A Chinese girl with mandibular hypoplasia, deafness, progeroid features, and lipodystrophy (MDPL) diagnosed *via POLD1* mutation detection

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To the Editor: A 15-year-old girl from Chengdu (Sichuan province, China) came to our hospital in December 2019. Her mother stated that the girl's body was thin since she was 3 years old, but no other abnormalities were noted. She visited the hospital because of developing tinnitus and hearing loss over the last 5 months. On admission, it was found that she had low subcutaneous fat and particular facial features, including small jaw, thin lips, mandibular dysplasia, and crowded teeth [Figure 1]. Her height was 1.50 m, and the body mass index (BMI) was 13.3 kg/m^2. Dual energy X-ray absorptiometry (DXA) scan showed a total fat mass of 6.65 kg. The calculated fat mass index (FMI) was 2.96 kg/m^2, indicating a fat deficit. Triglycerides level was 1.40 mmol/L, the cholesterol level was 3.08 mmol/L, and the uric acid level was 476 μmol/L. Abdominal ultrasound showed a fatty liver. The level of human growth hormone was 0.1 μg/L, and estradiol was 64 pg/mL. An oral glucose tolerance test showed that fasting serum glucose, serum glucose at 1 h after meal and serum glucose at 2 h after meal were 4.64 mmol/L, 7.75 mmol/L, and 7.12 mmol/L, respectively. Fasting serum insulin, serum insulin at 1 h after meal and serum insulin at 2 h after meal were 25.7 μU/mL, 253.6 μU/mL, and 257.4 μU/mL, respectively. Fasting serum C-peptide, serum C-peptide at 1 h after meal and serum C-peptide at 2 h after meal were 25.7 nmol/L, 253.6 nmol/L, and 257.4 nmol/L, respectively. These results indicated normal glucose tolerance with increased insulin resistance. A plain magnetic resonance imaging (MRI) scan of the internal auditory canal showed no obvious abnormalities bilaterally. Further otolaryngologic examination demonstrated sensorineural hearing loss. Craniocerebral MRI plain scan did not detect clear abnormalities, and bone density examination revealed osteoporosis. Given the special clinical manifestations of the patient, an underlying genetic disease was considered. Therefore, a trio whole-exome sequencing was performed for the patient and her parents. The results showed no abnormalities in both parents, but a *de novo* variation in the DNA polymerase δ1 catalytic subunit (*POLD1*) gene [NM_002691.3: c.1812_1814del, p. (Ser605del)] in the patient. The girl was diagnosed with the mandibular hypoplasia, deafness, progeroid features, and lipodystrophy (MDPL) syndrome based on the combination of clinical manifestations and the genetic test.

MDPL syndrome is an extremely rare lipodystrophic disease with autosomal dominant inheritance, first reported by Shastry et al[1] in 2010. The clinical manifestations include mandibular hypoplasia, sensorineural deafness, progressive lipodystrophy, skin scleroderma and telangiectasia, ligament contractures, reduced limb muscle mass, hypogonadism, and diabetes. So far, 24 cases of the MDPL syndrome have been reported worldwide, of which 19 have the molecular feature of the deletion of the highly conserved serine residue in *POLD1* p.(Ser605del), which is the most common genetic variation.[2] Therefore, MDPL is considered to be caused by mutations in the *POLD1*. DNA polymerase δ1 (Pol δ1) protein belongs to the family of human DNA polymerases and has both polymerase and 3' to 5' exonuclease activity. It is responsible for the synthesis of the lagging DNA strand during replication. *POLD1* functionally interacts with Werner helicase during DNA replication and DNA repair,[3,4] and has been implicated in human aging.[5]

The clinical manifestations of MDPL are similar to other lipodystrophy syndromes, and, currently, diagnostic guidelines for MDPL are not available. Thus the clinical diagnosis of this condition is a significant challenge. Moreover, there is no effective treatment for MDPL. Current therapies aim

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000986

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Chinese Medical Journal 2020;133(16)

Received: 07-04-2020 **Edited by:** Pei-Fang Wei

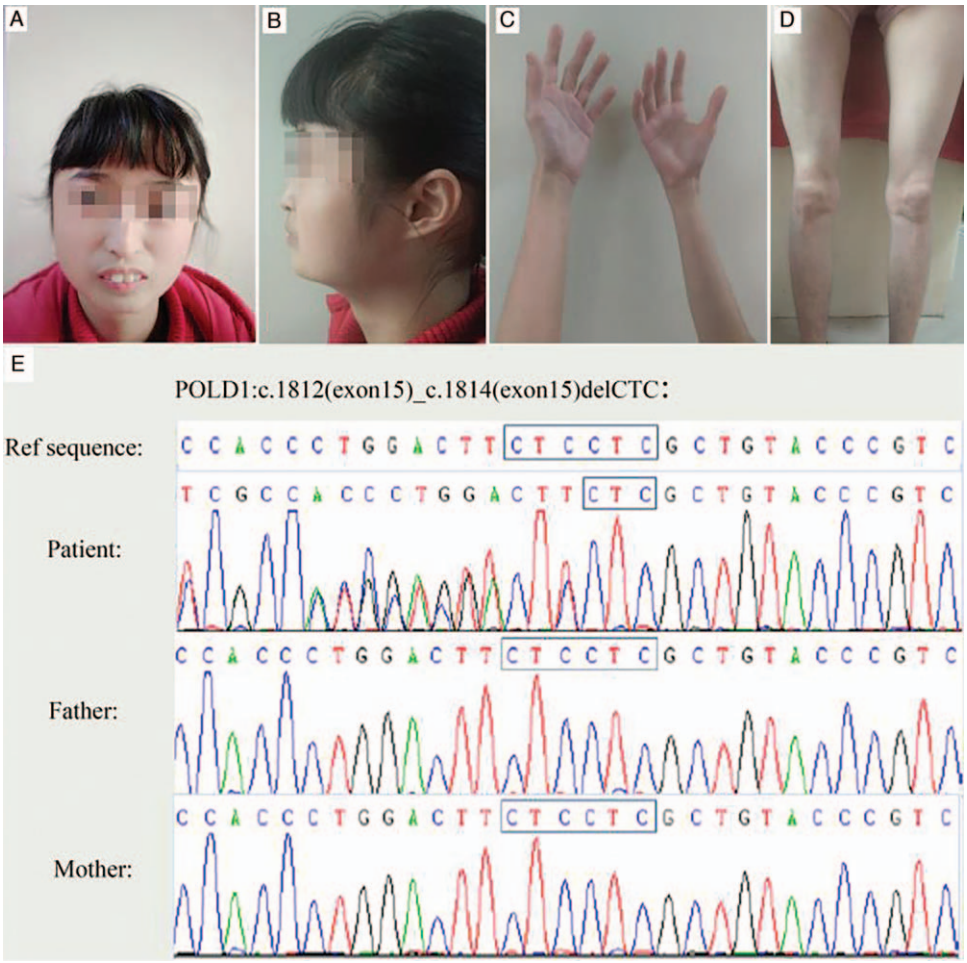

Figure 1: Profile of the patient with mandibular hypoplasia, deafness, progeroid features, and lipodystrophy. (A) Special facial features in front view: small jaw thin lips and crowded teeth. (B) Special facial features in side view. (C) Less subcutaneous fat of forearms. (D) Less subcutaneous fat of lower limbs. (E) A *de novo* variation in *POLD1* gene of the patient: c.1812_1814del.

only at the prevention or amelioration of the symptoms of MDPL, so the early diagnosis is very important. For all lipodystrophy syndromes, molecular genetics is a key tool to confirm the clinical diagnosis and identify mutations in the causal genes. In this case, the patient had clinical manifestations of the MDPL syndrome. However, it is difficult to accurately diagnose this disease because of its rarity and the similarity of its symptoms to other lipodystrophy syndromes such as mandibuloacral dysplasia-associated lipodystrophy and the Werner syndrome. Molecular genetic testing enables an accurate differential diagnosis for genetic diseases and constituted the basis of the final diagnosis in the current case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient and patient's guardians have given their consent for the images and other clinical information to be reported in the journal. The patient and patient's guardians understand that their names and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 81770875), the Science and Technology Department of Sichuan Province (No. 2018SZ0142), the Sichuan University (No. 2018SCUH0093), the National Clinical Research Center for Geriatrics of West China Hospital (No. Z2018B05), and the 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. 2020HXFH008, No. ZYJC18003).

Conflicts of interest

None.

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How to cite this article: Wang XW, Lu LY, Xie Y, Yu XJ. A Chinese girl with mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) diagnosed via *POLD1* mutation detection. Chin Med J 2020;133:2009–2011. doi: 10.1097/CM9.0000000000000986