

## Supplementary Materials

### Recurrent acute liver failure in alanyl-tRNA synthetase-1 (AARS1) deficiency

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#### Supplementary Table 1

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**Table 1. Summary of clinical symptoms of patients with autosomal recessive aaRS deficiencies and liver symptoms.**

			cytosolic							This report
			GARS	IARS1	LARS1	MARS1	FARS1	YARS1	AARS1	AARS1
		N	22	6	25	32	6	10	5	1
Central nervous system	MRI abnormalities		■	■	■	■	■	■	■	■
	Psychomotor retardation		■	■	■	■	■	■	■	■
	Microcephaly		■	■	■	■	■	■	■	■
	Hypotonia		■	■	■	■	■	■	■	■
	Seizures		■	■	■	■	■	■	■	■
	Encephalopathy		■	■	■	■	■	■	■	■
	Spasticity		■	■	■	■	■	■	■	■
	Ataxia		■	■	■	■	■	■	■	■
	Episodic excited states		■	■	■	■	■	■	■	■
	Senses	Sensorineuronal deafness		■	■	■	■	■	■	■
Visual loss/retinal abnormalities			■	■	■	■	■	■	■	■
Strabismus			■	■	■	■	■	■	■	■
Nystagmus			■	■	■	■	■	■	■	■
Dysmorphisms	Chubby cheeks		■	■	■	■	■	■	■	■
	Facial dysmorphisms		■	■	■	■	■	■	■	■
	Abnormalities hands/feet/fingers		■	■	■	■	■	■	■	■
Growth	Dysmaturity		■	■	■	■	■	■	■	■
	Failure to thrive		■	■	■	■	■	■	■	■
Gastrointestinal tract	Poor feeding (tube/parenteral)		■	■	■	■	■	■	■	■
	Diarrrhea/constipation/vomiting		■	■	■	■	■	■	■	■
Liver	Liver failure/hepatomegaly/cirrhosis		■	■	■	■	■	■	■	■
	↓ albumin/protein		■	■	■	■	■	■	■	■
Lungs	Interstitial lung disease		■	■	■	■	■	■	■	■
	Clubbing		■	■	■	■	■	■	■	■
	Cystic lung disease		■	■	■	■	■	■	■	■
	Oxygen dependency		■	■	■	■	■	■	■	■
Bone marrow	Anemia		■	■	■	■	■	■	■	■
	Leukocytosis		■	■	■	■	■	■	■	■
	Thrombocytosis/thrombocytopenia		■	■	■	■	■	■	■	■
Kidneys	Tubulopathy		■	■	■	■	■	■	■	■
	Acute kidney failure		■	■	■	■	■	■	■	■
	Anatomical/ultrasound abnormalities		■	■	■	■	■	■	■	■
Spleen	Splenomegaly		■	■	■	■	■	■	■	■
	Accessory spleen		■	■	■	■	■	■	■	■
Heart	Cardiomyopathy/LVH		■	■	■	■	■	■	■	■
	Anatomical abnormalities		■	■	■	■	■	■	■	■
Muscles	Exercise intolerance/myalgia/weakness		■	■	■	■	■	■	■	■
Other symptoms	Skin abnormalities		■	■	■	■	■	■	■	■
	Hydrocele testis		■	■	■	■	■	■	■	■
	Hernia inguinalis		■	■	■	■	■	■	■	■
Laboratory findings	Endocrine abnormalities		■	■	■	■	■	■	■	■
	Various		■	■	■	■	■	■	■	■
	Mitochondrial dysfunction		■	■	■	■	■	■	■	■
	Other metabolic abnormalities		■	■	■	■	■	■	■	■
Periods of increased symptom severity	First years of life		■	■	■	■	■	■	■	■
	Infections		■	■	■	■	■	■	■	■

■ reported for 1 patient  
 ■ reported for >1 patient

## Legend to Supplementary Table 1

**Table 1. Summary of clinical symptoms of patients with autosomal recessive aaRS deficiencies and liver symptoms.** Presented are cases reported in literature and supplemented by the case of this report (last column).

Gray squares represent symptoms reported for 1 patient, black squares symptoms reported for >1 patient.

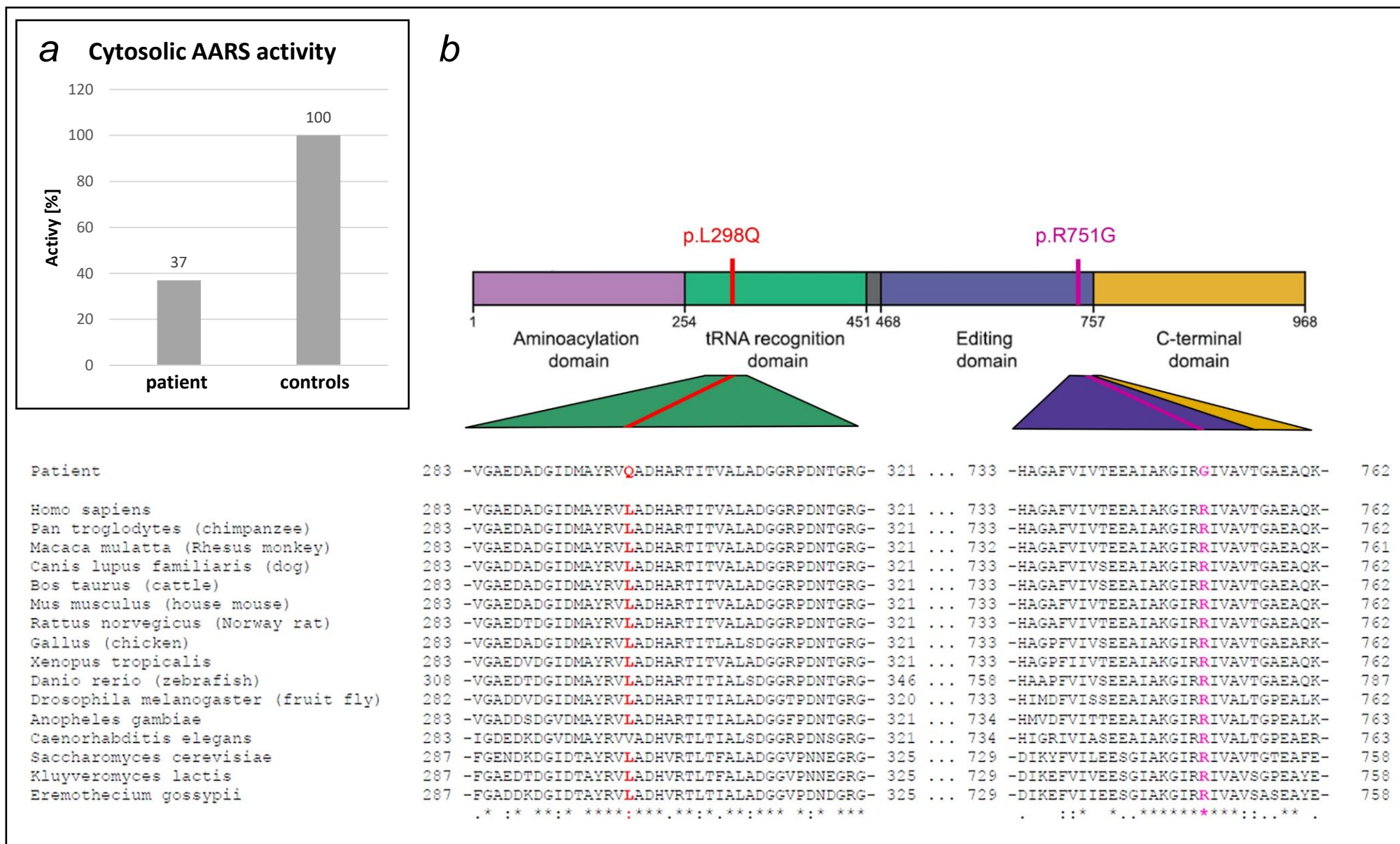
mt, mitochondrial;

MRI, magnetic resonance imaging;

LVH, left ventricular hypertrophy

(modified from Fuchs et al.<sup>S1</sup> with additional data from Williams et al.<sup>S2</sup>, Tracewska-Siemiatkowska et al.<sup>S3</sup>, Xu et al.<sup>S4</sup>, Krenke et al.<sup>S5</sup>, Casey et al.<sup>S6</sup>, Lenz et al.<sup>S7</sup> and Johannesen et al.<sup>S8</sup>)

Supplementary Figure 1



## Legend to Supplementary Figure 1.

### Enzymatic and molecular genetic findings of the reported patient.

**a** Cytosolic AARS activity in patient and control fibroblasts.

**b** Multiple alignment of amino acid sequences of AARS1 from different species. Presented are regions of the protein close to the sites where variants were found in the patient. The maternal *AARS1* variant p.Leu298Gln (p.L298Q, LOVD variant ID 0000701819), affecting the tRNA recognition domain, is indicated in red; the paternal variant p.Arg751Gly (p.R751G, LOVD variant ID 0000701825), located in the editing domain is highlighted in pink (*modified from Simons et al*<sup>S8</sup>). The figure demonstrates the high conservation of the affected regions which indicates pathogenicity. This is further confirmed by the prediction '*disease-causing*' by MutationTaster software<sup>S10</sup> with high scores for both variants. Furthermore, p.Leu298Gln has neither been observed in the '*1000 genomes*' database nor in the Exome Aggregation Consortium (ExAC) and Genome Aggregation database (gnomAD). The *AARS1* variant p.Arg751Gly (rs143370729) has been observed in one heterozygous individual listed in '*1000 genomes*' and 6 heterozygous individuals in the ExAC database (among 66446 European [non-Finnish] individuals) (*data retrieval* Nov 6, 2020). Moreover, it is known to be functionally relevant since it was found in homo- and compound heterozygosity in patients suffering from epileptic encephalopathy type 29 (EIEE29, OMIM #616339) and resulted in severe impairment of enzyme activity during *in vitro* expression.<sup>S9,S11</sup> Compound heterozygosity for the two variants in our patient resulted in the diminished cytosolic AARS activity depicted in panel a.

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