *LMNA* gene [16,32].

3.5. *Werner Syndrome (WRN)*

WRN, also called adult progeria, is a rare autosomal recessive syndrome (MIM #277700), characterized by premature aging with onset in the third decade of life and with cardinal clinical features including bilateral cataracts, short stature, graying and thinning of scalp hair, characteristic skin disorders and premature onset of additional age-related disorders. WRN is caused by mutations in the *WRN* gene, which codes for one of the five RecQ helicases in humans [33]. Such mutations all lead to genome instability. Interestingly, a relatively high prevalence of WRN was described in Sardinia (18 patients from multiple families) with an intronic mutation, c.2089-3025A>G in intron 19 creating a new exon and reflecting a founder mutation [34]. Partial lipodystrophy with severe insulin resistance can reveal WRN-linked premature aging syndrome. Recently 2 women with a partial lipodystrophic syndrome with hypertriglyceridemia, insulin resistance and liver steatosis were reported [35]. One of them had also diabetes. Both patients showed a peculiar, striking lipodystrophic phenotype with sc lipoatrophy of the four limbs contrasting with truncal and abdominal fat accumulation, and were found to be affected by WRN syndrome due to homozygous (p.Q748X) or compound heterozygous (p.Q1257X/p.M1329fs) mutations. Further studies are needed to eventually link the lipodystrophic clinical presentation to specific WRN mutations. Primary alterations in DNA replication and/or repair should be considered as possible causes of lipodystrophic syndromes.

3.6. *Proteasome-associated Autoinflammatory Syndromes - Autoinflammatory Lipodystrophy Syndrome (PRAAS)*

This autosomal recessive systemic autoinflammatory disorder (MIM #256040) is characterized by early childhood onset of annular erythematous plaques on the face and extremities with subsequent development of partial lipodystrophy and laboratory evidence of immune dysregulation. Features that are more variable include recurrent fever, severe joint contractures, muscle weakness and atrophy, hepatosplenomegaly, basal

ganglia calcifications, and microcytic anemia. This disorder encompasses Nakajo–Nishimura syndrome (NKJO); joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP syndrome); and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE). Independent studies have identified mutations in the human proteasome subunit b type 8 (*PSMB8*) gene, which result in a sustained inflammatory response in all syndromes [36–38]. The discovery of *PSMB8* mutations in these syndromes unifies them within one spectrum of disease, also referred to as proteasome-associated autoinflammatory syndromes (PRAAS).

3.7. *Short stature, Hyperextensibility of Joints and/or Inguinal Hernia, Ocular Depression, Reiger Anomaly and Teething Delay Syndrome (SHORT)*

SHORT (MIM #269880) is a rare autosomal dominant condition whose name is the acronym of short stature, hyperextensibility of joints, ocular depression, Rieger anomaly and teething delay. Other typical features are low birth weight, lipodystrophy, delayed bone age, inguinal hernias, low body mass index and a marked progeroid appearance characterized by wrinkled skin, a triangular face with a small chin, low-set posteriorly rotated ears and thin alae nasi. All these clinical features go along with a usually normal intellect. Three groups have independently reported the finding of mutations in *PIK3R1* as the primary cause of SHORT syndrome [39–41], encoding the regulatory subunit of the phosphatidylinositol 3 kinase (PI3K) an intracellular enzyme with a central role in insulin signaling. Remarkably, a single missense mutation (c.1945C>T; p.R649W) was found in 10 families and apparently represents a mutational hotspot in this gene [42].

3.8. *Neonatal Progeroid Syndrome/Wiedemann–Rautenstrauch Syndrome (WR)*

This is an autosomal recessive syndrome (MIM #264090) with approximately 25 reported cases. Newborns with this syndrome have a triangular, old-looking face with relatively large skull (progeroid appearance), prominent veins on the scalp, sparse scalp hair, large anterior fontanelle and generalized lipodystrophy. However, sc fat in the sacral and gluteal areas is spared. Approximately 50% of patients reported died before the age of 6.

3.9. *Marfanoid–Progeroid–Lipodystrophy Syndrome (MPL)*

Recently, Jacquinet et al., [43] proposed a new marfanoid entity comprised of congenital lipodystrophy, a neonatal progeroid appearance, and a peculiar growth profile and caused by rare mutations in the penultimate exon of *FBN1*. All reported mutations in MPL induce production of a truncated mRNA predicted to encode a shorter protein with an altered protein sequence at the C-terminus [43–47]. The pathogenesis of MPL syndrome remains partially unsolved, and several, non-mutually exclusive hypotheses, have been presented. Although insulin resistance may be evident in mid-childhood or adolescence, diabetes mellitus typically does not develop until early adulthood.

3.10. *Congenital Generalized Lipodystrophy (CGL)*

Also known as Berardinelli–Seip syndrome, this is a rare autosomal recessive disorder [48] with world prevalence 1 in 10 million. Patients with CGL are characterized by total absence of adipose tissue since birth, marked muscular appearance due to the almost total adipose tissue loss, prominent veins, acanthosis nigricans and hepatomegaly. During early childhood, patients have marked appetite and grow at an accelerated rate. They present acromegaloid features with slightly enlarged hands, feet and mandible. The symptoms and severity of the syndrome can vary greatly from one person to another. CGL is associated with metabolic complications due to the inability to store triglycerides in adipocytes resulting in ectopic deposition of lipids in tissues such as skeletal muscle and liver, leading to insulin resistance and extreme hypertriglyceridemia. Hepatomegaly secondary to hepatic steatosis and skeletal muscle hypertrophy occur in all affected individuals. Many patients develop splenic enlargement. In female patients mild hirsutism is common. Irregular menstrual periods, lack of menstruation, and polycystic ovaries could be observed and most of affected females are unable to conceive. There are four different subtypes of CGL: CGL1, CGL2, CGL3 and CGL4, all caused by homozygous or compound heterozygous mutations in different genes.

3.10.1. *CGL Type 1 (MIM #608594): AGPAT2 Mutations*

AGPAT2 (1-acylglycerol-3-phosphate-O-acyltransferese 2) is an enzyme that catalyzes the synthesis of phosphatidic acid from acyl-CoAs in the endoplasmic reticulum (ER) of adipocytes, the site of lipid droplet (LD) formation [49]. AGPAT2 deficiency might thus prevent triglycerides synthesis and mature lipid adipocytes droplet formation. In addition, it may also impair the synthesis of other lipids involved in adipocyte differentiation [50].

3.10.2. *CGL Type 2 (MIM #269700): BSCL2*

Berardinelli–Seip congenital lipodystrophy 2 (*BSCL2*) gene codes for Seipin, an integral protein of the ER involved in the adipogenesis process [51]. At the ER level, it mediates the lipidation of nascent LDs and their maintenance and regulates fatty acid monoinsaturation [52].

3.10.3. *CGL Type 3 (MIM #612526): CAV1 [53]*

Caveolin-1 (CAV1) is the major coating protein of caveolae, plasma membrane invaginations particularly abundant in adipocytes and facilitating cellular functions, such as endocytosis, lipid regulation and signal transduction, but can also be found at the LD surface [54]. Caveolin-1 regulates several signaling pathways in adipocytes, including insulin signaling and lipolysis. Caveolin-1 deficient adipocytes show a global alteration of phospholipid composition of the LD surface, suggesting a regulatory role of caveolin-1 on LD expandability [55,56].

3.10.4. *CGL Type 4 (MIM #613327): PTRF*

The *PTRF* gene encodes cavin-1, an essential factor in the biogenesis of caveolae, which are 50- to 100-nm invaginations of cell-surface membranes putatively involved in numerous processes, including signal transduction and membrane and

lipid trafficking. Mutations in this gene lead to a mixed phenotype of generalized lipodystrophy and muscular dystrophy [57] Cavin-1 is colocalized with caveolin-1 on the adipocyte LD [56] and is involved in the stabilization and last phase of biogenesis of caveolae. Loss of cavin-1 causes loss of caveolae and a reduced expression and mislocalization of the caveolins [58]. However, the exact underlying mechanisms that lead to these diseases still require further clarification.

Some individuals with CGL (<20%) do not have a mutation in any of these genes, suggesting that additional, yet unidentified genes can be implicated in the disorder.

3.11. *Familial Partial Lipodystrophy (FPLD)*

FPLD comprises a group of rare autosomal dominant syndromes characterized, in most cases, by lipoatrophy mostly involving the extremities with variable fat loss from the trunk, with possible excess of sc fat deposition in non lipodystrophic regions (e.g. neck, face, and intra-abdominal regions). The body fat distribution is unremarkable at birth and during childhood, with progressive loss of fat occurring during late childhood or after puberty. The diagnosis should be suspected in patients who show signs of insulin resistance early in life manifested by acanthosis nigricans or polycystic ovarian syndrome (menstrual irregularity, hirsutism) and early onset of diabetes and severe hypertriglyceridemia. Females are more easily diagnosed but also are more severely affected with metabolic complications and have a higher risk of coronary artery disease and arteriosclerosis. The extent of adipose tissue loss usually determines the severity of the associated metabolic complications. Several distinct subtypes of FPLD have been reported and the molecular genetic basis of seven different subtypes is known.

3.11.1. *FPLD Type 1 (MIM #608600): Kobberling Variety: unknown*

FPLD type 1 (FPLD1), or Köbberling-type lipodystrophy, is characterized by fat loss from the extremities, and central obesity with normal or increased distribution of fat on the face, neck, and trunk. In 2000, a review considered FPLD1 a rare condition because only a few affected women from two small pedigrees, and 4 sporadic cases had been reported [59]. However, a more recent paper [60] reporting 13 subjects with FPLD1, suggested that this syndrome is more common than previously thought. Only women have been diagnosed with FPLD1 to date. FPLD1 appears to be familial for some subjects, but may also occur spontaneously. The age of onset of lipodystrophy and the mode of inheritance are not clear. The genetic basis for this particular variety is unknown. The study of some pedigrees suggested a possible X linked dominant mode of transmission, lethal in the hemizygous (XY) state [61].

3.11.2. *FPLD Type 2 (MIM #151660): Dunnigan Variety: LMNA*

Dunnigan-type familial partial lipodstrophy (FPLD2) is the most common subtype of FPLD. It is characterized by a loss of sc adipose tissue from the trunk, buttocks and limbs around the time of puberty; fat accumulation in the neck, face, axillary and pelvic regions; muscular hypertrophy; and usually associated with metabolic complications such as insulin resistance, diabetes mellitus, dyslipidemia and liver steatosis. It is an autosomal-dominantly inherited laminopathy, due to missense lamin A/C (*LMNA*) mutations, which in 75% of cases is the substitution p.R482W in exon 8 of the *LMNA* gene [62,63]. Recently Vadrot et al., [64] reported that this mutation affects the regulatory activity of sterol response element binding protein 1 (SREBP1), a transcription factor that regulates hundreds of genes involved in lipid metabolism and adipocyte differentiation. Thus, deregulation of SREBP1 by mutated A-type lamins constitutes one underlying mechanism of the physiopathology of FPLD2. These data suggest that SREBP1 targeting molecules could be considered in a therapeutic context. Other mutations (exon 11 and exon 1) can lead to atypical lipodystrophies, more frequently associated with other laminopathic phenotypes (muscular and/or cardiac dystrophies, accelerated aging).

3.11.3. *FPLD Type 3 (MIM #604367): PPARG*

Familial partial lipodystrophy type 3 (FPLD3) is an autosomal dominant condition caused by peroxisome proliferator-activated receptor gamma (*PPARG*) mutations [65]. More than 15 FPLD3 families have been identified, and in contrast to FPLD2, no FPLD3 subject has yet been reported to have any muscular, neurological, or cardiac involvement. *PPARG* encodes a key transcription factor highly expressed in adipose tissue and involved in adipocyte differentiation. Missense mutations in PPARG cause FPLD due to defective differentiation of adipocytes. Patients with PPARG mutations develop less severe lipodystrophy than those with FPLD and sc fat loss is more prominent from the distal extremities (calf and forearm) than from the thighs and arms. Starting in adolescence, there is variable loss of adipose tissue in the face, gluteal area, and distal limbs with increased truncal adiposity and hepatic steatosis.

3.11.4. *FPLD Type 4 (MIM #613877): PLIN1*

Perilipin (PLIN1) [66,67] is the most abundant protein coating LDs in adipocytes. It is considered essential for formation and maturation of LDs and storage of triglycerides as well as release of fatty acids from these LDs. Five FPLD patients have been reported with mutations in *PLIN1* and all of them had fatty liver, hypertriglyceridemia and hyperinsulinemia. Lipodystrophy was most striking in the lower limbs and gluteo-femoral (buttocks) depots. Recent information suggests that mutant forms of PLIN1 fail to bind to AB-hydrolase containing 5, which results in constitutive co-activation of adipose triglyceride lipase and increased basal lipolysis.

3.11.5. *FPLD Type 5 (MIM #615238): CIDEC*

Recently, a patient with autosomal recessive FPLD has been identified with homozygous mutation in the Cell Death-Inducing DFF-like effector C (*CIDEC*) gene [68]. CIDEC is an LD-associated protein that promotes intracellular triglyceride (TAG) storage. Adipose tissue biopsy of the affected patient showed multilocular lipid droplets in comparison to normal one large LD in adipocytes. Nishino et al., [69] found that Fsp27 (mouse orthologue of CIDEC) ablation in mice reduced the amount of epididymal and sc white adipose tissue and caused the formation of multiple LD in white adipocytes.

3.11.6. *FPLD Type 6 (MIM #615980): LIPE*

LIPE encodes for the hormone-sensitive lipase (HSL), a key enzyme for lipolysis. Two mutations have been reported so far. In 4 sibs from an Old Order Amish family with familial partial lipodystrophy-6, Albert et al. [70] identified homozygosity for a

19-bp deletion (c.2300_2318del) in exon 9 of the *LIPE* gene, causing a frameshift predicted to result in a premature termination codon (p.V767Gfs*102). These 4 individuals had dyslipidemia, hepatic steatosis, systemic insulin resistance, T2D, and evidence for redistribution of body fat. Evaluation of the 4 homozygous sibs as well as 3 heterozygous and 3 non-carrier sibs showed that carriers of the deletion had higher triglyceride and insulin levels and lower HDL cholesterol and serum adiponectin levels than did non carriers. A second mutation, a 2-bp insertion in the *LIPE* gene predicted to result in a premature termination codon (A507fs fs*563) was found by Farhan et al., [71] in 2 Italian siblings from a consanguineous family with FPLD6. Both sibs had a late-onset form of partial lipodystrophy with elevated levels of creatine kinase. The sister exhibited mild proximal muscle weakness and dystrophic changes on muscle biopsy, whereas her brother had normal strength.

3.11.7. *FPLD Type 7 (MIM #125853): AKT2*

V-AKT murine thymoma oncogene homolog 2 (AKT2) is a phosphoinositide-dependent serine/threonine kinase, also known as protein kinase B, and is an important intermediate of insulin signaling. An AKT2 heterozygous mutation p.R274H has been reported in 4 members of a family who had hypertension, severe insulin resistance, and diabetes mellitus [72]. Insulin resistance appears around the ages of 20 to 30. Lipodystrophy most prominently affects the arms and legs, suggesting that AKT2 may play a role in adipogenesis. The loss of adipose tissue in patients with heterozygous mutations in AKT2 may be due to either reduced adipocyte differentiation or dysfunctional post insulin receptor signaling. Mice deficient in Akt2 exhibit fed and fasting hyperglycemia, hyperinsulinemia, glucose intolerance, and impaired muscle glucose uptake [73].

3.11.8. *Other Types of FPLD*

It appears that all described loci for FPLD, may not be able to explain the genetic basis of all the patients with FPLD, thus additional loci could be involved. In depth characterization of the clinical phenotype related to the pattern of loss of fat in FPLD patients with mutations in different genes may be helpful in identification of different phenotypes without resorting to molecular diagnosis.

4. Discussion

Considering the wide phenotypic heterogeneity and complexity among various types of lipodystrophies and that their classification is still a work in progress, the clinical diagnosis is often challenging. Whole exome sequencing can thus be a valuable tool to identify the molecular basis of such rare conditions. As in other cases, whole exome sequencing successfully helped us to diagnose a patient, where an atypical form of progeria had been previously assigned based on clinical manifestation. A critical revaluation of the clinical phenotype of the proband after identification of a *de novo* mutation in the *POLD1* gene, was consistent with the previously reported MDPL phenotype, a novel variety of progeroid syndrome with lipodystrophy (Fig. 1 and Supplementary Table 2). We found the fifth MDPL patient with the same *de novo* p.S605del mutation in *POLD1*, providing: 1) further genetic evidence that this is a disease-causing mutation; 2) a plausible molecular mechanism responsible for this recurring event; 3) indication to consider the probability that a very rare disease may be the result of a *de novo* mutation even in the presence of consanguinity; 4) evidence that although mutated in very few cases, *POLD1* should be considered among the candidate genes to be tested in patients with a progeroid syndrome associated with hypertriglyceridemia and skinny phenotype.

5. Conclusions

Although the molecular basis of lipodystrophies is heterogeneous, most mutated genes lead to impaired adipogenesis, adipocyte lipid storage, and/or formation or maintenance of the adipocyte lipid droplet, showing that primary alterations of adipose tissue can result in severe systemic metabolic and endocrine consequences [6]. However, the hypothesis that lipodystrophy could also be secondary to cellular senescence was raised by the studies of progeroid syndromes associated lypodystrophy, although the mechanism underlying selective loss of only some adipose depots across all these conditions is currently unclear. Fat tissue, frequently the largest organ in humans, is at the interconnection of mechanisms involved in longevity and age-related metabolic dysfunction. Fat distribution and function change dramatically throughout life. Obesity is associated with accelerated onset of diseases common in old age, while fat ablation and certain mutations affecting fat increase life span. Exciting new data are beginning to point to the cell biological and molecular mechanisms that determine how aging impacts fat tissue function and how this, in turn, leads to age-related disease. Lessons from what happens in obesity are especially illuminating. In particular, inflammatory processes linked to cellular senescence in fat tissue could be pivotal [74].

These studies highlight the leading role of adipose tissue for global metabolic homestasis, and help to better understand its complex pathophysiology. The identification of new genes/targets could lead to the discovery of new and innovative therapeutic strategies not only for lipodystrophy syndromes but also for more common human disease such as metabolic syndrome and T2D.

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Conflict of Interest

The authors have no conflicting interests to disclose.

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