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Case Report

Short stature as the first manifestation of mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) syndrome

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Abstract: Mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) syndrome is an autosomal dominant disorder caused by heterozygous mutations in the polymerase, delta 1, catalytic subunit (*POLD1*) gene. Here, we report the clinical description of a 10-year-old boy who first presented with short stature and hypogonadism. We screened this patient for mutations by focused exome sequencing and verified the results by Sanger sequencing. This boy is the 13th MDPL patient reported with a *de novo* p.S605del mutation in *POLD1* and the first MDPL patient reported in Eastern Asia. Growth hormone (GH) stimulation tests revealed that the patient's GH level was normal, but the baseline IGF-1 level was extremely low. He was treated with recombinant human growth hormone (rhGH) therapy, which caused accelerated fat loss. Moreover, rhGH therapy might increase the cancer risk; thus, it should be contraindicated in MDPL patients. Therefore, MDPL syndrome is a possible diagnosis in boys with both short stature and hypogonadism, and rhGH therapy should be initiated only when this syndrome is excluded.

Keywords: MDPL syndrome, *POLD1* gene, short stature, gonadal failure, lipodystrophy

Introduction

Mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) syndrome (Online Mendelian Inheritance in Man 615381) is an autosomal dominant disorder characterized by mandibular hypoplasia, sensorineural deafness, progressive lipodystrophy, skin scleroderma and telangiectasia, ligament contractures, and reduced limb muscle mass, as well as hypogonadism and undescended testes in males. This syndrome was first described by Shastry et al. in 2010 [1]. In 2013, Weedon et al. found that the polymerase (DNA directed), delta 1, catalytic subunit (*POLD1*) gene was the causal gene of MDPL syndrome [2]. Nineteen MDPL syndrome patients have been reported in the literature, including 10 males and 9 females (**Table 1**). Among them, 12 have the p.Ser605del mutation, and 2 carry p.Arg507Cys [1-5]. The *POLD1* gene encodes the p125 catalytic subunit of human DNA polymerase δ (polδ), which plays central roles in chromosomal DNA replication, repair, and recombination [6, 7]. Thus far, the exact mechanism by which the *POLD1* gene mutations causing MDPL syndrome remains unclear.

Previous reports of the endocrine aspects of MDPL syndrome are limited. Here, we describe a boy who first presented for endocrine evaluation with short stature and hypogonadism and was ultimately diagnosed with MDPL syndrome by focused exome sequencing. We also review the endocrine manifestations of MDPL syndrome in light of our experience with this patient.

Case report

In 2011, a 6-year-old boy presented to our clinic with short stature. The boy's prenatal history was not significant. He was born at full term by vaginal delivery, and his birth weight and height were 3.5 kg and 50 cm, respectively. His parents were non-consanguineous and were both healthy. His father's height was 165 cm, and his mother's height was 157 cm. He also had a

Table 1. Clinical characteristics, body composition, and metabolic parameters of our patient compared with 19 previously reported patients with *POLD1* mutations [1-5]

	Study patient	Summary of 19 Patients	Summary of 9 Female Patients	Summary of 10 Male Patients	Summary of 4 children with MDPL
Age	10.0	10-63	10-48	10-63	10-12
Sex	Male	10 M; 9 F	Female	Male	1 M; 3 F
Ethnicity	Chinese	18 Caucasian; 1 Indian; 1 Hispanic	Caucasian	8 Caucasian; 1 Indian; 1 Hispanic	Caucasian
Birth Weight (kg)	3.3	2.4-4.2 (5 NA)	2.4-3.8 (3 NA)	2.6-4.2 (2 NA)	2.6-3.6
Height (m)	1.25	1.45-1.91 (1 NA; 4 child)	1.45-1.62 (3 child)	1.61-1.91 (1 NA; 1 child)	3 short (1.23-1.30), 1 normal
Weight (kg)	21.5	34.0-69.7 (1 NA; 4 child)	34.0-54.7 (3 child)	39.1-69.7 (1 NA; 1 child)	17.2-31
BMI (kg/m^2)	13.8	12.2-21.3 (1 male 26.8 with p.R507C)	12.2-18.3 (1 women 21.9)	13.9-21.3 (1 male 26.8 with p.R507C)	12.2-18.3
Age at onset (year)	4	4 (4 NA)	2-8 (4 NA)	4 (8 NA)	2-10 (1 NA)
Body composition (DXA)					
DEXA bone density Z score	0.2	(-2.8) to (+0.1) (15 NA)	(-1.5) and (+0.1) (7 NA)	(-2.1) and (-2.8) (8 NA)	4 NA
Whole-body fat (%)	15.4	14.0-29.9 (11 NA)	20.2-29.9 (6 NA)	14.0-22.6 (5 NA)	1 child 29.9 (3 NA)
Truncal fat/leg fat (%)	1.4	0.8-4.3 (11 NA)	0.8-2.0 (6 NA)	2.2-4.3 (5 NA)	1 child 0.8 (3 NA)
Metabolic profile					
Diabetes mellitus(age at diagnosis, yr)	N	7/19 Yes (14-52)	2/9 Yes (28 and 29)	5/10 Yes (14-52)	0/4 Yes
OGTT Fasting glucose (mmol/l)	3.86	4.20-7.7 (7 NA)	4.20-5.28 (2 NA)	4.67-7.7 (5 NA; 1 man > 7.1 mmol/l)	4.22-5.17 (1 NA)
OGTT 2 hour glucose (mmol/l)	4.69	8.9-16.4 (14 NA)	2 female 8.9 and 10.22 (7 NA)	14.8-16.4 (7 NA)	4 NA
Fasting Insulin (pmol/l)	42.1	60.2-237.5 (11 NA; 1 man 734.1 pmol/l)	235.0-237.5 (6 NA)	60.2-212.0 (5 NA; 1 man 734.1 pmol/l)	1 child 237.5 (3 NA)
Hepatic steatosis (age at diagnosis, yr)	N	7/11 Yes (8 NA)	4/6 Yes (3 NA)	3/5 Yes (5 NA)	0/2 Yes (2 NA)
Abnormal liver function tests	N	6/10 Yes (9 Na)	4/6 Yes (3 NA)	2/4 Yes (6 NA)	1/2 Yes (2 NA)
Hypertriglyceridemia	N	12/17 (2 NA)	6/8 Yes (1 NA)	6/9 Yes (1 NA)	1/2 Yes (2 NA)
Total Cholesterol (mmol/l)	4.27	4.2-5.87 (1 child 3.00; 8 NA)	4.42-5.87 (1 child 3.00; 2 NA)	4.2-5.4 (6 NA)	3.00 and 5.87 (2 NA)
HDL-Cholesterol (mmol/l)	1.22	0.41-1.24 (7 NA)	0.41-1.22 (4 NA)	0.65-1.24 (3 NA)	0.84 (2 NA)
Clinical features					
Tight skin	Y	17/17 Yes (2 NA)	9/9 Yes	8/8 Yes (2 NA)	4/4 Yes
Telangectasia	Y	13/18 Yes (1 NA)	7/9 Yes	6/9 Yes (1 NA)	2/4 Yes
Bird like faces	Y	15/15 Yes (4 NA)	6/6 Yes (3 NA)	9/9 Yes (1 NA)	3/3 Yes (1 NA)
Mandibular hypoplasia	Y	19/19 Yes	9/9 Yes	10/10 Yes	4/4 Yes
Dental overcrowding	Y	13/16 Yes (3 NA)	8/9 Yes	5/7 Yes (3 NA)	4/4 Yes
High pitched voice	Y	8/11 Yes (2 Hoarse; 6 NA)	2/4 Yes (2 Hoarse; 3 NA)	6/7 Yes (3 NA)	2 Yes; 1 Haorse; 1 NA
Deafness (age diagnosis, yrs)	Y (8)	16/19 Yes (6-33 yr)	7/9 Yes(7-14 yr)	9/10 Yes (6-33 yr)	4/4 Yes (8-14 yr, 1 NA)
Joint Contractures	Y	11/11 Yes (8 NA)	4/4 Yes (5 NA)	7/7 Yes (3 NA)	2/2 Yes (2 NA)
Osteoporosis	N	5/12 Yes (7 NA)	2/7 Yes (2 NA)	3/5 Yes (5 NA)	1/3 Yes (1 NA)
Hypogonadism	Y	9/10 Yes	1/9 Yes (secondary amenorrhea)	8/10 Yes	1 Male cryptorchidism; 3 Female No
POLD1 mutation	c.1812_1814 delCTC p.S605del	12/14 p.S605del; 2/14 p.R507C (5 NA)	7/8 p.S605del; 1/8 p.R507C (1 NA)	5/6 p.S605del; 1/6 p.R507C (4 NA)	3/3 p.S605del (1 NA)

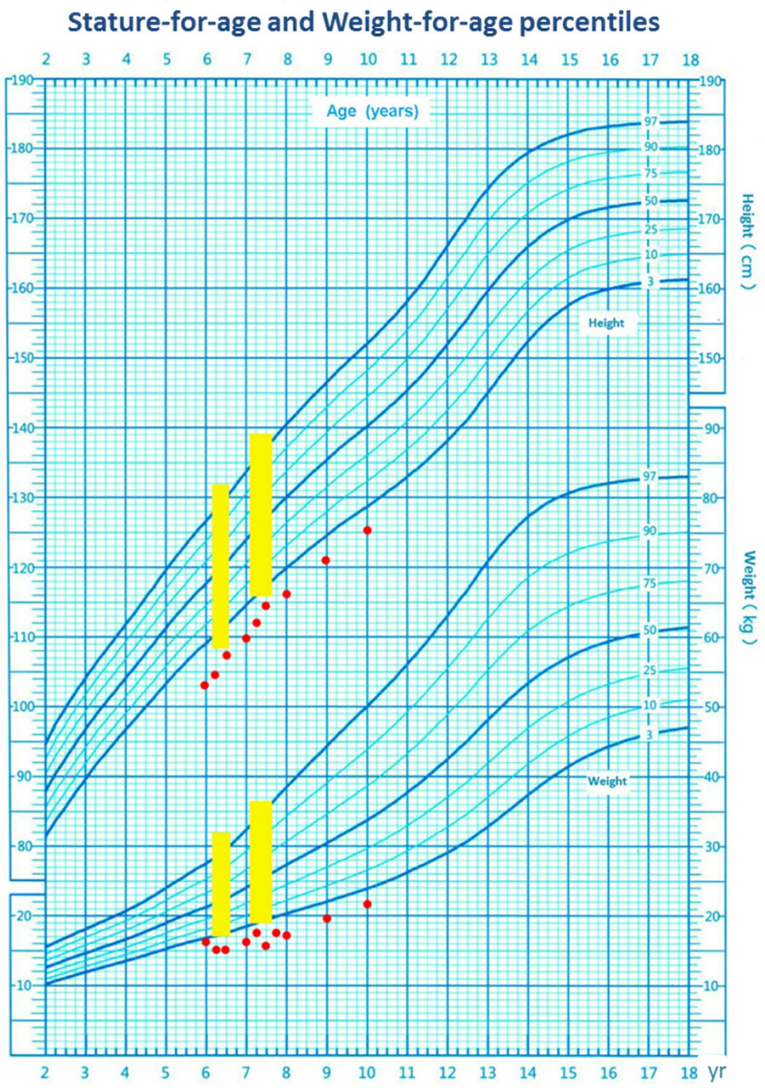

Figure 1. Growth chart showing the patient's growth curve. The yellow rectangle on the chart represents the time of growth hormone treatment.

healthy younger sister. During his first year of life, he developed five respiratory infections, had diarrhoea once, often cried for unknown reasons and refused to be fed. After infancy, he was still susceptible to respiratory infections and had a poor appetite. His growth velocity decreased gradually during infancy and was 4.6 cm/yr before he came to our clinic. His developmental milestones were normal. On physical examination, his height was 103 cm (-2.90 SD) and weight was 16 kg (-2.06 SD). His testes were not palpable. The stretched penile length was 2.5 cm.

Laboratory investigations revealed results within the reference ranges for the electrolyte, renal, liver, glucose, adrenal, and thyroid profiles. The proband's karyotype was 46, XY. GH provocative tests revealed that his maximum serum GH levels were 5.57 μg/L (arginine) and 12.01 μg/L (L-dopa). The luteinizing hormone-releasing hormone (LHRH) test showed 22.43 IU/L for the follicle-stimulating hormone (FSH) peak and 1.90 IU/L for the luteinizing hormone (LH) peak. The baseline testosterone level was 10.6 ng/dL, and the testosterone level after human chorionic gonadotropin (HCG) stimulation was 29.4 ng/dL. In addition, the insulin-like growth factor-1 (IGF-1) level was 46.4 ng/mL (<-2 SD), and the insulin-like growth factor binding protein 3 (IGFBP3) level was 2.56 μg/dl (<-2 SD). Magnetic resonance imaging (MRI) showed a small pituitary gland. The patient's bone age was approximately 3 yr. Ultrasonography showed that his testes were quite small (9*3*3 mm^3 for the left testicle, and 9*4*3 mm^3 for the right testicle).

He was diagnosed with idiopathic short stature (ISS) and hypogonadism, and rhGH therapy was initiated at approximately 6 yr of age. During this therapy, the patient's growth velocity was approximately 10.5 cm/yr. However, he began to lose fat and became skinny. Therefore, therapy was discontinued 1.5 yr later (**Figure 1**). Orchidopexy was performed at approximately 6.75 yr of age, and bilateral testicular atrophy was observed during surgery.

At 10 yr of age, the boy returned to our clinic with apparent fat loss (**Figure 2**). Examination revealed generalized fat loss. His upper eyelashes were long. He had bilateral exophthalmos, mild myopia and astigmatism. Cataract and other ocular abnormalities were excluded by eye examination. The skin over his feet, legs and arms was tight, and his skin was dry.

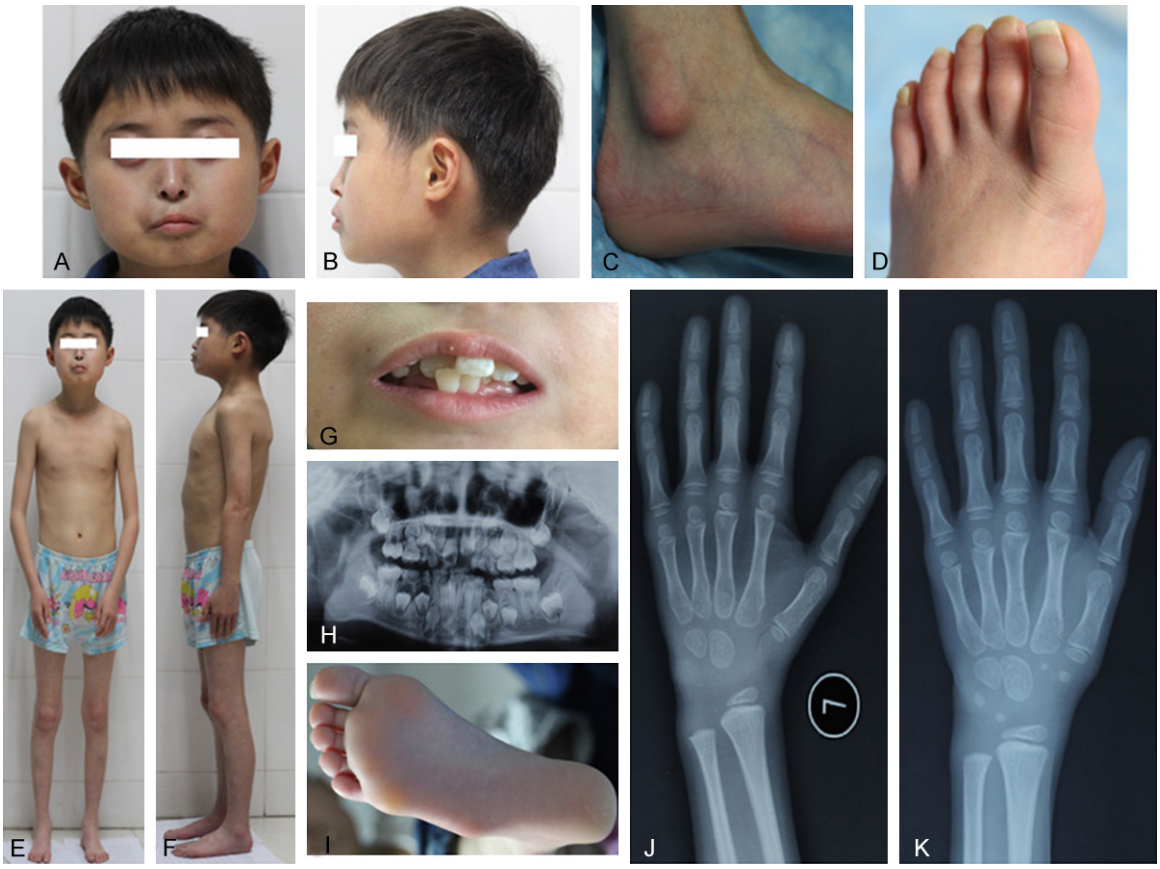

Figure 2. Clinical characteristics of the patient. The images show the 10-year old patient with MDPL syndrome exhibiting the typical facial characteristics (A and B), telangiectasia (C), white discoloration of the skin over joints (D), lipodystrophy affecting the entire body (E and F), dental crowding (G and H), marked loss of subcutaneous fat from the sole (I), and delayed bone age (J and K).

Further, he had telangiectasia. He did not have clavicle dysplasia, acro-osteolysis, cutaneous atrophy or hair loss. Two years prior, progressive hearing loss was noted. Brainstem-evoked response audiometry and auditory steady-state response tests were performed, and severe sensorineural hearing loss was documented. Laboratory investigations revealed that the AMH level was almost undetectable (0.85 pmol/L). The oral glucose tolerance test showed normal glucose tolerance and insulin levels. Hepatic function and triglyceride and cholesterol levels were also normal. Abdominal ultrasound showed no hepatosteatosis.

To determine the reason for the patient's fat loss, focused exome sequencing was performed. The results revealed a deletion mutation, c.1812_1814delCTC (p.Ser605del), in the *POLD1* gene. This mutation was subsequently confirmed by traditional Sanger sequencing, and it was not detected in any of the other three family members (**Figure 3**). No mutation in the Lamin A/C (*LMNA*), Werner syndrome, RecQ helicase-like (*WRN*), or Zinc metalloproteinase (*ZMPSTE24*) gene or any other lipodystrophy-related genes were identified. Because this mutation was not present in either of the proband's parents, the variant was a *de novo* occurrence in the proband. Careful re-evaluation of the proband's clinical phenotype revealed that it was consistent with the previously reported MDPL syndrome (**Table 1**). This boy is the 13th MDPL patient reported with this *POLD1* gene mutation and the first MDPL patient reported in Eastern Asia.

Discussion

The *POLD1* gene has a key role in DNA replication, and it has been demonstrated to function in cooperation with WRN, a DNA helicase, to maintain genome stability [8]. Therefore, mutations in this gene cause genomic instability in

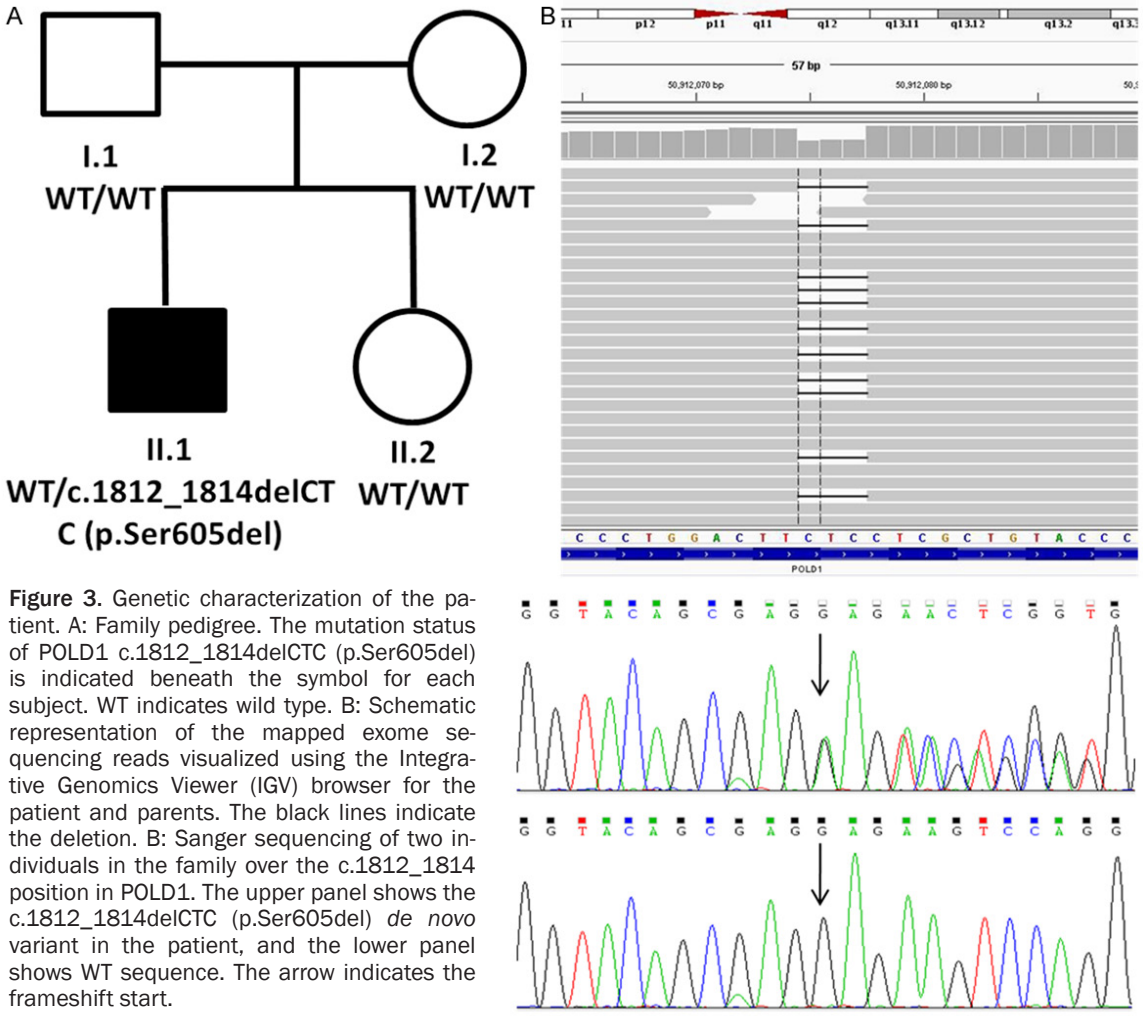

Figure 3. Genetic characterization of the patient. A: Family pedigree. The mutation status of POLD1 c.1812_1814delCTC (p.Ser605del) is indicated beneath the symbol for each subject. WT indicates wild type. B: Schematic representation of the mapped exome sequencing reads visualized using the Integrative Genomics Viewer (IGV) browser for the patient and parents. The black lines indicate the deletion. B: Sanger sequencing of two individuals in the family over the c.1812_1814 position in POLD1. The upper panel shows the c.1812_1814delCTC (p.Ser605del) *de novo* variant in the patient, and the lower panel shows WT sequence. The arrow indicates the frameshift start.

MDPL patients. As DNA damage can suppress GH/IGF-1 endocrine signalling [9], short stature is a common feature in many syndromes with genomic instability, including Werner syndrome, Bloom syndrome, Hutchinson-Gilford progeria syndrome, and SPRTN (SprT-Like N-Terminal Domain) syndrome [8, 10-12]. Short stature has been described in 9 out of 19 MDPL patients. Adult heights are approximately 157-162 cm for short males and 145-148 cm for short females. Our patient was 103 cm at his first visit (-2.9 SD). He had normal GH production according to provocative tests, consistent with the GH provocative test results previously reported for patients with Werner syndrome and Bloom syndrome [13, 14]. Moreover, his IGF-1 level was quite low (<-2 SD). This result is in line with a previous study of disorders of DNA damage showing that IGF-1 suppression is peripheral and secondary in these patients and is not the result of a central pituitary defect [12]. However, low baseline IGF-1 and IGFBP-3 levels have not been detected in all patients with segmental progeroid syndrome presenting with short stature [14, 15]. Thus, other mechanisms may cause growth retardation besides that involving the GH/IGF-1 axis. The rate of IGF-1 synthesis in tissues and its secretion into systemic circulation depend on not only pituitary growth hormone but also nutrient intake [16]. Therefore, the low IGF-1 level detected in the patient in this report might also be related to his poor nutrient status.

The proband was first diagnosed with ISS and was treated with GH therapy. During GH treatment (50 μg/kg/d), his IGF-1 level increased to the normal range (-0.2 SD), and his growth velocity was approximately 10.5 cm/yr. However, while he was receiving therapy, he stopped

gaining weight and eventually lost weight. His subcutaneous adipose tissue loss gradually became obvious. As a result, we had to discontinue his GH therapy. GH stimulates lipolysis in adipose tissues, resulting in an increased flux of free fatty acids into circulation [17]. As a result, GH therapy accelerates the loss of subcutaneous adipose tissue and aggravates symptoms in MDPL patients. Moreover, because IGF-1 has mitogenic and antiapoptotic properties, GH treatment could increase the risk of cancer [18]. Thus, GH therapy is contraindicated in patients with other DNA repair disorders. Notably, a Colombian woman, the mother of a 17-year-old girl with MDPL syndrome caused by a *POLD1* mutation, has been reported who had features of MDPL syndrome and died of ovarian cancer [4]. Furthermore, heterozygous germline mutations in the exonuclease domain of POLD1 increase the risks of colorectal [19] and endometrial cancers [20]. Hence, we do not recommend using rhGH to treat MDPL patients.

Including our patient, 11 male MDPL patients have been described, among whom 9 had hypogonadism [1-5]. Of the two male patients who did not have hypogonadism, one was 18 yr old and had been out of contact for 10 yr. Thus, his information might not be accurate. The other male patient was 62 yr old and had one healthy child. He had a p.R507C mutation in *POLD1*, which differed from the mutations in the other male patients with MDPL syndrome. Therefore, it is possible that the p.R507C mutation causes milder testicular dysfunction than the p.S605del mutation. The boy in the present case had undescended testes, which were found to be atrophic during orchidopexy. His testosterone level after HCG stimulation and AMH level were extremely low, which suggested that he had both Sertoli and Leydig cell failure. The mechanisms by which *POLD1* mutations cause hypogonadism remain unknown. The *POLD1* gene is involved in testicular development [21]. It is expressed in spermatogonia instead of spermatocytes [22] and is down-regulated in spermatogonia in patients with spermatogenic failure, suggesting that it is critical for proper germ cell development [23]. Therefore, *POLD1* mutations can cause spermatogenic failure in male MDPL patients. Interestingly, among the 9 female patients, only one had secondary amenorrhoea, while the others all had regular menstruation, and 2 had children. Although *POLD1* is also expressed in oocytes during the germinal vesicle stage, its expression is lower than that of other DNA polymerases [24]. Hence, *POLD1* expression during DNA repair in oocytes may not be as important as it is in spermatogonia.

Patients with lipodystrophy are predisposed to type 2 diabetes mellitus (T2DM). The underlying mechanisms are similar to those in patients with obesity. The absence of protective subcutaneous fat due to lipodystrophy causes severe insulin resistance [25]. Excessive non-esterified fatty acids, which cannot be stored in adipose tissue, cause β-cell dysfunction and apoptosis [26]. Including the patient described in this report, 20 MDPL patients have been described to date. At least 7 of these patients were diagnosed with T2DM, 3 had impaired glucose tolerance, and another 3 had obvious insulin resistance. Female patients with this syndrome appear to retain more subcutaneous fat than male patients, and they also tend to be less susceptible to diabetes. Including our patient, 5 children with MDPL have been reported. None of them had diabetes, and their fasting glucose levels were all normal. Insulin resistance was not observed in our patient. Thus, in MDPL patients, insulin resistance may develop during late childhood, while glucose intolerance usually emerges during young adulthood. These patients tend to develop impaired postprandial glucose tolerance prior to developing impaired fasting glucose tolerance. During the early stage, their diabetes progresses slowly and can be treated with dietary intervention or insulin sensitizers. When insulin therapy is initiated, very large doses are needed. Some MDPL patients develop severe diabetic complications, including diabetic retinopathy, limb amputation, and occlusion of the coronary arteries [1-5].

In conclusion, we have described the abnormal endocrinologic features in a boy with MDPL syndrome. Our findings suggest that MDPL syndrome is a possible diagnosis in boys presenting with both short stature and hypogonadism and that rhGH therapy should be initiated only when this syndrome is excluded. Early diagnosis is critical for proper therapy and counselling.

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Disclosure of conflict of interest

None.

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