CASE REPORT

A 1-year and 4-month-old child with mucopolysaccharidoses type II: A clinical case report from Ethiopia

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Abstract

Mucopolysaccharidoses (MPSs) are a class of lysosomal storage disorders resulting in progressive disease manifestations and are caused by pathogenic variants in genes coding for enzymes needed to degrade glycosaminoglycans. While most of the seven MPSs are autosomal recessive disorders, MPS II, also known as Hunter syndrome, is inherited in an X-linked recessive manner and is the most common MPS. Here, we report a 1-year and 4-month-old boy who presented with delayed developmental milestones, back deformity, and left scrotal swelling noticed by parents at one year of age. He has coarse facial appearance with macrocephaly, widened wrists, congenital dermal melanocytosis on his back, kyphotic deformity in the thoracolumbar area and left-sided inguinal hernia all consistent with a suspected MPS II diagnosis. The MPS II diagnosis was subsequently confirmed with genetic testing of the *IDS* gene. To our knowledge, this is the first case of MPS II reported from Ethiopia. This case shows the importance of early clinical recognition of genetic conditions and the utility of genetic testing for confirmation. The diagnosis provided important surveillance and natural history information for the patient's providers and family.

KEYWORDS
glycosaminoglycans, Hunter syndrome, iduronate-2-sulfatase, mucopolysaccharidosis

1 | INTRODUCTION

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders resulting in progressive disease manifestations and arel caused by pathogenic variants of genes coding for enzymes needed to degrade glycosaminoglycans. Glycosaminoglycans (GAG) are long-chain complex carbohydrates composed of uronic acids, aminosugars, and neutral sugars. The major GAGs are chondroitin-4-sulfate, chondroitin-6-sulfate, heparin sulfate, dermatan sulfate, keratin sulfate, and hyaluronan. These substances are synthesized, with the exception of hyaluronan, linked to protein to form proteoglycans and are major constituents of the ground substance of connective tissue and of

nuclear and cell membranes. Degradation of proteoglycans starts with proteolytic removal of the protein core, followed by the stepwise degradation of the GAG moiety.[1]

Each MPS is caused by the deficiency of distinct lysosomal enzymes required for the stepwise degradation of GAGs. Failure of this degradation process, due to an absence or dysfunctional lysosomal enzyme, results in the intralysosomal accumulation of GAG fragments. Distended lysosomes accumulate in the cell, interfere with cell function, and lead to characteristic patterns of clinical, radiologic and biochemical abnormalities.[1]

Seven types of MPS are classified based on deficiency of one of the eleven specific lysosomal enzymes and are numbered MPS I through MPS IX (excluding MPSV and VIII which are no longer used). The difference in clinical finding of these seven MPSs is indicated in the table below (Table 1). Most mucopolysaccharidoses (MPS-I-H/ Hurler syndrome, MPS-I-S/Scheie syndrome, MPS III/ Sanfilippo syndrome, MPS IV/Morquio syndrome, MPS VI/Maroteaux-Lamy syndrome, MPS VII/Sly syndrome, MPS IX, MPS-Plus Syndrome/MPS-PS) are autosomal recessive disorders with the exception being MPS II (Hunter syndrome) which is X-linked recessive. Given this, Hunter syndrome typically affects males; however, it has been rarely seen in females secondary to skewed X-inactivation of the normal X-chromosomes and expression of the maternally inherited mutated *IDS* allele.[1,2]

Hunter syndrome (Mucopolysaccharidosis type II, OMIM# 309900) was first described by Charles Hunter in 1917, a Canadian Professor of Medicine, when he reported medical histories of two affected brothers. Hunter syndrome is one of the most common MPSs[3] with an estimated prevalence of 1 in 100,000 to 170,000 male births[2,4] It is a life-limiting multisystemic disorder caused by deficiency of iduronate-2-sulfatase (IDS). The *IDS* gene is mapped to Xq28 with pathogenic sequence variants of *IDS* detected in about 80% of patients with MPS II with major deletion or rearrangements of *IDS* found in the remaining 20% with these usually associated with a more severe clinical phenotype. The deficiency of IDS leads to an accumulation of heparan sulfate and chondroitin sulfate B (dermatan sulfate) in cellular lysosomes, interfering with their function.[2,5,6]

The clinical presentation of patients with Hunter syndrome (MPS II) varies from severe to milder forms with signs and symptoms apparent usually by two to four years of age. Findings of affected patients include macrocephaly, short neck, broad chest, delayed tooth eruption, hearing loss, coarse facial features with thick lips, thick nostrils, and macroglossia. Patients have also impaired growth, short stature, joint stiffness with restriction of movements, and dysostosis multiplex noted on radiographs. Chronic diarrhea may also occur as a result of GAG accumulation in the gastrointestinal system with other features including hepatosplenomegaly, inguinal and umbilical hernias. Neurologic system involvement includes intellectual disability, delayed developmental milestones, communicating hydrocephalus due to thickened meninges and spastic paraplegia. Cutaneous manifestations include congenital dermal melanocytosis observed in African and Asian patients with grouped skin papules found in some patients.[3] A distinguishing feature of MPS II is an absence of corneal clouding which is often present in patients with MPS I. In patients with MPS II, total urinary GAGs are elevated, particularly Dermatan and Heparan sulfate, with a definitive diagnosis made by identifying deficient iduronate-2-sulfatase activity or a pathogenic *IDS* variant.[7]

Individuals with milder forms of MPS II will have slow progression of somatic symptoms with minimal neurologic involvement and have been reported to live 65 and

Manifestations	Mucopolysaccharidosis (MPS) type						
	I-H	I-S	II	III	IV	VI	VII
Intellectual disability	+	−	±	+	−	−	±
Coarse facial features	+	(+)	+	+	−	+	±
Corneal clouding	+	+	−	−	(+)	+	±
Visceromegaly	+	(+)	+	(+)	−	+	+
Short stature	+	(+)	+	−	+	+	+
Joint contractures	+	+	+	−	−	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	−	+	+
Mucopolysacchariduria	+	+	+	+	+	+	+

TABLE 1 Clinical Profiles of: I-H, Hurler syndrome; I-S, Scheie syndrome; II, Hunter syndrome; III, Sanfilippo syndrome; IV, Morquio syndrome; VI, Maroteaux-Lamy syndrome; VII, Sly syndrome

Abbreviations: (+), mild manifestation; −, absence of manifestation; +, Presence of manifestation; ±, possible presence of manifestation; I-H, Hurler syndrome; II, Hunter syndrome; III, Sanfilippo syndrome; I-S, Scheie syndrome; IV, Morquio syndrome; VI, Maroteaux-Lamy syndrome; VII, Sly syndrome[1].

87 years. Severely affected patients with MPS II will show progressive symptoms including significant neurologic deficits which may be present for 10–15 years preceding death.[3]

2 | CASE PRESENTATION

The proband is an Ethiopian boy seen initially at 1 year and 4 months of age whose parents brought him to St. Paul's Hospital in Addis Ababa, due to left side scrotal swelling, lower back swelling, and delayed sitting, standing, and walking initially noted at one year of age. The family identified the back swelling as a possible cause for the delayed sitting, standing, and walking. The mother claimed that she saw the scrotal swelling especially during periods of the patient crying. He had no history of swallowing difficulty, vomiting, or diarrhea with no difficulty breathing or shortness of breath or abnormal body movements. The patient was exclusively breastfed for the first 6 months of his life then complemented with porridge made of mixed cereals and cow's milk. Gradually his parents noted decreased oral intake of uncertain etiology with a resultant decrease in growth. He was exposed to sunlight at least 3 times per week since the age of 3 months without the application of any ointment. Currently, he is fully vaccinated as per the Ethiopian vaccination program schedule.

The proband's mother has no history of previous abortions or stillbirths with normal antenatal follow-up and negative routine tests. She delivered the proband via spontaneous vaginal delivery, with the baby noted to cry immediately and not requiring a neonatal intensive care unit (NICU) admission. He is the first child from a nonconsanguineous marriage of an orthodox Christian family. The mother is 25 years old, and the father is 32 years old with no similar family history present though the two maternal aunts have no children yet.

On the initial presentation to our hospital, the diagnosis of rickets was made with wrist X-ray and was treated with megadose of Vitamin D and Calcium supplementation. On examination (Figures 1-3), he had coarse facial features with a broad and large forehead and a flattened nasal bridge. At his initial evaluation, his pulse rate was 122 beats per minute, respiratory rate was 18/minute and axillary body temperature was 36.8°C. His anthropometries showed a body weight of 10.3 kg (between 0 and −1 SD* for his age), length of 73 centimeters (below −3SD for his age); weight/length ratio between +1 and +2 SD and a head circumference of 52 centimeters which is over+3SD for his age. He had pale conjunctiva with no icterus or corneal clouding. His tongue was not enlarged. His neck was short with no

lymphadenopathy. His chest was broad and symmetric, without deformity and clear lung sounds with good air entry. Cardiovascular examination revealed a well heard and normal S1 and S2 with no gallop or murmurs. His abdomen was protuberant, soft and moved with respiration with no tenderness or mass and normoactive bowel sounds. There was a 4 × 5 cm left reducible mass extending from the inguinal area to the scrotum. On genitourinary examination, there was a normal external male genitalia with bilaterally descended testicles. On musculoskeletal examination, he had broad hands and widened wrists with kyphosis of the thoracolumbar area which was non-tender. On cutaneous examination, he multiple hyper-pigmented macules and patches were noted on his back, the dorsum of his left hand and on the left side of his face. Neurologically he was alert, both pupils were midsized and reactive to light, with normal tone and 5/5 strength with deep tender reflexes of 2/4 in all extremities.

2.1 | Ophthalmologic evaluation

Normal visual acuity in both eyes for his age, normal intraocular pressure in both eyes, pupils were symmetrically round, reactive, and regular in both eyes. Normal eyelids and well oriented lashes, normal conjunctiva, some dark-brown pigmentary changes on the sclera (benign melanocytic nevi), clear and normal-sized cornea, deep anterior chamber, brown and normal iris, clear lens, clear vitreous, pink oval and normal optic disc, shiny macula, no pigmentary retinal changes, and normal vasculature.

2.2 | ENT evaluation

Bilaterally normal hearing tests.

2.3 | Laboratory workup

His white blood count was 8,300/mm³ (normal for age: 4,000–12,000/mm³) with Neutrophils of 38.7%, Lymphocytes of 54%. Hemoglobin was 6.6 g/dl (normal for age 10.5–14 g/dl) hematocrit of 23.8% (normal for age 32%–42%), platelet count of 235,000/mm³ (normal for age: 150,000–400,000/mm³), serum Phosphorous of 0.88 mmol/L (normal for age: 1.25–2.10 mmol/L), Alkaline phosphatase 1158 U/L (Normal for age 145–420 U/L), ionized calcium 1.18 mmol/L (normal for age 1.2–1.38 mmol/L), and serum vitamin D,25-hydroxy of 40.18 (normal value 75–250).
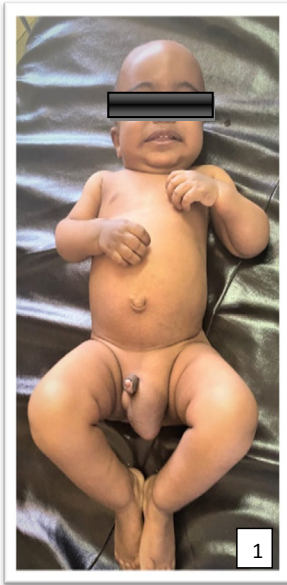
FIGURE 1 Supine Picture of the proband: coarse facial appearance, prominent forehead, flat nasal bridge, widened wrists, and left inguinal hernia
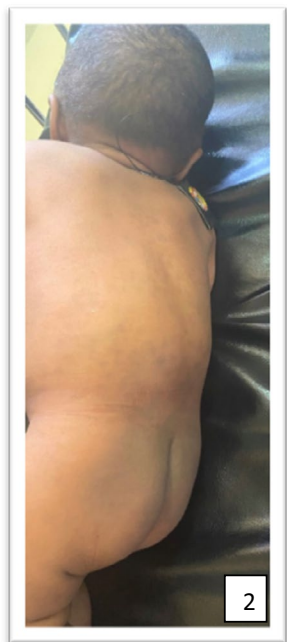

FIGURE 2 Right lateral picture of the proband: Kyphotic bulge on his lower back, macular skin lesions over lower 2/3 of his back and congenital dermal melanocytosis over the buttocks

3 | IMAGING RESULTS

Radiologic evaluation included thoracolumbar X-rays that showed normal bone mineral density though with 17 degree dextroscoliosis from T4 to T11 and kyphosis of the lumbar vertebrae at L1-3. There was also hypoplasia of the L2 vertebral body with grade one retrospondylolisthesis,
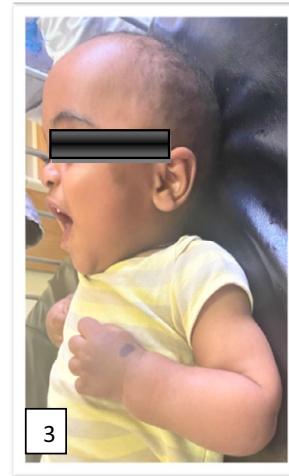

FIGURE 3 Hyperpigmented macular lesions over the left side of the proband's face and left hand

FIGURE 4 Thoracolumbar X-ray of the proband showing normal bone mineral density with 17 degree dextroscoliosis from T4 to T11 and kyphosis of the lumbar vertebrae at L1-3. There was also hypoplasia of the L2 vertebral body with grade one retrospondylolisthesis, cortical discontinuity of the pedicle of L2 vertebra noted as well as irregularity of the L2 vertebra. MRI (not indicated here) showed anterior irregular beaking of the L2 vertebra, narrow L1-L2 intervertebral disc space

cortical discontinuity of the pedicle of L2 vertebra noted as well as irregularity of the L2 vertebra (Figures 4 and 5). MR imaging of the same area showed anterior irregular beaking of the L2 vertebra, narrow L1-L2 intervertebral disc space with no other abnormalities detected. There was though noted decreased bone mineralization with cupping and fraying over the distal ulnar and radial metaphysis of both right and left wrist X-rays (Figure 6). Skull

FIGURE 5 Thoracolumbar X-ray of the proband showing normal bone mineral density with 17 degree dextroscoliosis from T4 to T11 and kyphosis of the lumbar vertebrae at L1-3. There was also hypoplasia of the L2 vertebral body with grade one retrospondylolisthesis, cortical discontinuity of the pedicle of L2 vertebra noted as well as irregularity of the L2 vertebra. MRI (not indicated here) showed anterior irregular beaking of the L2 vertebra, narrow L1-L2 intervertebral disc space
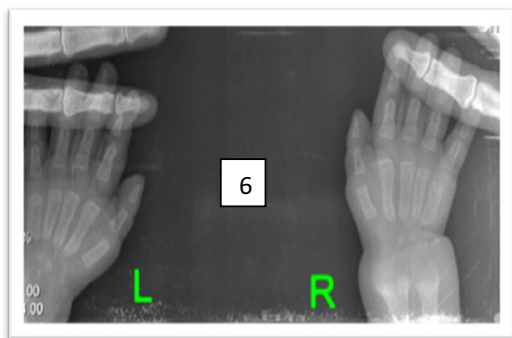
FIGURE 6 Right and left wrist X-rays of the proband: showed decreased bone mineralization with cupping and fraying over the distal ulnar and radial metaphysis of both bones

X-ray was reported as normal (Figure 7). An echocardiogram revealed concentric hypertrophy of the left atrium and left ventricles with no other abnormalities detected.

4 | MOLECULAR ANALYSIS

The Multiplex ligation-dependent probe amplification (MLPA) method (Schouten et al. 2002)[8] kits P125, P164,
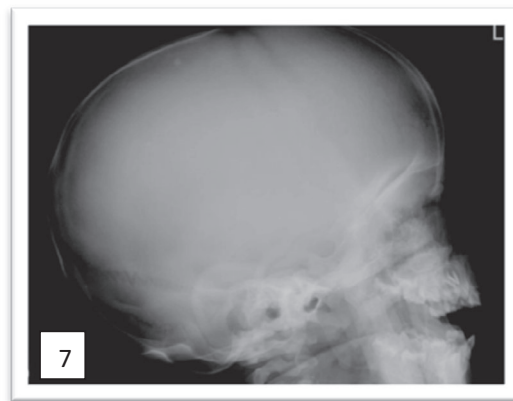

FIGURE 7 Skull X-ray of the proband reported as normal

and P309 (MRC-Holland, The Netherlands) were used to screen the DNA which was obtained from peripheral blood sample of the Proband and his mother for copy number changes, deletions, and duplication on the *IDS* gene located on the Xq28 region of the X chromosome.

The MLPA investigation also included searching for other possible causes of metabolic disorders as a result of genetic alteration on the chromosomal and mitochondrial DNA. The extent of rearrangement or copy number changes on the Xq28 region was investigated using MLPA probes targeting genes (*FMR1* and *AFF2*) located upstream and (*IDSP1*, *MTM1*, *MTMR1*, *FLNA*, *DKC1*) located down stream of the *IDS* gene. Testing showed deletions of exons 4, 5, 6, and 7 of the *IDS* gene (Figure 8); further sequencing could not be done since it is not available in our setup/country.

The MLPA analysis was also performed on a DNA obtained from the mother. The result showed heterozygous deletions of exons 4, 5, 6, and 7 of the *IDS* gene (Figure 9).

In addition, deletion of the *RNR1* and *RNR2* genes, which code for mitochondrial ribosomal RNA, were incidentally noted (Figure 10). The significance of the incidental finding, a "deletion" of the mitochondrial 16s rRNA gene, to the clinical scenario cannot be determined from this test and requires a more thorough investigation as this was identified by deletion of four MLPA probes flanking the gene. Further enzyme testing and sequencing of both the *IDS* and rRNA genes are required to identify the molecular etiology, which we do not have in our setting. The deletions observed on the *RNR1* and *RNR2* genes were also present in the mother just as in the proband (Figure 11).

5 | DISCUSSION

Hunter syndrome is an X-linked recessive, multisystemic, and progressive disease. Here, we present the first case of Hunter Syndrome reported from Ethiopia. Patients with
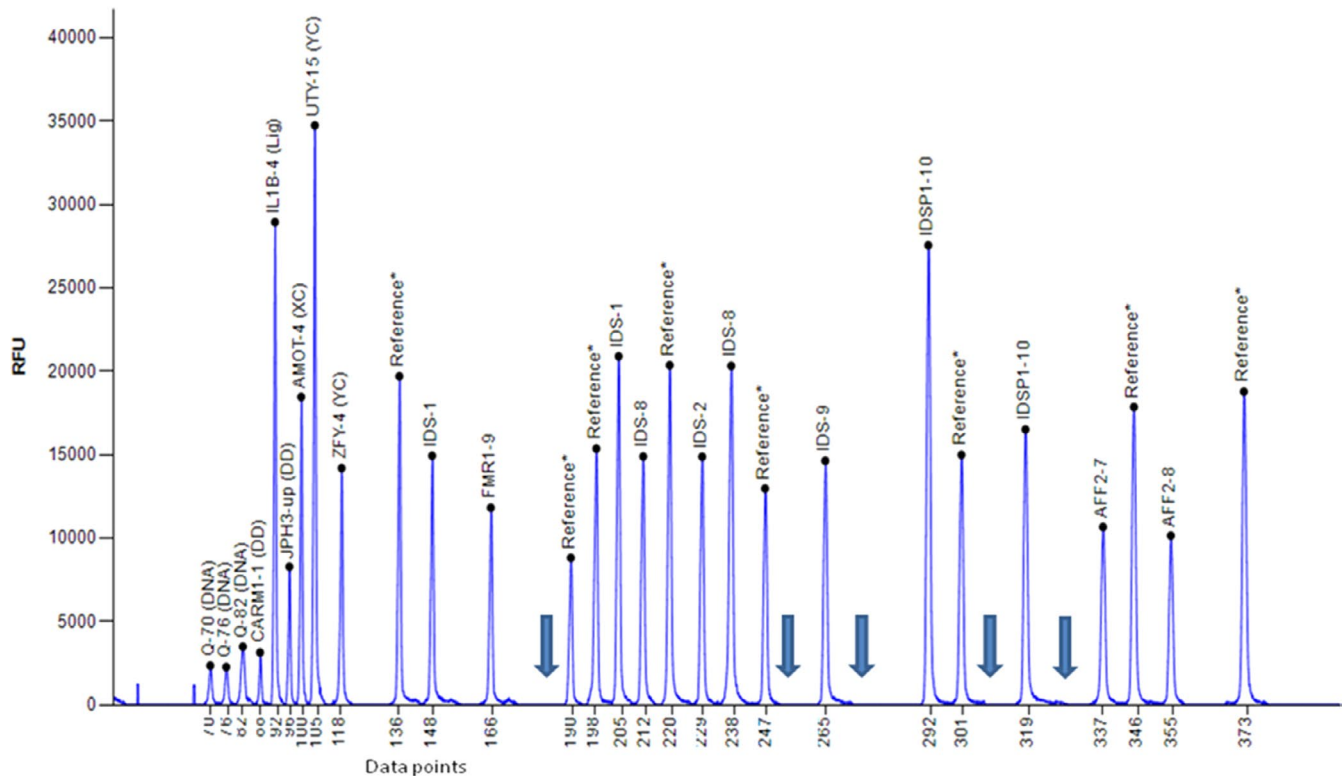
FIGURE 8 Capillary electrophoresis pattern obtained from MLPA results using IDS kit P164 from the proband. The location of the absent peaks indicating deletions (184nt for (exon 7), 256nt (exon3), 276nt (exon4), 310nt (exon5), and 328nt for (Exon6) genes) are indicated by arrows

Hunter syndrome typically present between 2 and 4 years of age though severe forms may present between 6 and 24 months of age. Based on the age of presentation, phenotype consistent with MPS II, and the multi-exonic *IDS* deletion; this patient's presentation is consistent with a severe Hunter Syndrome presentation. This is especially important to note as a previously reported patient with a similar *IDS* variant presented with an attenuated form of the disease.[9]

The proband had coarse facial features with macrocephaly, short neck, broad chest, inguinal hernia with impaired growth, and short stature similar to individuals with Hunter syndrome. The patient did though lack other features of the condition including thick lips, thick nostrils delayed tooth eruption, large tongue, hearing loss, and chronic diarrhea, though with time these features may develop.[3]

Individuals with Hunter syndrome often have joint stiffness with restriction of movements and dysostosis multiplex with thickened ribs and ovoid vertebrae. The proband at the time of evaluation was 1 year and 4 months old and was unable to sit, stand and walk, parents ascribed this to the back deformity, his imaging also showed dextroscoliosis of 17° from T4 to T11, kyphosis of lumbar vertebrae at L1-3, with hypoplasia of the L2 vertebral body with grade one retrospondylolisthesis, cortical discontinuity of pedicle of L2 vertebra with irregularity of the right superior end plate and ovoid lumbar (1–4) vertebrae.[3]

Neurologic system involvement of MPS II typically includes intellectual disability, delayed developmental milestones for age, communicating hydrocephalus, and spastic paraplegia. Our patient had noted delayed developmental milestone but no other neurologic deficits. Cutaneous manifestations include congenital dermal melanocytosis observed in African and Asian patients and grouped skin papules which was seen in our patient.[3,7]

Though we were unable to measure urinary GAGs or iduronate-2-sulfatase activity the clinical findings and *IDS* molecular analysis support the MPS II diagnosis. We identified deletions on exons 4, 5, 6, and 7 of the *IDS* gene on both the proband and maternal DNA. Similar variant has been described previously in a patient with an attenuated form of MPS II.[9] Among the previously described alternations, 28.2% are large alterations that include complete and partial deletions and rearrangements and 71.8% are small deletions and single nucleotide polymorphisms resulting in various mutations.[10,11] Additionally Complex rearrangements due to illegitimate recombinations of these regions resulting in Hunter syndrome are reported.[12-14]

The incidental finding of the *RNR1* and *RNR2* deletions is of uncertain significance at this point. The *IDS*
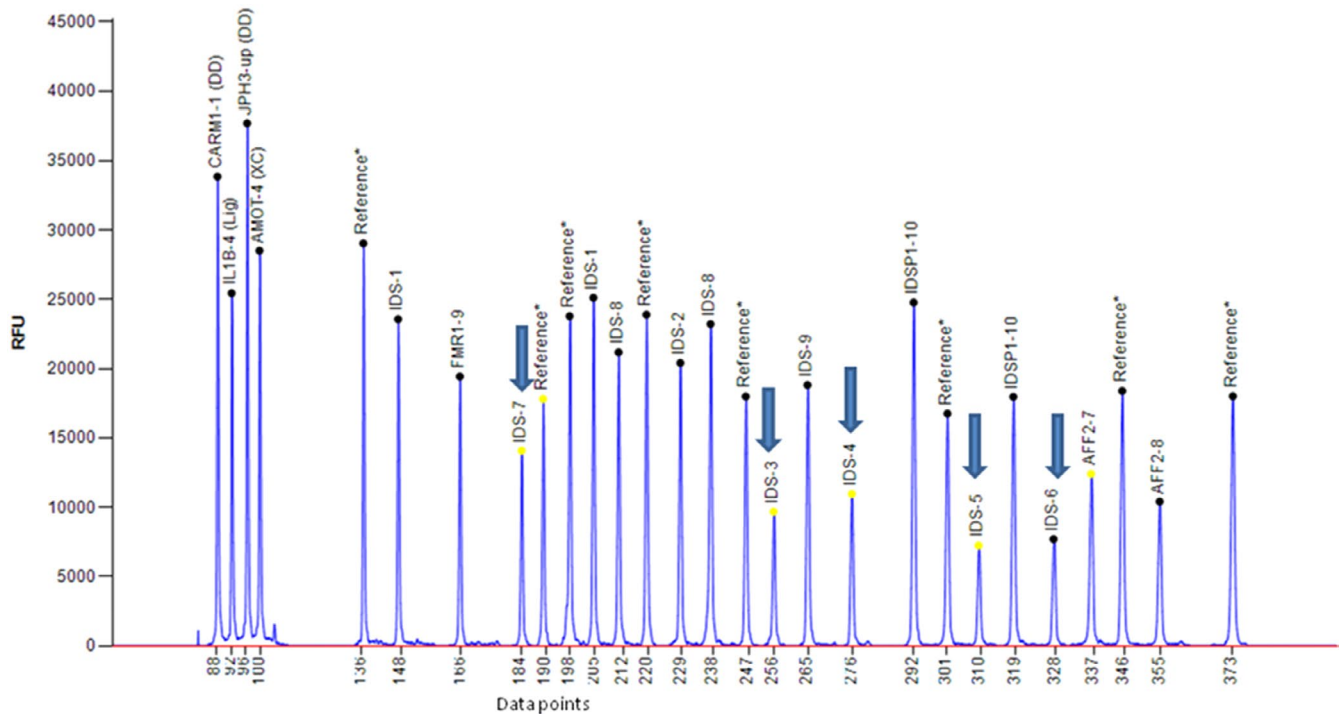
FIGURE 9 Capillary electrophoresis pattern obtained from MLPA results using IDS kit P164 on maternal DNA. The location of the peaks indicating heterozygous deletions (184nt for (exon 7), 256nt (exon3), 276nt (exon4), 310nt (exon5), and 328nt for (Exon6) genes) are indicated by arrows
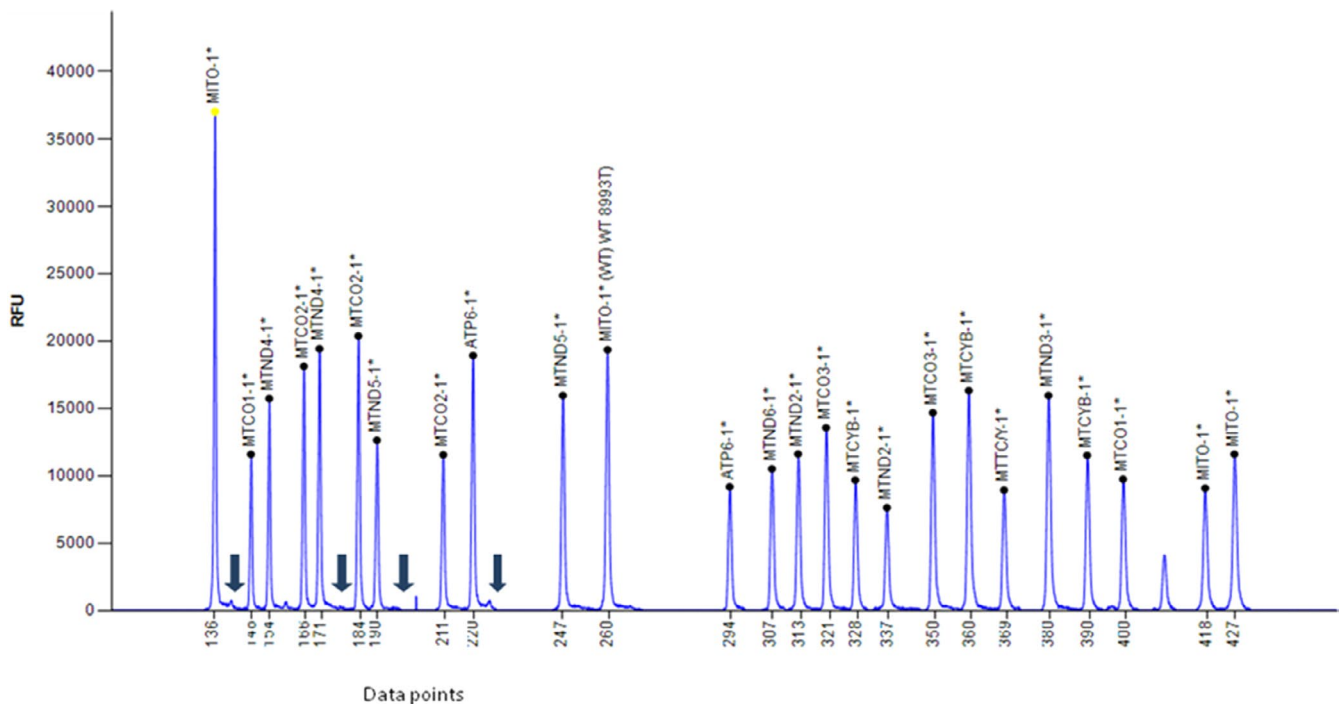

FIGURE 10 Capillary electrophoresis pattern obtained from MLPA results using mitochondrial kit P125 on DNA from the proband. The location of the absent peaks (142nt for RNR1, and 178nt, 202nt, and 226nt for RNR2 genes) are indicated by arrows

exon deletions were felt to be causative as similar deletions have been seen in previously reported Hunter syndrome patients.[9,15] Further enzyme testing and sequencing are required to identify the significance further (which we do not have in our setting); though pathogenic variants in these 2 genes have not yet been identified to cause human disease. The maternal screening confirms the inheritance of the deleted exons on the
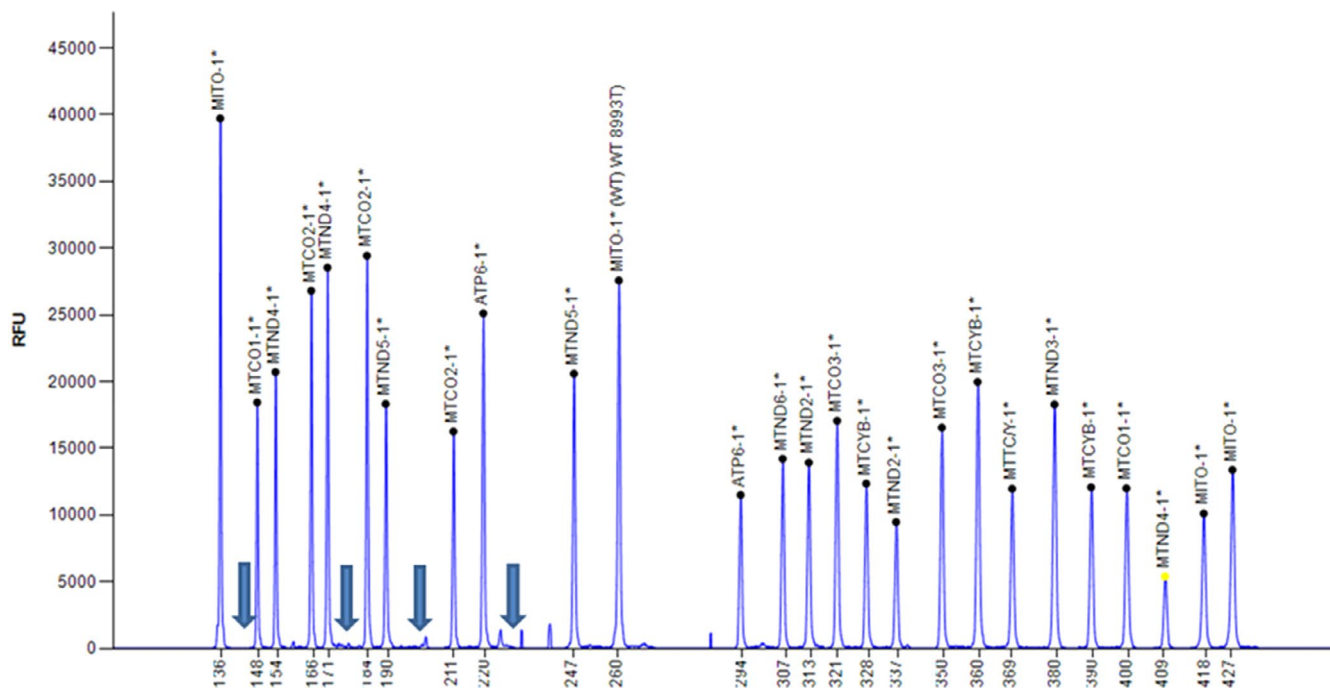
FIGURE 11 Capillary electrophoresis pattern obtained from MLPA results using mitochondrial kit P125 on maternal DNA. The location of the absent peaks (142nt for RNR1, and 178nt, 202nt, and 226nt for RNR2 genes) are indicated by arrows

IDS gene as well as the deletion of the maternally inherited mitochondrial rRNA gene.

In patients with Hunter syndrome early enzyme replacement therapy is indicated before irreversible organ damage occurs, however, this management is not available in Ethiopia. Follow-up of this patient should involve a multidisciplinary team including pediatririans, orthopedists, neurosurgeons, ophthalmologists, otorhinolaryngologists, and cardiologists, which is feasible in our setting for the proband.

CONFLICT OF INTEREST
The authors do not have any conflict of interest.

AUTHOR CONTRIBUTIONS
1st Author: Solomie Jebessa Deribessa, who is also the corresponding author, has made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and has been involved in drafting the manuscript or revising it critically for important intellectual content. 2nd Author: Mekdes Endale Bisrat has made substantial contributions to conception and design, or acquisition of data, and has been involved in drafting the manuscript. 3rd Author: Zewdu Terefework has made substantial contributions to design, or acquisition of data, or analysis and interpretation of data; and has been involved in drafting the manuscript or revising it critically for important intellectual content. 4th Author: Shane C. Quinonez has made substantial contributions to design, interpretation of data; and has been involved in drafting the manuscript or revising it critically for important intellectual content.

CONSENT
Written consent has been obtained from the patient parent.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ENDNOTE
* SD: Standard Deviation: all SD measurements according to the World Health Organization growth charts for children under five years of age.

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