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CORRESPONDENCE

Neonatal lactic acidosis explained by *LARS2* defect

Pediatric Research (2023) 93:740–743; https://doi.org/10.1038/s41390-022-02169-7

Back in the year 2009, we presented in this journal a neonate with an unusual combination of congenital lactic acidosis and bilateral calcifications in the adrenal medulla[1]. After prenatal ultrasound examination at 21 weeks had revealed intrauterine growth retardation and pericardial effusions, labor was induced at 38 weeks of pregnancy. The patient was hypotonic at birth, had respiratory insufficiency necessitating intubation and artificial ventilation, hepatomegaly and severe cardiomegaly. Intensive care was withdrawn in accordance with parents' wishes on day 38. At the time, the patient's causal genetic defect had remained unknown, yet clinical and biochemical evidence ticked all the boxes of an underlying mitochondrial defect. Postmortem spectrophotometric evaluation then revealed decreased oxidative phosphorylation activities in heart muscle (complex IV) and liver (complexes I, III, IV and V), and normal activities in skeletal muscle and cultured skin fibroblasts. Blue-native polyacrylamide gel electrophoresis of liver extracts confirmed decreased activities of complexes III and IV and showed the presence of subcomplexes of complex V. Thanks to the great genetic leap forward taken by medical research ever since, we were now able to thoroughly investigate the patient's whole exome extracted from preserved cultured skin fibroblasts. These investigations picked up compound heterozygous missense variants in the gene encoding the mitochondrial leucyl-tRNA synthetase (*LARS2*): c.302 A > G (p.His101Arg) and c.516 G > T (p.Arg172Ser). Nuclear-encoded mitochondrion-specific aminoacyl-tRNA synthetases exist for 17 of the 20 proteogenic amino acids, and pathogenic mutations have now been reported for each one of these[2]. At the time we published our casus, *LARS2* defects had not been reported, yet between the year 2013 and now, a total of 23 patients have been described that carry disease-causing *LARS2* variants (Table 1)[1,3–13]. Their diverse associated disease phenotypes, which include Perrault syndrome, multisystem disease, leukodystrophy and intellectual disability, do not appear to have an obvious link with genotype. With the casus we presented in this journal and now have characterized at the molecular level, more than twenty patients with 18 unique combinations of disease-causing *LARS2* variants have been reported so far, only one was homozygous the others concerned compound heterozygous variants.

Mitochondrial aminoacyl-tRNA synthetase defects unavoidably lead to defective intramitochondrial translation, disturbing the synthesis of mitochondrion-encoded subunits and the integrity of the oxidative phosphorylation complexes. LARS2 protein loads leucine onto its destined tRNA to form an aminoacylated tRNA, subsequently allowing addition of the amino acid to a growing polypeptide chain. To establish this function, LARS2 protein contains a catalytic domain, an anticodon binding domain, and a dimerization domain. Both variants reported in this patient lie within the catalytic domain, the protein domain that binds ATP, leucine and the 3′ end of $tRNA^{Leu}$, allowing the release of leucyl-tRNA. The c.516 G > T variant has been described before alongside the c.1028 C > T variant in compound heterozygous form, in a patient with congenital sensorineural hearing loss[9]. The variant is present at low frequency in the general population and is categorized as possibly damaging with a score of 0.623 on PolyPhen-2 v2.2.2r398. In addition, the patient carries the not previously described heterozygous *LARS2* variant c.302 A > G (p.His101Arg), a missense alteration categorized as probably damaging with a score of 1.000 on PolyPhen-2 v2.2.2r398. Both variants are predicted to be disease causing using Mutation Taster[14], and the affected positions are more than 80% conserved.

The majority of reported *LARS2* variants are missense mutations, as are the ones we report in this patient. This is consistent with the essential activity of the gene reflected by a probability of loss of function intolerance of 0 on gnomAD (https://gnomad.broadinstitute.org), as complete loss of function most probably would lead to fetal death. Many patients suffer from a combination of gonadal dysgenesis and deafness termed Perrault syndrome. The disease phenotype of this previously reported patient is, however, a more severe form of LARS2 deficiency. In fact, this is only the second reported case of a patient carrying *LARS2* variants who dies within the first 2 months of life. Both reported patients suffered from congenital lactic acidosis and had impairment of heart and lung function, but our patient is the only one in which adrenal abnormalities were noted. It has been established that seemingly comparable mutations in different mitochondrial aminoacyl tRNA synthetases lead to diseases with extremely different age of onset and may affect tissues differentially. Such phenotypic heterogeneity could be due to modifying genetic factors to which we now remain largely ignorant. We are hopeful that such insight will appear after persevering research in mitochondrial defects for the decades to come.

Received: 4 May 2022 Accepted: 22 May 2022
Published online: 24 June 2022

Table 1. Published patients carrying disease-causing *LARS2* variants.

#	Gender	cDNA sequence	Amino acid change	Lifespan	Clinical features	Biochemistry/imaging	Reference
1	F	c.302 A > G c.516 G > T	p.His101Arg p.Arg172Ser	38 days	Hypotonia, bilateral adrenal medulla calcifications. Respiratory insufficiency, cardiomegaly, hepatomegaly.	Lactic acidosis; Postmortem MRI shows lesions with abnormal signal intensities in the left thalamus. Spectrophotometry: liver low complex I, III, IV, V; heart low complex IV; muscle normal; fibroblasts normal	[1]
2	F	c.1565 C > A homozygous	p.Thr522Asn	>17 years	Sensorineural hearing loss from age 3-5 years. Primary amenorrhea. (Perrault sy).		[3]
3	F	c.1077delT c.1886C > T	p.Ile360Phefs*15 p.Thr629Met	>30 years	Severe hearing loss. Menarche at age 13, ovarian failure at 18 years. (Perrault sy)		[3]
4	F	c.1289 C > T c.1565 C > A	p.Ala430Val p.Thr522Asn	5 days	Hydrops, hyaline membrane disease, impaired cardiac function, coagulopathy, pulmonary hypertension, progressive renal disease.	Lactic acidosis, sideroblastic anemia Spectrophotometry: muscle low complex I,IV; liver low complex IV, both not sufficiently low to call deficient; fibroblasts normal	[4]
5	F	c.899 C > T c.1912G > A	p.Thr300Met p.Glu638Lys	>31 years	Progressive profound sensorineural hearing loss. Menarche at 13 years. Ovarian failure at 28 years. (Perrault sy)		[5]
6	M	c.899 C > T c.1912G > A	p.Thr300Met p.Glu638Lys	>33 years	Congenital bilateral sensorineural hearing loss.		[5]
7	F	c.1358 G > A c.1886C > T	p.Arg453Gln p.Thr629Met		Cleft palate. Moderate hearing loss since before the age of 3 years. Primary amenorrhea. (Perrault sy)		[6]
8	F	c.351 G > C c.1565 C > A	p.Met117Ile p.Thr522Asn	>25 years	Profound sensorineural hearing loss diagnosed at 2.5 years. Mild facial dysmorphia. Menarche, but small uterus and ovaries. (Perrault sy)		[7]
9	M	c.351 G > C c.1565 C > A	p.Met117Ile p.Thr522Asn	>26 years	Profound sensorineural hearing loss diagnosed at 2.5 years. Mild facial dysmorphia. Hypospadias.		[7]
10	F	c.880 G > A c.1556 C > T	p.Glu294Lys p.Thr519Met	>13 years	Congenital hearing loss, delayed development. Learning disabilities. Primary amenorrhea diagnosed at 11 years. (Perrault sy)		[8]
11	F	c.462delT c.1120 A > C	p.Lys155Asnfs*3 p.Ile374Leu	respiratory failure 35 years	Sensorineural deafness diagnosed shortly after birth, mild development delay. Premature menopause due to ovarian failure at 29 years. (Perrault sy) Motor decline at age 33 y. Cerebellar ataxia, spasticity, supranuclear gaze palsy, left-sided central facial palsy, progressive swallowing difficulties.	MRI at age 32 y shows extensive cerebral white matter abnormalities. Repeated MRIs at ages 33 y and 34 y show progression with increasing involvement of frontal white matter and corpus callosum.	[9]
12	M	c.371 A > T c.1987C > T	p.Asn124Ile p.Arg663Trp	>37 years	Hypotonia, macrocephaly and inguinal hemia at birth. Early development delay. Sensorineural deafness diagnosed at 18 months. Behavioral problems (autism, hyperactivity, aggression). Atypical seizures with atonic and hypertonic crises from age 17 y. Obesitas, developed metabolic syndrome with hepatic steatosis, diabetes in his 20 s. In his 30 s, gait ataxia.	MRI at 24 years shows abnormalities in the parieto-occipital white matter. Subsequent MRIs at ages 32 y, 36 y and 37 y show progression.	[9]

Table 1. continued

#	Gender	cDNA sequence	Amino acid change	Lifespan	Clinical features	Biochemistry/imaging	Reference
					Developed supranuclear gaze palsy and extrapyramidal dysfunction with resting tremor and dystonia at age 33 y. Acute hemiparesis at age 36 y. Wheel-chair bound.		
13	M	c.516 G > T c.1028 C > T	p.Arg172Ser p.Thr343Met	>8 years	Hypotonic at birth. Delayed early development. Sensorineural deafness diagnosed at 1.5 years. Abnormal movements, hyperkinesia and behavioral problems (aggression) at 4 years. Improved behavior at 8 years.	Normal MRI at 3 years	[9]
14	F	c.683 G > A c.880 G > A	p.Arg228His p.Glu294Lys	>48 years	Congenital sensorineural deafness. Normal early development. Menarche at 16 years, soon followed by amenorrhea due to ovarian failure. (Perrault sy) From 45 years right-sided coordination problems. At age 46 y subacute right-sided weakness with orientation and concentration problems. Pyramidal dysfunction on the right side and axial ataxia. Walks with support at age 48 y due to bilateral spasticity.	MRI at 46 years shows extensive cerebral white matter abnormalities.	[9]
15	F	c.457 A > C c.1565 C > A	p.Asn153His p.Thr522Asn	>8 years	bilateral severe sensorineural hearing loss at age 7.		[10]
16	M	c.683 G > A c.1313 A > G	p.Arg228His p.Asp438Gly	>2 years	Neonatal cholestasis, sensorineural hearing loss, developmental delay	Lactic acidosis, anemia	[11]
17	M	c.440 A > C c.1607C > T	p.Gln147Pro p.Pro536Leu	>10 months	Hepatosplenomegaly, sensorineural hearing loss	Lactic acidosis, anemia	[11]
18	M	c.308 G > A c.1552 G > A	p.Arg103His p.Asp518Asn	>55 years	Reversible myopathy, neck muscle degeneration, developmental delay	Lactic acidosis; Spectrophotometry: muscle complex I deficiency; fibroblasts normal Western blotting: muscle reduced LARS2 and NDUFB8 levels, fibroblasts normal LARS2 and oxidative phosphorylation complex subunits Histology: evidence of mitochondrial myopathy	[11]
19	M	c.388 G > A c.2099 C > T	p.Ala130Thr p.Thr700Ile	1 day	facial purpura, hepatosplenomegaly	Lactic acidosis, severe anemia and hypoglycemia	[11]
20	M	c.388 G > A c.2099 C > T	p.Ala130Thr p.Thr700Ile	>17 years	Hepatosplenomegaly, sensorineural hearing loss, developmental delay	Lactic acidosis, anemia	[11]
21	F	c.880 G > A c.2108 T > C	p.Glu294Lys p.Ile703Thr	>23 years	bilateral moderate sensorineural hearing loss at 2 years old progressing to severe mixed hearing loss by age 22. Primary ovarian failure Normal intelligence.		[12]
22	F	c.1481dup c.1886C > T	p.Leu495Thrfs*31* p.Thr629Met	>8 years	Profound bilateral sensorineural deafness		[13]
23	F	c.1481dup c.1886C > T	p.Leu495Thrfs*31* p.Thr629Met	>12 years	Profound bilateral sensorineural deafness		[13]

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AUTHOR CONTRIBUTIONS

Conceptualization and data curation: B.D.P., J.S., R.K. and A.V.; formal analysis and methodology: A.V., R.V.C. and H.P.; project administration, resources and supervision: R.V.C. and A.V.; manuscript draft preparation: B.D.P.; review, editing and approval of the final version: all authors.

COMPETING INTERESTS

R.V.C. and A.V. are members of the European Reference Network for Hereditary Metabolic Disorders, MetabERN. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

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