Expansion of the clinical and neuroimaging spectrum associated with NDUFS8-related disorder

Milena M. Andzelm1 | Shanti Balasubramaniam2,3 | Edward Yang4 | Alison G. Compton5,6 | Kate Millington7 | Jia Zhu7 | Irina Anselm1 | Lance H. Rodan8 | David R. Thorburn5,6,9 | John Christodoulou5,6,9 | Siddharth Srivastava1

1Department of Neurology, Children’s Hospital Boston, Boston, Massachusetts, USA
2Western Sydney Genetics Program, The Children’s Hospital at Westmead, Sydney, New South Wales, Australia
3Department of Metabolic Medicine and Rheumatology, Perth Children’s Hospital, Perth, Western Australia, Australia
4Department of Radiology, Children’s Hospital Boston, Boston, Massachusetts, USA
5Murdoch Children’s Research Institute, Melbourne, Victoria, Australia
6Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia
7Division of Endocrinology, Department of Pediatrics, Children’s Hospital Boston, Boston, Massachusetts, USA
8Division of Genetics and Genomics, Manton Center for Orphan Disease Research, Department of Pediatrics, Children’s Hospital Boston, Boston, Massachusetts, USA
9Victorian Clinical Genetic Services, Melbourne, Victoria, Australia

Correspondence
Siddharth Srivastava, Department of Neurology, Children’s Hospital Boston, 300 Longwood Avenue, Boston, MA 02115, USA.
Email: siddharth.srivastava@childrens.harvard.edu

Funding information
National Health and Medical Research Council; National Institute of Neurological Disorders and Stroke, Grant/Award Number: K23NS119666-01A1; Royal Children’s Hospital Foundation

Communicating Editor: Areeg El-Gharbawy

Abstract
Biallelic pathogenic variants in NDUFS8, a nuclear gene encoding a subunit of mitochondrial complex I, result in a mitochondrial disorder characterized by varying clinical presentations and severity. Here, we expand the neuroimaging and clinical spectrum of NDUFS8-related disorder. We present three cases from two unrelated families (a girl and two brothers) homozygous for a recurrent pathogenic NDUFS8 variant [c.460G>A, p.(Gly154Ser)], located in the [4Fe-4S] domain of the protein. One of the patients developed auto-antibody positive diabetic ketoacidosis. Brain MRIs performed in two of the three patients demonstrated diffuse cerebral and cerebellar white matter involvement including corticospinal tracts, but notably had sparing of deep gray matter structures. Our report expands the neuroimaging phenotype of NDUFS8-related disorder to include progressive leukodystrophy with increasing brainstem and cerebellar involvement, with relative sparing of the basal ganglia. In addition, we describe autoimmune diabetes in association with NDUFS8-related disorder, though the exact mechanism of this association is unclear. This paper provides a comprehensive review of case presentation and
INTRODUCTION

NDUFS8 (NADH:Ubiquinone Oxidoreductase Core Subunit S8) is a nuclear gene that encodes a core subunit of mitochondrial complex I (CI), an enzyme complex that catalyzes the first step in the electron transport chain resulting in the generation of energy in the form of ATP. NDUFS8 is a highly conserved protein with an iron–sulfur [4Fe-4S] binding site, which facilitates electron transfer to ubiquinone as part of the Q module of CI.1

In humans, biallelic pathogenic variants in NDUFS8 often underlie severe presentations of mitochondrial disease, including Leigh syndrome and mitochondrial encephalopathy (MIM # 602141).2,3 NDUFS8-related disorder was first described in an infant with Leigh syndrome (LS) and cardiomyopathy who died at 11 weeks of age.4 Since then, several other patients have been described with severe manifestations, often including cardiomyopathy, as well as epilepsy, severe developmental delays and imaging abnormalities often involving the white matter, basal ganglia and brainstem.4–6

Recent studies have demonstrated milder clinical phenotypes associated with NDUFS8-related disorder. These patients generally presented in childhood, and MRI brain demonstrated signal change in the putamen.7,8 Their symptoms were slowly progressive over years with variable manifestations of Leigh syndrome. For example, one study described a 9-year-old girl with late-onset LS manifesting as nystagmus, dysarthria, dystonia, involuntary hand movements, toe walking, and ataxic gait.7 Another study described a family with three children with Leigh syndrome, still alive at 9–13 years old, presenting with variable features of developmental delay, dysarthria, progressive external ophthalmoplegia, ptosis, muscle weakness, and ataxia.8

Given that the total number of individuals reported with NDUFS8-related disorder is small, the overall knowledge about this disorder is limited. In this report, we present three affected individuals from two unrelated families (a girl and two brothers) with a recurrent homozygous pathogenic variant in NDUFS8, c.460G>A; p.(Gly154Ser). The two brothers, but not the girl, have been previously reported, though with limited clinical information.6 All three individuals developed regression and died after subsequent regressive setbacks in the setting of illness. The girl acutely decompensated in association with an upper respiratory viral infection and diabetic ketoacidosis (DKA) in the setting of new autoimmune diabetes.

KEY POINTS

1. We have provided comprehensive review of the neuroimaging findings of the patients, which is much needed given that brain MRI can be a first step toward this molecular diagnosis.
2. We have expanded the clinical spectrum of NDUFS8-associated neurological disease to include progressive leukodystrophy with increasing brainstem and cerebellar involvement, with relative sparing of the basal ganglia.
3. We describe autoimmune diabetes in association with NDUFS8-related disorder, though the mechanism of this association is unclear.

CLINICAL REPORT

See Table 1 for summary of clinical details.

Patient 1

Patient 1 was born at 36 weeks gestation with a birth weight of 4 pounds (small for gestational age). Early
| Genomics          | Patient 1                                           | Patient 2                                           | Patient 3 (sibling of patient 2)                      |
|-------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Variant           | c.460G>A, p.(Gly154Ser), homozygous, heterozygous in parents | c.460G>A, p.(Gly154Ser), homozygous in both affected siblings, heterozygous in parents | c.460G>A, p.(Gly154Ser), homozygous in both affected siblings, heterozygous in parents |
| Consanguinity     | No                                                  | No                                                  | No                                                  |
| Demographics      |                                                     |                                                     |                                                     |
| Ethnicity         | Indian                                              | Sudanese                                           | Sudanese                                           |
| Sex               | Female                                              | Male                                               | Male                                               |
| Age at last exam  | 24 months                                           | 14 months                                          | 14 months                                          |
| Deceased          | Yes (24 months)                                     | Yes (14 months)                                    | Yes (15 months)                                    |
| Cause of death    | Bradycardic arrests in setting of metapneumovirus virus infection | Parainfluenza pneumonia                           | Uncontrolled seizures and respiratory compromise |
| Perinatal history |                                                     |                                                     |                                                     |
| Gestational age   | 36 weeks                                            | 41 weeks                                           | 39 weeks                                           |
| Birth weight      | 1.81 kg                                             | 3.54 kg                                            | 3.28 kg                                            |
| Systemic features |                                                     |                                                     |                                                     |
| Cardiomyopathy    | Y                                                   | Not known                                           | Not known                                           |
| Diabetes mellitus | Y                                                   | Not known                                           | Not known                                           |
| Development       |                                                     |                                                     |                                                     |
| Regression        | Yes                                                 | Yes                                                | Yes                                                |
| Onset of regression | 9 months (after viral illness)                     | 6 months (after febrile illness)                   | 5 months (after febrile illness)                   |
| Nature of regression | Lost ability to sit independently, crawl, or pull to stand | Lost ability to sit with support, roll over, bear weight on legs, and reach for objects. | Lost musical vocalizations                          |
| Language abilities | 18 months: could smile socially, laugh out loud, babble, say mama nonspecifically | 7 months: could smile socially, mouth objects | 5 months: could make musical vocalizations |
| Motor abilities   | 18 months: could lift head up in prone              | 7 months: poor head control, unable to roll over    | 5 months: could roll to side but not supine to prone or prone to supine; in prone unable to lift head or chest against gravity |
| Neurological features |                                                     |                                                     |                                                     |
| Seizures          | N                                                   | N                                                   | Y                                                   |
| Axial hypotonia   | Y                                                   | Y                                                   | Y                                                   |
| Appendicular spasticity | Y                                               | Y                                                   | Y                                                   |
| Dystonia          | Y                                                   | N                                                   | N                                                   |
| Hyperreflexia     | Y                                                   | Y                                                   | Y                                                   |
| MRI features      |                                                     |                                                     |                                                     |
| Age of latest scan | 24 months                                          | 7 months                                           | Not done                                           |
| Involvement of diffuse cerebral white matter | Y                                                   | Y                                                   |                                                     |
| Involvement of corticospinal tracts | Y                                             | Y                                                   |                                                     |
| Involvement of middle cerebellar peduncles | Y                                             | N                                                   |                                                     |

(Continues)
development was notable for typical acquisition of motor milestones until motor regression at 8 months of age. She crawled and rolled at 6 months of age, and she sat unsupported at 7 months of age. However, at 8 months of age, a few days after a viral illness, she lost the ability to roll over, crawl, sit independently, and reach for objects. She developed irritability and sleeping difficulty.

Family history was notable for the father having a history of IgA nephropathy and kidney transplantation, and the paternal grandfather also had a history of kidney transplantation. Family history was otherwise negative for neurodevelopmental or other autoimmune disorders. There was no known consanguinity.

On her neurological exam at 10 months, she appeared irritable. She had axial hypotonia, appendicular spasticity (lower > upper) with admixed dystonia. She could not sit independently, reach for objects, or transfer objects from one hand to another. Reflexes were 3+ with upgoing toes bilaterally.

She developed failure to thrive requiring eventually G-tube placement. Echocardiogram demonstrated concern for hypertrophic cardiomyopathy. At the age of 24 months, she presented with DKA secondary to new-onset diabetes mellitus in the setting of metapneumovirus infection. Her pancreatic autoantibodies (anti-GAD, anti-IA2, anti-insulin, anti-Zn62) were pan-positive. Despite treatment and resolution of her DKA, she died after developing episodes of bradycardic arrests thought to be secondary to progressive brainstem dysfunction.

Initial metabolic investigations included urine organic acids with trace quantities of 3-hydroxyisobutyric, ethylmalonic, fumaric and malic acids, plasma very long chain fatty acids with ratio of C24/C22 and C26/C22 slightly higher than normal but normal amount of C26:0. Plasma amino acids with elevated alanine but obtained with tourniquet. Blood ammonia and white blood cell lysosomal enzyme activity were normal. Blood lactate was 1.8 mmol/L (normal range 0.5–2.0), pyruvate was not obtained. CSF metabolic studies were not obtained.

Initial MRI brain at 10 months of age showed confluent, symmetric areas of T2 prolongation in the cerebral white matter, as well as parts of the middle cerebellar peduncles and cerebellar white matter. There was diffusion restriction in these areas, except for areas in the deep white matter which appeared mildly expansile and diffusion facilitated. By 24 months, this pattern had evolved, showing new/increased expansile T2 signal abnormality involving the lateral thalami, internal capsules, pons, middle cerebellar peduncles, medullary olives, cerebellar white matter, and cervicomedullary junction. At the same time, preexisting areas of cerebral white matter diffusion restriction had resolved apart from the subcortical U-fibers (previously, there was near homogeneous involvement of the subcortical, deep, and periventricular white matter) and in many locations had undergone cavitation (Figure 1). MR spectroscopy showed a depressed NAA peak and new lactate accumulation.

GeneDx Leukodystrophy Xpanded Panel revealed a homozygous variant in \( \text{NDUFS8} \) (c.460G>A, p.Gly154Ser), with each parent being a heterozygous carrier.

### 3.2 Patient 2

Patient 2 was previously reported, though clinical details of his presentation in that report are limited. He was the first child of Sudanese parents not known to be consanguineous. The pregnancy was uncomplicated. He was born at 41 weeks gestation by lower segment cesarean section for failure to progress. Apgar scores were 9 and

| Involvement of cerebellar white matter | Y | Y |
| Diffusion restriction in affected areas | Y (10 months: more diffuse; 24 months: receded to subcortical U fibers) | Y |
| Enhancement | Y | N |
| Elevated lactate on MRS | Y (at 24 months), N (at 10 months) | Y (7 months) |
| Sparing of basal ganglia | Y | Y<sup>a</sup> |

<sup>a</sup>For patient 2, basal ganglia spared on initial imaging, though were involved on histopathological analysis on autopsy 7 months later.
9 at 1 and 5 min of life, respectively, and there were no perinatal problems. His birthweight, length, and head circumference were within normal range.

He had normal development during the first 6 months of life. However, at 6 months of age, he had an acute neurological deterioration following an intercurrent febrile illness, with loss of previously attained skills, including head control and ability to roll, and slow recovery. At this time, he was centrally hypotonic, peripherally hypertonic, with scissoring of his lower limbs, and exhibited hyperreflexia and fisting of his hands. Weight was 9.2 kg (50th–90th percentile) and head circumference was 46.1 cm (90th percentile).

Over the first 12 months of life, he had several intercurrent respiratory or gastrointestinal illnesses without apparent metabolic decompensation. However, at 14 months of age, he developed a parainfluenza respiratory tract infection and rapidly deteriorated, requiring mechanical ventilation. Despite intensive management over several weeks, there was no improvement. He died after treatment was withdrawn.

Normal metabolic investigations included urine amino acids, urine organic acids, blood ammonia, plasma very long chain fatty acids, white blood cell lysosomal enzyme activities. Blood lactate levels ranged from 3 to 3.6 mmol/L (normal range 0.0–2.0). CSF lactate was marginally elevated at 2.3 mmol/L (normal <2.0) at a time when his blood lactate was 3.0.

MRI brain at 7 months of age showed involvement of the supratentorial white matter, corticospinal tracts, and cerebellar white matter with restricted diffusion in a similar distribution; MR spectroscopy demonstrated lactate peak (Figure 2). There was no enhancement on post-contrast imaging.

At autopsy, his brain showed a spongiform leukoencephalopathy involving the cerebrum (with focal involvement of the basal ganglia and thalami), brainstem, and cerebellum, with relative preservation of gray matter and the corpus callosum. Liver histology was normal. Muscle histology showed mild steatosis and occasional fibers with subsarcolemmal accumulation of NADH staining. SDH staining was normal and no COX negative fibers were seen, nor were there any overt ragged red fibers. Lungs showed a severe organizing pneumonia. The kidneys were mostly normal, although there were some sclerosing glomeruli with cellular crescents and focal interstitial inflammation, consistent with a mild focal glomerulonephropathy.
Next-generation sequencing identified a homozygous variant in \textit{NDUFS8} (c.460G>A, p.Gly154Ser).\textsuperscript{6} Mitochondrial respiratory chain enzymology was performed in liver and muscle collected within 2 h of death. Biochemical testing revealed significantly decreased complex I activity in skeletal muscle (8\% of normal control mean) and liver (21\% of normal control mean). Activity of other electron transport chain enzymes (complexes II, III, and IV) were in the normal range in skeletal muscle (107\%, 82\%, and 52\%, respectively) and elevated in liver (141\%, 175\%, and 144\%, respectively). All activities were measured as reported elsewhere\textsuperscript{9} and expressed as percent of control mean relative to citrate synthase activity.

\section*{3.3 | Patient 3}

Patient 3, the younger sibling of patient 2, was born at term by elective lower segment cesarean section following a pregnancy complicated by gestational diabetes treated with insulin. His Apgar scores were 9 and 9 at 1 and 5 min of life, respectively. Birthweight, length, and head circumference were within normal ranges. There were no problems in the postnatal period.

When evaluated at 5 months of age, he was noted to have developmental delay. At 7 months of age, his weight was 8.43 kg (41st percentile), length was 74 cm (94th percentile), and head circumference was 47 cm (97th percentile). He was unable to sit unaided and was unable to hold his head upright for a prolonged time. Cardiovascular, respiratory, and abdominal examinations were normal. He had mild central and peripheral hypotonia. Deep tendon reflexes were increased.

His urine amino acids and urine organic acid screen was normal, and blood lactate was mildly elevated at 2.6 mmol/L. A vitamin cocktail containing riboflavin, vitamin C, vitamin K, and coenzyme Q was commenced but did not provide clinical benefit. He was subsequently lost to follow up and died at home at age 15 months.

Targeted sanger sequencing confirmed that he had the same \textit{NDUFS8} variant as his brother. Electron transport chain enzyme activities in skin fibroblast
mitochondria were below the normal range for complex I (53%) and normal to elevated for complexes II, III, and IV (225%, 171%, and 105%, respectively).

## DISCUSSION

In this report we have described three patients with the same homozygous variant in *NDUFS8*. There is strong evidence of pathogenicity of the *NDUFS8* c.460G>A (p.-Gly154Ser) variant reported in these patients. This variant affects a highly conserved residue of a key functional domain, the Fer4 iron–sulfur cluster binding domain, which is important for electron transport (Figure 3).

In silico prediction tools suggest that this variant is probably damaging (polyphen2 score 1.000; REVEL score 0.958; and CADD score 32.0). This variant results in a non-conservative amino acid substitution that likely alters polarity within this highly conserved [4Fe-4S] binding site. It is not observed at a significant frequency in large population cohorts (heterozygous in 3 of 183,606 alleles per gnomAD v2.1.1 and v3.1.1 combined).

Finally, CI activity in patients 2 and 3 was significantly reduced in all tissues tested.

The three patients described in this report had severe presentations with death within the first 2 years of life. This degree of disease severity is likely in part attributable to the disruption of this critical [4Fe-4S] binding site.

In addition, patient 1 presented with severe DKA with positive anti-pancreatic antibodies, suggestive of an autoimmune etiology. The exact relationship between the mitochondrial disorder and the pancreatic autoimmunity in this patient is unclear. Diabetes is a well-recognized complication of mitochondrial disease, and indeed certain mutations in mitochondrial DNA are well associated with diabetes, for example, maternally inherited diabetes and deafness (MIDD). However, mitochondrial diabetes is not usually associated with the presence of pancreatic autoantibodies, and HLA-polymorphisms associated with increased susceptibility to Type 1 diabetes are not associated with the diabetes phenotype in MIDD.

Autoimmune or “Type 1-like” diabetes has only been rarely reported in MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) and MIDD. Thus, it may be possible that there is coincidental overlap between NDUFS8-related disorder and autoimmune diabetes in this case. Indeed, patient 1 had a family history of autoimmunity with her father having IgA nephropathy, which may represent an underlying predisposition to autoimmune disease. However, it is intriguing to consider the possibility that mitochondrial dysfunction may also promote a loss of immune tolerance, similar to that hypothesized in some models of rheumatoid arthritis pathophysiology. Additionally, it is possible that beta-cell destruction secondary to mitochondrial dysfunction may lead to anti-pancreatic antibody generation. Regardless, the severe presentation of diabetes mellitus in patient 1 emphasizes the importance of monitoring for diabetes in patients with mitochondrial disease from a young age.

Imaging findings in the patients in our cohort demonstrated initial confluent involvement of cerebral more than cerebellar white matter as well as progressive involvement of the brainstem and thalami. Interestingly, the basal ganglia were relatively spared in the imaging of patients 1 and 2. This contrasts with prior reports noting that the basal ganglia are sometimes the primary site of involvement in patients with NDUFS8-related disorder, or more broadly in patients with complex I deficiencies. In the case of patient 2, the basal ganglia were ultimately involved as seen on autopsy, however, this was 7 months after initial imaging. However, our imaging findings are similar to cavitating leukoencephalopathies seen with mutations in other mitochondrial oxidative phosphorylation components. In addition, recent work suggested that in pediatric Leigh syndrome, nuclear DNA...
pathogenic variants are more likely than mitochondrial DNA pathogenic variants to have white matter involvement. In summary, we have presented three children from two unrelated families with an identical homozygous NDUFS8 variant underlying a presentation of late infantile regression and progressive neurological decline. These variants are predicted to significantly disrupt NDUFS8 function, corroborated by functional studies demonstrating decreased complex I activity. Patient 1’s serial imaging demonstrates the severe progressive leukoencephalopathy that can be seen with disruptions of this gene, including involvement of the cerebellum and brainstem. We also provide an example of a severe presentation of new-onset autoimmune diabetes in a patient with mitochondrial dysfunction, highlighting the importance of surveillance for diabetes in patients with mitochondrial disease.

AUTHOR CONTRIBUTIONS
Siddharth Srivastava and Milena M. Andzelm were physicians who cared for patient 1 and drafted the original manuscript. Edward Yang assisted in critical interpretation of the radiological findings. John Christodoulou cared for patients 2 and 3 and John Christodoulou, Shanti Balasubramaniam and David R. Thorburn provided their clinical information and biochemical workup. Alison G. Compton provided mutational analysis. Kate Millington, Jia Zhu, Irina Anselm and Lance H. Rodan provided critical feedback of the manuscript and contributed to intellectual content. All authors have read/critically revised the manuscript.

ACKNOWLEDGMENT
We would like to thank the families.

FUNDING INFORMATION
This work was supported by a Fellowship (David R. Thorburn) and grants (David R. Thorburn, John Christodoulou, Alison G. Compton) from the Australian National Health and Medical Research Council and the Victorian Government’s Operational Infrastructure Support Program. The Chair in Genomic Medicine awarded to John Christodoulou is generously supported by The Royal Children’s Hospital Foundation. We are grateful to the Crane and Perkins families for their generous financial support. Funding to Siddharth Srivastava is provided by the NIH NINDS (1K23NS119666-01A1).

CONFLICT OF INTEREST
Milena Andzelm, Shanti Balasubramaniam, Edward Yang, Alison Compton, Kate Millington, Jia Zhu, Irina Anselm, Lance Rodan, David Thorburn, John Christodoulou, and Siddharth Srivastava declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT
This manuscript does not have associated supporting data.

ETHICS STATEMENT
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. We have de-identified patient data to the standards of the HIPAA Privacy rule and do not believe the information provided allows the identification of the patients through other means. Based on this, and because this is three or less cases, this does not meet the standards of human subjects research in accordance with the IRB standards of Boston Children’s Hospital. This publication has also received ethics and governance approval from The Children’s Hospital at Westmead.

ANIMAL RIGHTS
This article does not contain any studies with animal subjects performed by any of the authors.

ORCID
Milena M. Andzelm https://orcid.org/0000-0002-9189-1691
Siddharth Srivastava https://orcid.org/0000-0001-7008-1879

REFERENCES
1. Mimaki M, Wang X, McKenzie M, Thorburn DR, Ryan MT. Understanding mitochondrial complex I assembly in health and disease. Biochim Biophys Acta Bioenerg. 2012;1817(6):851-862. doi:10.1016/j.bbabio.2011.08.010
2. Alves CAPF, Teixeira SR, Martin-Saavedra JS, et al. Pediatric Leigh syndrome: neuroimaging features and genetic correlations. Ann Neurol. 2020;88(2):218-232. doi:10.1002/ANA.25789
3. Roosendaal SD, van de Brug T, Alves CAPF, et al. Imaging patterns characterizing mitochondrial leukodystrophies. Am J Neuroradiol. 2021;42(7):1334-1340. doi:10.3174/AJNR.A7097
4. Loeffen J, Smeitink JAM, Triepels R, et al. The first nuclear-encoded complex I mutation in a patient with Leigh syndrome. Am J Hum Genet. 1998;63:1598-1608. doi:10.1086/302154
5. Haack TB, Haberberger B, Frisch EM, et al. Molecular diagnosis in mitochondrial complex I deficiency using exome sequencing. J Med Genet. 2012;49:277-283. doi:10.1136/jmedgenet-2012-100846
6. Calvo SE, Tucker EJ, Compton AG, et al. High-throughput pooled sequencing identifies mutations in NUBPL and FOXRED1 in human complex I deficiency. Nat Genet. 2010;42: 851-858. doi:10.1038/ng.659
7. Procaccio V, Wallace DC. Late-onset Leigh syndrome in a patient with mitochondrial complex I NDUFS8 mutations.
Della MA, Schara U, Pyle A, et al. NDUFS8-related complex I deficiency extends phenotype from “PEO plus” to Leigh syndrome. JIMD Rep. 2013;10:17-22. doi:10.1007/8904_2012_195

Frazier AE, Vincent AE, Turnbull DM, Thorburn DR, Taylor RW. Assessment of mitochondrial respiratory chain enzymes in cells and tissues. Methods in Cell Biology. Vol 155. Academic Press; 2020:121-156. doi:10.1016/bs.mcbb.2019.11.007

Haeussler M, Zweig AS, Tyner C, et al. The UCSC genome browser database: 2019 update. Nucleic Acids Res. 2019;47(D1):D853-D858. doi:10.1093/nar/gky1095

Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. Nat Methods. 2010;7(4):248-249. doi:10.1038/nmeth0410-248

Ioannidis NM, Rothstein JH, Pejaver V, et al. REVEL: an ensemble method for predicting the pathogenicity of rare missense variants. Am J Hum Genet. 2016;99(4):877-885. doi:10.1016/j.ajhg.2016.08.016

Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M. CADD: predicting the deleteriousness of variants throughout the human genome. Nucleic Acids Res. 2019;47(D1):D886-D894. doi:10.1093/nar/gky1016

Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581(7809):434-443. doi:10.1038/s41586-020-2308-7

Schaefer AM, Walker M, Turnbll DM, Taylor RW. Endocrine disorders in mitochondrial disease. Mol Cell Endocrinol. 2013;379:2-11. doi:10.1016/j.mce.2013.06.004

Van Essen EHR, Roep BO, T’Hart LM, et al. HLA-DQ polymorphism and degree of heteroplasmy of the A3243G mitochondrial DNA mutation in maternally inherited diabetes and deafness. Diabet Med. 2006;23(12):841-847. doi:10.1046/j.1464-5491.2000.00379.x

Huang CN, Jee SH, Hwang JJ, Kuo YF, Chuang LM. Autoimmune IDDM in a sporadic MELAS patient with mitochondrial tRNA(Leu[UUR]) mutation. Clin Endocrinol (Oxf). 1998;49(2):265-270. doi:10.1111/j.1365-2265.1998.00455.x

Murphy R, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. Diabet Med. 2008;25:383-399. doi:10.1111/j.1464-5491.2007.02359.x

Oka Y, Katagiri H, Yazaki Y, Murase T, Kobayashi T. Mitochondrial gene mutation in islet-cell-antibody-positive patients who were initially non-insulin-dependent diabetics. Lancet. 1993;342(8870):527-528. doi:10.1016/0140-6736(93)91649-7

Qiu J, Wu B, Goodman SB, Berry GI, Goronzy JJ, Weyand CM. Metabolic control of autoimmunity and tissue inflammation in rheumatoid arthritis. Front Immunol. 2021;12:1038. doi:10.3389/fimmu.2021.652771

Lebre AS, Rio M, d’Arcier LF, et al. A common pattern of brain MRI imaging in mitochondrial diseases with complex I deficiency. J Med Genet. 2011;48(1):16-23. doi:10.1136/jmg.2010.079624

Zhang J, Liu M, Zhang Z, et al. Genotypic spectrum and natural history of cavitating leukoencephalopathies in childhood. Pediatr Neurol. 2019;94:38-47. doi:10.1016/j.pediatrneurol.2019.01.002

How to cite this article: Andzelm MM, Balasubramaniam S, Yang E, et al. Expansion of the clinical and neuroimaging spectrum associated with NDUFS8-related disorder. JIMD Reports. 2022;63(5):391-399. doi:10.1002/jmd2.12303