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CASE REPORT

The Expanding MEGDEL Phenotype: Optic Nerve Atrophy, Microcephaly, and Myoclonic Epilepsy in a Child with *SERAC1* Mutations

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Abstract The inborn errors of metabolism associated with 3-methylglutaconic aciduria are a diverse group of disorders characterized by the excretion of 3-methylglutaconic and 3-methylglutaric acids in the urine. Mutations in several genes have been identified in association with 3-methylglutaconic aciduria. We describe a patient of Saudi Arabian descent with 3-methylglutaconic aciduria, sensorineural hearing loss, encephalopathy, and Leigh-like pattern on MRI (MEGDEL syndrome), as well as developmental delay and developmental regression, bilateral optic nerve atrophy, microcephaly, and myoclonic epilepsy. The patient had an earlier age of onset of optic atrophy than previously described in other MEGDEL syndrome patients. Whole exome sequencing revealed two loss-of-function mutations in *SERAC1* in trans: c.438delC (p.T147Rfs*22) and c.442C>T (p.R148X), confirmed by Sanger sequencing. One of these mutations is novel (c.438delC). This case contributes to refining the MEGDEL phenotype.

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Introduction

Inborn errors of metabolism (IEM) with 3-methylglutaconic aciduria (3-MGA-uria) are a diverse group disorders associated with the excretion of 3-methylglutaconic and 3-methylglutaric acids in the urine. The IEMs with 3-MGA-uria were recently reclassified as primary 3-MGA-uria caused by defective leucine degradation or secondary 3-MGA-uria caused by defective phospholipid remodeling, mitochondrial membrane associated repair, or an unknown origin (NOS 3-MGA-uria) (Wortmann et al. 2013). Primary 3-MGA-uria is due to a deficiency of 3-methylglutaconic-CoA hydratase and due to mutations in the *AUH* gene (MIM #250950) (Ijlst et al. 2002; Ly et al. 2003; Wortmann et al. 2010). Mutations in other genes have been associated with the secondary 3-MGA-urias. Mutations in *TAZ* (MIM #300394) cause Barth syndrome, an X-linked disorder characterized by skeletal and cardiac myopathy, short stature, and neutropenia (Barth et al. 1983; Bione et al. 1996). *OPA3* (MIM #606580) mutations cause Costeff syndrome, characterized by early onset optic atrophy and neurological abnormalities including spasticity, extrapyramidal dysfunction, and cognitive deficits (Anikster et al. 2001; Sheffer et al. 1992). *DNAJC19* (MIM #608977) mutations cause DCMA syndrome, characterized by dilated cardiomyopathy and ataxia (Davey et al. 2006; Ojala et al. 2012). Defects in *TMEM70* (MIM #612418), involved in complex V of the electron transport chain, have been associated with cataracts, gastrointestinal dysfunction, and hypertonia (Jonckheere et al. 2012). Mutations in all of these genes have been associated with secondary 3-MGA-uria, but the mechanism responsible for the 3-MGA-uria has not been elucidated (Wortmann et al. 2013).

MEGDEL syndrome (MIM #614739) is another autosomal recessive form of secondary 3-MGA-uria that is caused

by defective phospholipid remodeling and was formerly classified as a form of type IV 3-MGA-uria. It is characterized by the features of defects of oxidative phosphorylation, sensorineural deafness, encephalopathy, dystonia, and Leigh-like syndrome. Wortmann et al. (2012) identified 14 different loss-of-function mutations in *SERAC1* in 15 patients with MEGDEL syndrome. A single patient with identified optic atrophy and microcephaly was found to have a homozygous nonsense mutation in *SERAC1* (Tort et al. 2013), and four patients with features of MEGDEL syndrome and infantile mitochondrial hepatopathy were found to have novel homozygous nonsense mutations in *SERAC1*, further expanding the phenotype of *SERAC1* (Sarig et al. 2013).

SERAC1 is a member of the PGAP-like protein domain family (PFAM PF07819) and is localized to the interface between the endoplasmic reticulum and the mitochondria that is necessary for phospholipid exchange. *SERAC1* mutations are associated with an abnormally increased ratio of phosphatidylglycerol-34:1 to phosphatidylglycerol-36:1. It is hypothesized that this leads to lower bis(monoacylglycerol)phosphate levels and accumulation of cholesterol in the perinuclear region. SERAC1 is hypothesized to be involved in phosphatidylglycerol remodeling and is essential for mitochondrial function and intracellular cholesterol trafficking (Wortmann et al. 2012). The abnormal cardiolipin profile that results from *SERAC1* mutations may in part explain the defects in oxidative phosphorylation in these patients (Wortmann et al. 2012).

Here we describe a patient with remote consanguinity who has compound heterozygous mutations in *SERAC1* detected by exome sequencing with symptoms of MEGDEL syndrome, with an earlier age of onset of optic atrophy than previously described in other MEGDEL syndrome patients.

Case Description

The proband is a 5-year-old boy with developmental delay and developmental regression, bilateral optic nerve atrophy, microcephaly, sensorineural hearing loss, myoclonic epilepsy, and 3-methylglutaconic aciduria. The child was born at 37 weeks gestation via spontaneous vaginal delivery following an uncomplicated pregnancy. The parents are of Saudi Arabian descent with a remote history of consanguinity as fourth cousins. His birth weight was 2,767 g (10th percentile) and birth length was 43.9 cm (<3rd percentile) with Apgar scores at 1 and 5 min of 9 and 10, respectively. At 24 h after birth, he was noted to have respiratory distress and an anion gap metabolic acidosis. He was treated with restricted protein intake and bicarbonate and improved within 24 h. Laboratory tests at the time revealed mildly elevated liver function tests, with ALT of 59 U/L (normal 7–41 U/L), GGT of 349 U/L (normal 9–58 U/L), and total serum bilirubin of 9.8 mg/dL (normal 0.3-1.3 mg/dL). Tyrosine was elevated at 519 μmol/L (normal <200 μmol/L) on amino acid profile, and 4-hydroxyphenylpyruvic acid and 4-hydroxyphenylacetic acid were elevated in the urine organic acid profile. No succinylacetone was detected in the urine. Diet was liberalized to an unrestricted diet.

Developmental milestones have all been severely delayed. He smiled at 3–4 months, rolled over at 6 months, sat independently at 12 months, walked unassisted at 26 months, and spoke his first words at 24 months. Bilateral hearing loss was first noted at 8 months of age, and he received cochlear implants at 3 years.

Metabolic testing at 2 years of age revealed slightly elevated lactic acid of 2.4 mmol/L (normal 0.5–2.0 mmol/L), mildly elevated pyruvic acid of 166 mmol/L (normal 30–90 mmol/L), and elevated ALT of 59 U/L (normal 7–41 U/L), and mildly increased AFP of 31.6 ng/mL (normal 0–11 ng/mL). Urine organic acids demonstrated 3-methylglutaconic acid of 82 mmol/mol creatinine (normal 1–9.2 mmol/mol creatinine) and 3-methylglutaric acid of 19 mmol/mol creatinine (normal 0.1–3.5 mmol/mol creatinine). Repeat urine organic acids at 29 months demonstrated 3-methylglutaconic acid of 119 mmol/mol creatinine and 3-methylglutaric acid of 38 mmol/mol creatinine. Plasma amino acids, ammonia, and CPK were normal.

An EEG recorded during sleep under chloral hydrate sedation, performed at 22 months, showed a reduction in background amplitude and theta slowing during sleep as well as a few sharp transients arising from the left frontotemporal region. The epileptiform discharges were considered suggestive of partial epilepsy. MRI of the brain at 2 years showed a Leigh-like pattern, with hyperintensity at the anterior aspect of the putamen and caudate, and to a lesser extent involving the globus pallidus. MR spectroscopy showed increased lactate in these areas. MRI findings were thought to be suggestive of a mitochondrial disorder. Follow-up MRIs demonstrated progressive basal ganglia and cerebellar volume loss.

Developmental regression was noted at 3 years of age by which time he could no longer walk, sit, or pick up objects, and his communication was limited to crying. He was hypertonic with dystonia and fisting in his upper extremities and limited movement in his lower extremities. Pharyngeal dysphagia and difficulty with oral motor coordination resulted in feeding difficulty. He demonstrated failure to thrive, with height consistently at the 10th

percentile and weight below the 3rd percentile. He has acquired microcephaly with head circumference measurements of 47 cm at 35 months (5–10th percentile), 47 cm at 43 months (<3rd percentile), and 47.5 cm at 83 months (<3rd percentile). At 4 years of age, he was diagnosed with myoclonic seizures and bilateral optic atrophy.

A right quadriceps biopsy was performed at 3 years of age due to suspicion of a mitochondrial disorder. The biopsy showed nonspecific changes, including slight myofiber atrophy and size variability. There were no ragged red fibers or fibers devoid of cytochrome oxidase staining.

The mitochondrial genome was sequenced from blood and analyzed for deletions due to suspicion of a mitochondrial disorder, and no mutations were detected. No mutations were detected in *AUH*, *TAZ*, *OPA3*, or *TMEM*. Whole exome sequencing and data analysis were subsequently conducted on a clinical basis as previously described (Yang et al. 2013). After multiple steps of variant filtering, 569 rare variants were retained including 124 variants in genes associated with Mendelian disorders and 445 variants in genes with no known association with Mendelian disorders at the time. Six missense variants of unknown clinical significance in five Mendelian genes including *DDX11*, *OTOF*, *PPT1*, *TECTA*, *TRIOBP* were identified as possible candidates. However, the pathogenicity of these changes was unknown and none of the findings could fully explain the patient's clinical phenotype. In addition to the missense changes, deleterious mutations in nine non-disease genes including a heterozygous single nucleotide deletion, c.438delC (p.T147Rfs*22), and nonsense mutation, c.442C>T (p.R148X), in the *SERAC1* gene were also detected and were consistent with 3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (MEGDEL) syndrome (Wortmann et al. 2012). Sanger sequencing of the proband and his father confirmed that the father was heterozygous for c.438delC and did not carry c.442C>T, establishing that the two mutations in *SERAC1* are in trans. One of these mutations (c.442C>T) has been previously identified in three patients with MEGDEL syndrome (Wortmann et al. 2012). The second mutation is novel (c.438delC) and not present in 1,000 genomes or EVS database. Both mutations are predicted to cause loss of function, with nonsense mediated decay with c.442C>T (p.R148X).

Discussion

We describe a patient with compound heterozygous mutations in *SERAC1* with 3-methylglutaconic aciduria, progressive neurologic deterioration, Leigh-like pattern on MRI, sensorineural hearing loss, acquired microcephaly, myoclonic epilepsy, bilateral optic nerve atrophy, and infantile hepatopathy.

Twenty other patients have been described with *SERAC1* mutations associated with 3-methylglutaconic aciduria, and clinical features including progressive spasticity, dystonia, encephalopathy, Leigh-like MRI, deafness, bilateral optic atrophy, microcephaly, and infantile hepatopathy (Sarig et al. 2013; Tort et al. 2013; Wortmann et al. 2012). Our patient shares similar clinical features to the other 20 patients with *SERAC1* mutations, although our patient had optic atrophy by the age of 4, much earlier than the only other patient diagnosed with optic atrophy at the age of 16 years (Table 1) (Tort et al. 2013).

Eighty percent of previously described patients with *SERAC1* mutations demonstrated developmental regression. What is notable in our patient is the rate of developmental regression, which is not completely attributable to the progressive dystonia and spasticity, given his cognitive decline in addition to the loss of his motor skills. Evidence of dystonia and delayed milestones was apparent by 6 months of age in our patient, with delayed sitting and walking. The patient's developmental regression began at 3 years of age, at which point he demonstrated a rapid decline. Though he had been able to walk at 26 months, by 39 months he was unable to walk, sit, or pick up objects, and he was no longer able to recognize or respond to his parents.

The SERAC1 protein has a serine lipase domain that is hypothesized to play a key role in its function (Wortmann et al. 2012). The majority of the mutations that have been identified in *SERAC1* have either been frameshift, nonsense, or missense mutations within or upstream of the lipase domain (Sarig et al. 2013; Tort et al. 2013; Wortmann et al. 2012). Both of our patient's mutations are upstream of the lipase domain. The frameshift mutation c.438delC (p.T147Rfs*22) and the stop gain mutation c.442C>T (p.R148X) are both disruptive mutations, accounting for the severity of his phenotype.

This case contributes to our understanding of the expanding phenotype of MEGDEL syndrome and the spectrum of *SERAC1* mutations.

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Synopsis

This case further characterizes the phenotype associated with *SERAC1* mutations and expands upon the previously described features of MEGDEL syndrome.

Table 1 Comparison of the clinical features of MEGDEL syndrome in previously reported patients with mutations in *SERAC1* and the patient described here (Sarig et al. 2013; Tort et al. 2013; Wortmann et al. 2012)

		Previously reported patients ($n = 20$)		
	Patient (age of onset)	Yes *N* (%)	No *N* (%)	Not reported *N* (%)
Consanguinity	+	11 (55)	9 (45)	0 (0)
Urinary 3-MGA	+	20 (100)	0 (0)	0 (0)
Sensorineural deafness	+	18 (90)	1 (5)	1 (5)
Leigh-like MRI	+	17 (85)	0 (0)	3 (15)
Dystonia	+	19 (95)	0 (0)	1 (5)
Psychomotor delay	+	19 (95)	0 (0)	1 (5)
Developmental regression	+ (3 years)	16[a] (80)	1 (5)	3 (15)
Microcephaly	+	1 (5)	19 (95)	0 (0)
Epilepsy	+ (4 years)	4[b] (20)	16 (80)	0 (0)
Infantile hepatopathy	+	4 (20)	16 (80)	0 (0)
Optic atrophy (bilateral)	+ (4 years)	1[c] (5)	19 (95)	0 (0)
Lactic acidemia	+	19 (95)	1 (5)	0 (0)
OXPHOS defects – muscle	NA	9 (45)	2 (10)	4 (20)

[a] Mean age of onset = 1.5 years
[b] Mean age of onset = 4 years
[c] Age of onset = 16 years
NA not available

Compliance with Ethics Guidelines

Conflict of Interest

Heidi Lumish, Ashley Wilson, and Wendy Chung declare that they have no conflict of interest.

Yaping Yang works for Baylor College of Medicine in a laboratory that generates revenue from performing clinical genetic tests.

Fan Xia works for Baylor College of Medicine in a laboratory that generates revenue from performing clinical genetic tests.

Informed Consent

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 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

Details of the Contributions of Individual Authors

Heidi Lumish was responsible for drafting the article.

Yaping Yang performed genomic sequencing and data interpretation and critical review of the manuscript.

Fan Xia performed genomic sequencing and data interpretation and critical review of the manuscript.

Ashley Wilson critically reviewed and revised the manuscript.

Wendy Chung was responsible for drafting the article and revising it for intellectual content. Guarantor.

References

Anikster Y, Kleta R, Shaag A, Gahl WA, Elpeleg O (2001) Type III 3-methylglutaconic aciduria (optic atrophy plus syndrome, or Costeff optic atrophy syndrome): identification of the OPA3 gene and its founder mutation in Iraqi Jews. Am J Hum Genet 69(6):1218–1224

Barth PG, Scholte HR, Berden JA et al (1983) An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes. J Neurol Sci 62(1–3):327–355

Bione S, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D (1996) A novel X-linked gene, G4.5. is responsible for Barth syndrome. Nat Genet 12(4):385–389

Davey KM, Parboosingh JS, McLeod DR et al (2006) Mutation of DNAJC19, a human homologue of yeast inner mitochondrial membrane co-chaperones, causes DCMA syndrome, a novel autosomal recessive Barth syndrome-like condition. J Med Genet 43(5):385–393

Ijlst L, Loupatty FJ, Ruiter JP, Duran M, Lehnert W, Wanders RJ (2002) 3-Methylglutaconic aciduria type I is caused by mutations in AUH. Am J Hum Genet 71(6):1463–1466

Jonckheere AI, Smeitink JA, Rodenburg RJ (2012) Mitochondrial ATP synthase: architecture, function and pathology. J Inherit Metab Dis 35(2):211–225

Ly TB, Peters V, Gibson KM et al (2003) Mutations in the AUH gene cause 3-methylglutaconic aciduria type I. Hum Mutat 21 (4):401–407

Ojala T, Polinati P, Manninen T et al (2012) New mutation of mitochondrial DNAJC19 causing dilated and noncompaction cardiomyopathy, anemia, ataxia, and male genital anomalies. Pediatr Res 72(4):432–437

Sarig O, Goldsher D, Nousbeck J et al (2013) Infantile mitochondrial hepatopathy is a cardinal feature of MEGDEL syndrome (3-Methylglutaconic aciduria type IV with sensorineural deafness, encephalopathy and leigh-Like Syndrome) caused by novel mutations in SERAC1. Am J Med Genet A 161(9):2204–2215

Sheffer RN, Zlotogora J, Elpeleg ON, Raz J, Ben-Ezra D (1992) Behr's syndrome and 3-methylglutaconic aciduria. Am J Ophthalmol 114(4):494–497

Tort F, Garcia-Silva MT, Ferrer-Cortes X et al (2013) Exome sequencing identifies a new mutation in SERAC1 in a patient with 3-methylglutaconic aciduria. Mol Genet Metab 110 (1-2):73–77

Wortmann SB, Kremer BH, Graham A et al (2010) 3-Methylglutaconic aciduria type I redefined: a syndrome with late-onset leukoencephalopathy. Neurology 75(12):1079–1083

Wortmann SB, Vaz FM, Gardeitchik T et al (2012) Mutations in the phospholipid remodeling gene SERAC1 impair mitochondrial function and intracellular cholesterol trafficking and cause dystonia and deafness. Nat Genet 44(7):797–802

Wortmann SB, Duran M, Anikster Y et al (2013) Inborn errors of metabolism with 3-methylglutaconic aciduria as discriminative feature: proper classification and nomenclature. J Inherit Metab Dis 36(6):923–928

Yang Y, Muzny DM, Reid JG et al (2013) Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med 369(16):1502–1511