Supplementary Materials

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

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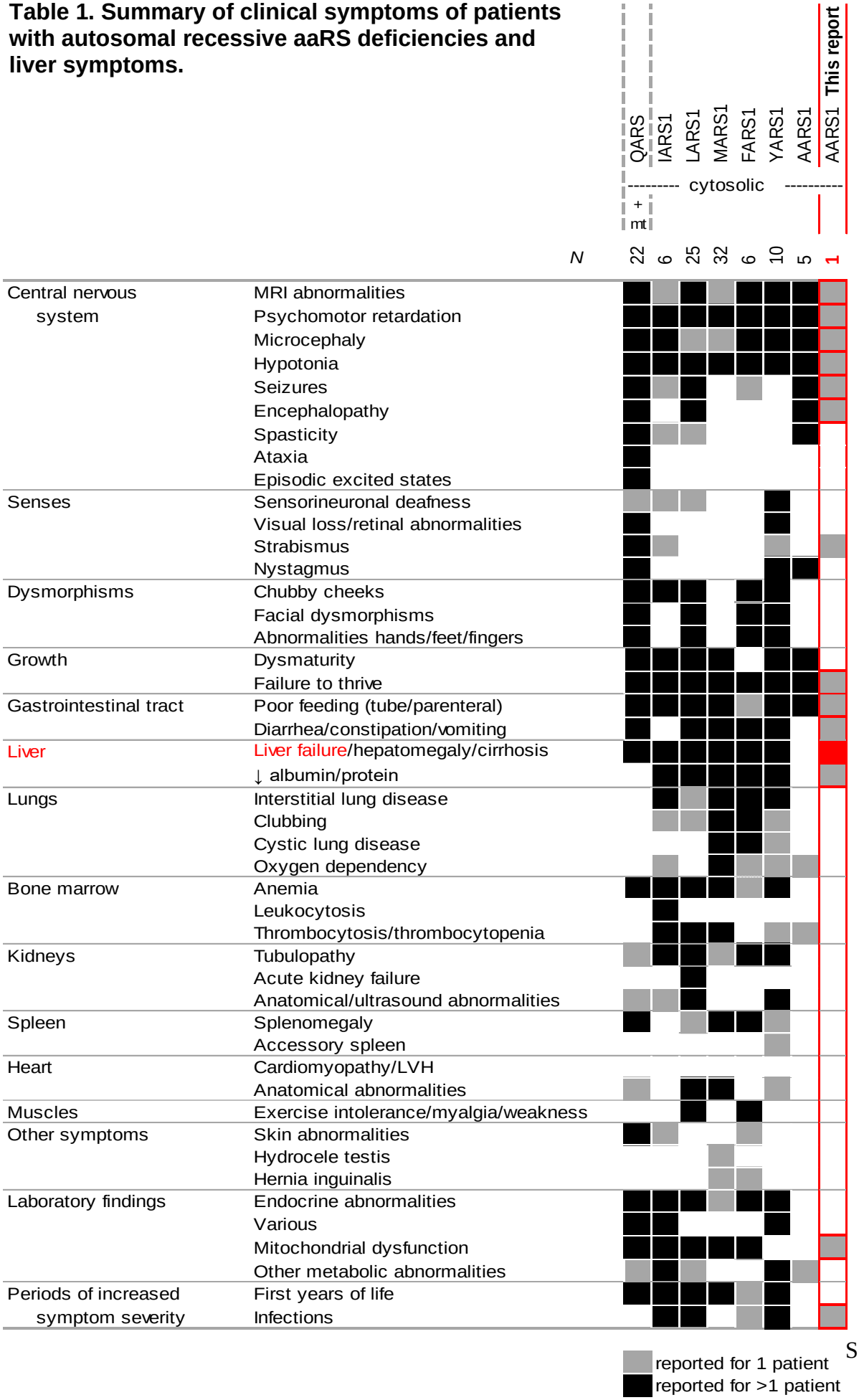
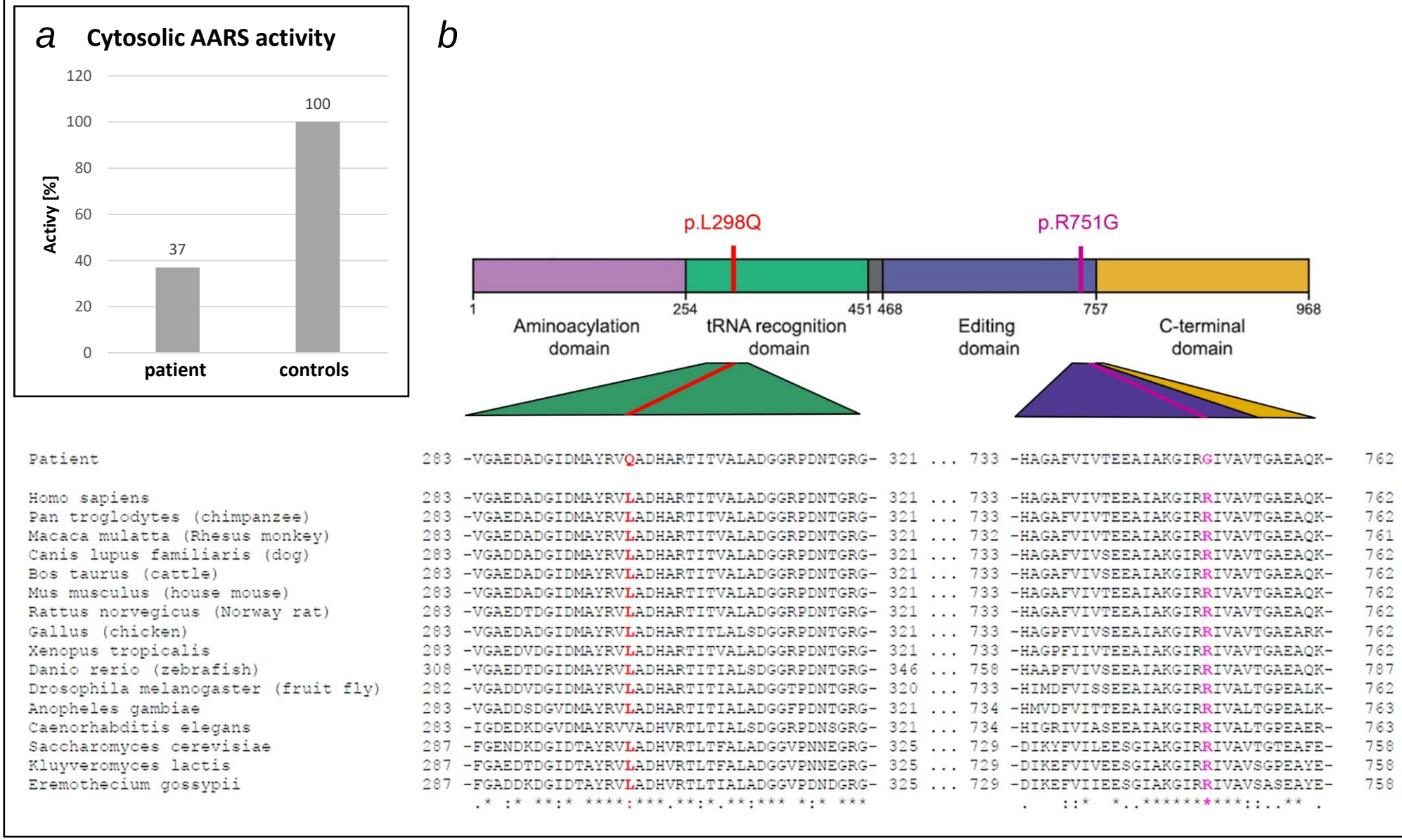
Table 1. Summary of clinical symptoms of patients with autosomal recessive aaRS deficiencies and liver symptoms.



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 [S1] with additional data from Williams et al. [S2], Tracewska-Siemiatkowska et al. [S3], Xu et al. [S4], Krenke et al. [S5], Casey et al. [S6], Lenz et al. [S7] and Johannesen et al. [S8])

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 [S8]). 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 [S10] 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. [S9,S11] Compound heterozygosity for the two variants in our patient resulted in the diminished cytosolic AARS activity depicted in panel *a*.

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