Severe congenital lactic acidosis and hypertrophic cardiomyopathy caused by an intronic variant in \textit{NDUFB7}

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Abstract
Mutations in structural subunits and assembly factors of complex I of the oxidative phosphorylation system constitute the most common cause of mitochondrial respiratory chain defects. Such mutations can present a wide range of clinical manifestations, varying from mild deficiencies to severe, lethal disorders. We describe a patient presenting intrauterine growth restriction and anemia, which displayed postpartum hypertrophic cardiomyopathy, lactic acidosis, encephalopathy, and a severe complex I defect with fatal outcome. Whole genome sequencing revealed an intronic biallelic mutation in the \textit{NDUFB7} gene (c.113-10C>G) and splicing pattern alterations in \textit{NDUFB7} messenger RNA were confirmed by RNA Sequencing. The detected variant resulted in a significant reduction of the \textit{NDUFB7} protein and reduced complex I activity. Complementation studies with expression of wild-type \textit{NDUFB7} in patient fibroblasts normalized complex I function. Here we report a case with a primary complex I defect due to a homozygous mutation in an intron region of the \textit{NDUFB7} gene.

KEYWORDS
cryptic splice site mutation, intrauterine clinical manifestations, isolated complex I deficiency, mitochondrial disease, \textit{NDUFB7}

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Next generation sequencing, with whole genome sequencing (WGS) and more recently RNA sequencing (RNA-Seq), has revolutionized the diagnosis of mitochondrial diseases. It has allowed the discovery of numerous genetic mutations underlying defects in the oxidative phosphorylation system (OXPHOS). Mutations exclusively restricted to complex I (proton-pumping NADH-ubiquinone oxidoreductase) together constitute the most common cause of respiratory chain deficiencies (MIM# 252010). These genetic alterations are responsible for a broad spectrum of clinical features, ranging from syndromes affecting multiple organs like Leigh syndrome and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), to single organ diseases including Leber hereditary optic neuropathy (LHON) or hypertrophic cardiomyopathy (Fassone & Rahman, 2012; Fiedorczyk & Sazanov, 2018; Rodenburg, 2016).

In addition, complex I defects have been associated with adult onset of neurodegenerative disorders such as Parkinson disease (Fassone & Rahman, 2012; Fiedorczyk & Sazanov, 2018). Mitochondrial respiratory chain complex I is the largest complex of OXPHOS. It is composed of 14 central subunits, conserved from bacteria to humans, at least 30 accessory subunits, and 14 or 15 assembly factors (Formosa et al., 2018; Guerrero-Castillo et al., 2017). Significant advances have recently been made on the elucidation of the structure and assembly steps of complex I. The structure resembles an L shaped form, where one arm is hydrophilic and oriented into the mitochondrial matrix, while the other is hydrophobic and integrated into the mitochondrial inner membrane. The hydrophilic arm is divided into an N module (NADH oxidation) and a Q module (ubiquinone reduction), while the hydrophobic arm is constituted by a P module (proton pumping). Due to the existence of four pumping sites, the P module can be divided in proximal, a and b (PP-a and PP-b), and distal, a and b (P-D-a and P-D-b). The last module P-D-b, in fully assembled complex I, is composed of the central subunit ND5 and accessory subunits NDUFB2, NDUFB3, NDUFB7, NDUFB8, and NDUFB9 (Formosa et al., 2018, 2020; Galemou Yaga et al., 2020; Guerrero-Castillo et al., 2017; Parey et al., 2018; Wirth et al., 2016). Deleterious alterations in proteins of the P-D-b module have been described and related with complex I disorders. Like other defects in this complex, these mutations could cause a wide range of clinical phenotypes. Mutations in MT-ND5 have been linked with distinct mitochondrial disorders such as Leigh syndrome (MIM# 256000), MELAS (MIM# 540000), and LHON (MIM# 535000; Danhelovska et al., 2020). The single pathogenic mutation described for NDUFB9 is characterized by progressive hypotonia and increased serum lactate (Haack et al., 2012b). Pathogenic variants in NDUFB3 are associated with intrauterine growth retardation, encephalopathy, myopathy, hypotonia, and lactic acidosis (Calvo et al., 2012; Haack et al., 2012a). Similarly, deleterious mutations in NDUFB8 have been reported in individuals with a progressive disease characterized by encephalomyopathy, cardiac hypertrophy, respiratory failure, hypotonia, and lactic acidosis. These patients displayed abnormalities in brain magnetic resonance imaging (MRI) consistent with Leigh syndrome (Piekutowska-Abramczuk et al., 2018). Regarding NDUFB7 and NDUFB2, no pathogenic mutations have been identified in patients. However, a critical role for NDUFB7 in complex I assembly in Yarrowia lipolytica has been suggested (Dröse et al., 2011). Furthermore, in vitro experiments have suggested that the absence of any of the accessory subunits of the P-D-b module may critically affect the assembly and function of human complex I (Dröse et al., 2011; Formosa et al., 2020; Stroud et al., 2016). Here we report the first case of a mitochondrial disorder caused by an intronic mutation leading to a cryptic splice site in the NDUFB7 gene. The affected patient was born in 2015 of consanguineous Iranian parents with an unaffected 2 years older sister. Pre-natal features included cardiomegaly detected at the gestational Week 25, intrauterine anemia (that required two transfusions) and intrauterine growth restriction. Pregnancy was further complicated by oligohydramnios and decreased umbilical cord blood flow that led to a cesarean section at gestational Week 36. The boy was born small for gestational age with a birth weight of 1827 g, length of 43 cm, head circumference of 31.5 cm, and an Apgar score of 6, 9, and 10. From the second day of life, he presented with lactic acidosis (plasma lactate maximum of 11.5 mmol/L, ref. 0.5–2.3 mmol/L), which normalized during dichloracetate treatment. Cardiac evaluation confirmed a hypertrophic cardiomyopathy with perimembranous ventricular septal defect, atrial septal defect and pulmonary hypertension. Physical examination revealed cryptorchidism and hypospadias, without any other visible dysmorphic features. He displayed a normal movement pattern without any obvious epileptic seizures and no apparent ophthalmological or hearing abnormalities. Brain MRI at Day 13 showed widely distributed cysts, likely due to prenatal events and possible dysplasia of the corpus callosum. MR spectroscopy revealed increased lactate and decreased N-acetylaspartate in the basal ganglia. The patient suffered from repeated desaturations and was treated in hospital until his death at 55 days of age from cardiorespiratory failure. Newborn screening did not reveal any underlying causes for the patient’s phenotype. Urinary organic acids were normal, except for a transiently increased excretion of lactate. Amino acids, acylcarnitines, and carnitine levels in plasma were also normal. Analysis of alpha-glucosidase enzyme activity was normal, excluding Pompe disease as a cause of disease. The PDHA1 gene was sequenced, since pathogenic mutations in this gene are a common cause of early lactic acidosis in children. Mitochondrial ATP production (Figure S1) and respiratory chain enzyme activities (Figure 1a) in mitochondria isolated from skeletal muscle were determined as previously described (Wibom et al., 2002). These analyses revealed a severe complex I defect that was later confirmed by Blue Native Polyacrylamide Gel Electrophoresis (BN-PAGE; Figure 1b). Morphological and histochemical investigations of the biopsy by light and electron microscopy were normal. The mitochondrial genome was analyzed by Sanger sequencing and Southern blot analysis and neither pathogenic mutations nor rearrangements were detected, albeit with a slight reduction in mtDNA content. Whole genome sequencing on DNA samples from patient and parents was performed, followed by in-house mutation identification pipeline analysis (MIP; Stranneheim et al., 2014) and validation by Sanger sequencing. MIP revealed two candidate genes,
FIGURE 1 (See caption on next page)
**NDUFB7** and **MVIP7L2**, both homozygous. Variants in other genes were excluded as they failed to display an appropriate inheritance model. MVIP7L2 (MIM# 616133) is an inner mitochondrial membrane protein, with a role in assembly and stability of the mitochondrial ribosome. This gene was discarded because the detected variant was common, with three homozygotes in Genome Aggregation Database (gnomAD). Another candidate mutation in the **HMGCR** gene (NC_000005.9: g.74646101G>A; NM_000859.2: c.682G>A, p.Glu228Lys) was also identified and investigated. HMGCR (MIM# 142910) is the rate-limiting step of the mevalonic acid pathway. Products of this pathway include molecules that are relevant for mitochondrial function, such as cholesterol, coenzyme Q10 (CoQ10) and heme α (Broniarek et al., 2020). This variant was rejected after determination of a normal HMGCR activity in patient fibroblasts (Figure S2). The exclusion of the aforementioned candidates led us to manually curate variants, namely by filtering those associated with complex I. One candidate gene, **NDUFB7**, was identified with a homozygous intronic variant potentially affecting splicing (NC_000019.9: g.14677755G>C, NM_004146.5: c.113-10C>G, Figure 1d). This variant was not present in the genome aggregation database (gnomAD) or in our local observation count database consisting of more than 3000 WGS samples (Magnusson et al., 2020). The **NDUFB7** gene (Gene ID: 4713, MIM# 603842) is located in the short arm of chromosome 19 (19p13.12) and encodes for a 137 amino acid protein (Uniprot P17568) located in the mitochondrial intermembrane space (Szkłarczyk et al., 2011) for which there is still no described function. Although no pathogenic variants have been described for **NDUFB7**, in vitro studies have demonstrated that knockouts of this protein lead to impaired complex I assembly in human cells (Formosa et al., 2020; Stroud et al., 2016) and in the yeast *Y. lipolytica* (Dröse et al., 2011). The intronic mutation detected in the **NDUFB7** gene prompted us to evaluate **NDUFB7** mRNA splicing by RNA-Seq in both patient and parent fibroblasts (Figure 1c). The analysis revealed a significant decrease in the total number of transcripts in the patient, as well as formation of an alternative transcript. Complementary DNA Sanger sequencing confirmed this alternative transcript, that included nine extra nucleotides from intron 1 (Figure 1e). Western blot analysis further confirmed an alternative transcript, that included nine extra nucleotides from intron 1 (Figure 1d). BN-PAGE with in-gel determination of complex I, IV, and V activity and measurement of respiration in permeabilized cells. Western blot procedures revealed diverse changes to different subunits of complex I. The decrease of NDUFB7 correlated with the decrease of NDUFB8 (P2-b module) and with proteins of the Q module (NDUFS3 and NDUFS2) but not with the N (NDUFV1) module. No effects were seen for the other OXPHOS complexes or for the mitochondrial loading control (Figures 2b and S3). Recovery of NDUFB7 expression in the transduced cell lines correlated with recovery of NDUFB8 expression (Figures 2b and S3), suggesting an intrinsic dependence that might be explained by their role in the subassembly of the P2-b module (Guerrero-Castillo et al., 2017) and also confirming what was demonstrated with the NDUFB8 ortholog in *Y. lipolytica* (Dröse et al., 2011). To evaluate if the recovery of NDUFB7 expression indicated recovery of complex I activity we assessed complex I function by BN-PAGE in-gel activity and by cellular respiration. In-gel activity demonstrated full recovery of complex I activity without major effects to complex IV and V activities (Figure 2c). Measurement of oxygen consumption in patient and control lines (transduced and non-transduced) with an Oxygraph (Oroboros) further confirmed these results, demonstrating a reduction of complex I respiration to approximately 30% of control in State III respiration and 20% of control in State IV respiration in the patient cell line, but a full recovery to control levels in both states in the NDUFB7 transduced patient cells. Oxygen consumption measurements also revealed an unaffected complex II respiration in both transduced and non-transduced cell lines (Figure 2d). Collectively, these results unequivocally point to the detected intronic mutation in the **NDUFB7** gene as causative of the complex I defect. To conclude, here we present the first clinical description of a complex I defect caused by an intronic homozygous mutation in the **NDUFB7** gene. Although we describe only one patient, the clinical characteristics presented here are in line with other reported deleterious variants in genes of the same module of complex I (Calvo et al., 2012; Danhelovska et al., 2020; Haack et al., 2012; 2012b; Plekutowska-Abramszuk et al., 2018). It is also noteworthy that the case reported herein is a prime example of the application of next generation sequencing methods in the clinical setting. Pathogenic intronic mutations, such as the one presented,

**Figure 1** Laboratory investigations in a patient with NDUFB7 intronic mutation. (a) Respiratory chain enzyme activities of complex I (NADH:coenzyme Q reductase), complexes I and II (NADH:cytochrome c reductase), complex II (succinate:coenzyme Q reductase), complexes II and III (succinate:cytochrome c reductase), complex IV (cytochrome c oxidase) were determined, and were expressed per citrate synthase (OXPHOS) complexes or for the mitochondrial loading control (Figures 2b and S3). Measurement of oxygen consumption in patient and control lines (transduced and non-transduced) with an Oxygraph (Oroboros) further confirmed these results, demonstrating a reduction of complex I respiration to approximately 30% of control in State III respiration and 20% of control in State IV respiration in the patient cell line, but a full recovery to control levels in both states in the NDUFB7 transduced patient cells. Oxygen consumption measurements also revealed an unaffected complex II respiration in both transduced and non-transduced cell lines (Figure 2d). Collectively, these results unequivocally point to the detected intronic mutation in the NDUFB7 gene as causative of the complex I defect. To conclude, here we present the first clinical description of a complex I defect caused by an intronic homozygous mutation in the NDUFB7 gene. Although we describe only one patient, the clinical characteristics presented here are in line with other reported deleterious variants in genes of the same module of complex I (Calvo et al., 2012; Danhelovska et al., 2020; Haack et al., 2012; 2012b; Plekutowska-Abramszuk et al., 2018). It is also noteworthy that the case reported herein is a prime example of the application of next generation sequencing methods in the clinical setting. Pathogenic intronic mutations, such as the one presented,
FIGURE 2  Protein status in NDUFB7 patient and complementation studies with retroviral transfection of WT-NDUFB7. (a) Representative western blot analysis of NDUFB7 protein in primary (p) and immortalized (i) fibroblasts from patient (P), control (C) and father (F). VDAC (Porin) was used as loading control. (b) Representative Western blot analysis of transduced and non-transduced immortalized fibroblasts. VDAC (Porin) was used as loading control and protein signal was determined as described with appropriate antibodies. Complex I modules are given between brackets. (c) In-gel activity of Complex I, IV, and V in BN-PAGE. Mitochondrial extracts were separated by BN-PAGE and gels were incubated with corresponding substrates as described. (d) Oxygen consumption in permeabilized cells from controls (white) and patient (black) and respective NDUFB7 transduced cells (diagonal bars). Measurements were performed in the presence of complex I substrates GMP (Glutamate, Malate, and Pyruvate) with ADP (State III) and without ADP (State IV); complex II substrates GMP, ADP, and Succinate; Complex II activity was measured in the presence of Rotenone. Bars represent mean ± SD (n = 4). BN-PAGE, Blue Native Polyacrylamide Gel Electrophoresis
are now possible to detect by WGS and evaluate by RNA-Seq. This combinatorial approach has allowed the resolution of cases with more challenging molecular causes and will undoubtedly support the ongoing improvement of mutation identification pipelines.

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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

WEB RESOURCES
Online Mendelian Inheritance in Man, OMIM®
https://www.omim.org/
The Genome Aggregation Database (gnomAD)
https://gnomad.broadinstitute.org/
National Center for Biotechnology Information
https://www.ncbi.nlm.nih.gov/
UniProt
https://www.uniprot.org/

DATA AVAILABILITY STATEMENT
Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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