LETTER TO THE EDITOR

Myopathy, lactic acidosis and sideroblastic anemia syndrome 1 (MLASA1): clinical hallmarks in a large pedigree with a novel *PUS1* R144Q mutation, remarkable response to somatropin, and review of the literature

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Supplemental table 1. Published MLASA1 cases with mutations, laboratory data and clinical features.

Patient (ref)	Country of origin	Sex	PUS1 mutation[#]	Hemoglobin (g/L)	Lactate (mmol/L)	Other laboratory features	Growth delay (height)	Intellectual Disability	GI symptoms	Exercise intolerance	Other clinical abnormalities	Transfusions	Therapy	Outcome
1 (1,2,3)	Iran	m	c.656C>T hom (R144W[##])	100 g/L at 8 y, 60 g/L at 18 y	3.20-12.48	GH def, impaired oxphos	yes (163 cm)	no	v at 6 y	yes, from 8 y onwards	td, vitiligo, ioc, k, lordosis, osteoporosis	yes, from 19 y		death at 37 y from respiratory failure
2 (1.2.3)	Iran	m	c.656C>T hom (R144W[##])	100 g/L at 17 y	1.42-7.83	ferritin high, no tr	yes (157 cm)	no		yes, from 8 y onwards	td, lordosis, osteoporosis	no		
3 (1,2)	Iran	f	c.656C>T hom (R144W[##])	anemic at 16 y, 60 g/l at 28 y	9.2-10.0					yes, from 11 y onwards	mild bilateral ptosis, distal muscle waisting	yes, from 16 y		
4 (1,2)	Iran	f	c.656C>T hom (R144W[##])	130 g/L at 12 y, 100 g/L at 16 y	5.9				v at 12 y	yes, from 12 y onwards	decreased grip strength			
5 (1,4)	Iran	f	c.656C>T hom (R144W[##])	anemic at age 14 y, 96 g/L at 28 y	5.99	low cyt content (in mms)	yes (152 cm)	yes	ap and d from 27 y onwards	yes, since childhood	face dysmorphia, k, gma		P and vitE n.e.	
6 (1,4)	Iran	m	c.656C>T hom (R144W[##])	90 g/L at 19 y (pallor at 10 y)	2.68-5.55	low cyt content (in mms)	yes (161 cm)	yes		yes, from 10 y onwards	face dysmorphia, gma		P n.e.	
7 (5)	Iran	m	c.656C>T hom (R144W[##])	103 g/L at 19 y	4.44	low act of rcc 1+4	yes	yes		yes	face dysmorphia			
8 (6)	Italian	m	c.658G>T (p.E200*), hom	50 g/L at 5 y	6.1	GH def, low act rcc 1+4	yes	no	mp/g-i	yes, from 5 y onwards	face dysmorphia, gma, nppr	yes	P n.e., GH given	death at 12 y from respiratory failure
9 (6)	Italian	m	c.658G>T (p.E200*), hom	118 g/L at 6 y	3.9	def of rcc 1+4		yes		yes	gma	no		
10 (7)		f	c.885C>T hom	anemia at 11 y						yes	gma	yes		
11 (7)		m	c.917C>T hom	anemia at 9 months						yes	gma	no		
12 (8)	Turkish	f	c.883C>T, p.R295W, hom	63 g/L at 1 year		def of rcc 1+4	yes (153 cm)	yes	chronic d, ap	yes	occasional headache	yes		clinically stable, tr-dep at 26 y; iron chelation
13 (9)	Italian	f	compound het c.487delA (p.I163Lfs*4) and c.884G>A (p.R295Q)	anemia at 25 y, 117 g/L at 43 y	5.5	normal act of all rcc		yes		yes	gma, odontopathy, lentiginosis; cmp, iddm	yes	azacitidine reduced the need for tr; CoQ10 n.e.	unable to walk at 42 y
14 (10)	Turkish	m	c.302A>G, p.Q101R, hom	anemia at 10 months of age	6.1	cyt c oxidase def in muscle	yes	yes		yes	gma, hyperlordosis	yes	CoQ10 improvement of muscle strength and anemia	death at 18 y from respiratory failure
15 (11)	Roma	f	c.896+2551_1061delinsATTTTACCA, hom	anemia at 3 y of age	2.4-4.3		yes	yes		apathy and hypotony from birth	hypertrophic cardiomyopathy	yes		Death at 5 y

16 (11)	Roma	m	c.896+2551_1061delinsATTTTTACCA, hom	anemia at 6 y of age	4-19		yes	yes		onset of symptoms at 5 y	strabismus, sensorineural hearing loss	yes		Death at 24 y
17 (12)	Turkish	f	c.931G>T hom, p.E311*	anemia at 8 months, 83 g/L at 11 y	4.38		yes (110 cm)	yes	chronic d	yes	dysmorphia of the face, gma, hip dysplasia	yes, from 8 months	CoQ10 and levocarnitine n.e.	
18 (12)	Turkish	f	c.931G>T hom, p.E311*	anemia at 1.5 y, 70 g/L at 3.5 y	8.35		yes (89 cm)	no	d from 1.5 y onwards	yes	gma	yes	CoQ10 and levocarnitine n.e.	
19 (present publication)	Syrian	m	c.431G>A p.R144Q	56 g/L at 28 y	3.4-12.7	GH def; elevated EPO	yes (150 cm)	yes	diffuse ap and occasional d	yes	gma; syncopes	yes	P, CoQ10 n.e.; somatotropin improvement of anemia	progressive myopathy and use of a wheel chair
20 (present publication)	Syrian	f	c.431G>A p.R144Q	96 g/L at 33 y	4.9-11.1		yes (148 cm)	yes	chronic ap and cramps	yes	gma; POTS; chronic headache; pgp; sleep disturbancy	no		progressive myopathy and use of a wheel chair

#, Annotation following Ensemble genome annotation database >ENST00000376649.8 (PUS1).

##, R116W in the original publication; R144W according to Ensemble genome annotation database >ENST00000376649.8 (PUS1).

ref, reference; m, male; f, female; hom, homozygous; het, heterozygous; y, years; oxphos, oxidative phosphorylation; GH, growth hormone; rcc, respiratory chain complexes; cyt, cytochrome; mms, muscle mitochondrial suspension; def, deficiency; act, activity; EPO, erythropoietin; GI, gastrointestinal; ap, abdominal pain; mp/g-i, milk protein and gluten intolerance; v, vomiting; d, diarrhoea; td, thyreoid dysfunction; ioc, iron overload cardiomyopathy; k, kyphoscoliosis; gma, generalized muscle atrophy; nppr, non-progressive pigmentary retinopathy; cmp, cardiomyopathy; iddm, insulin-dependent diabetes mellitus; POTS, postural orthostatic tachycardia syndrome; pgp, parotid gland pathology; P, pyridoxine; VitE, vitamin E; n.e., not effective; tr, transfusion; tr-dep, transfusion-dependent

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