Table e-3 New and published *QARS* variants.

Patient ID	*QARS* variants (NM_005051.2)		Domain	Zygosity	Coding effect	Classification of variants according to Richards et al. 2015 (1)	SIFT	Polyphen (PolyPhen-2 v2.2.2r398)	gnomAD 2.0.1 (Allele Frequency, ALL)	Known *QARS* variation
1	c.1381delC	p.(Gln461Argfs*43)	CATD	compound heterozygous	frameshift	**pathogenic** (PVS1, PM2, PP2, PP3, PP4)	-	-	0	novel
	c.199C>T	p.(Arg67Trp)	NTD		missense	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	deleterious (score: 0.02, median: 3.43)	probably damaging (score 0.999, sensitivity: 0.14, specificity: 0.99)	0	novel
2	c.1132C>T	p.(Arg378Cys)	CATD	compound heterozygous.	missense	**likely pathogenic** (PM2, PM3, PM5, PP2, PP3, PP4)	deleterious (score: 0, median: 3.47)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.0072 %	dbSNP: rs185476065
	c.1567C>T	p.(Arg523*)	CATD		nonsense	**pathogenic** (PVS1, PM2, PP2, PP3, PP4)	-	-	0.00081 %	dbSNP: rs767667312
3	c.1133G>A	p.(Arg378His)	CATD	homozygous	missense	**likely pathogenic** (PM2, PM3, PM5, PP2, PP3, PP4)	deleterious (score: 0.01, median: 3.47)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.00081 %	dbSNP: rs777116688
4	c.1375del	p.(Glu459Asnfs*45)	CATD	compound heterozygous	frameshift	**pathogenic** (PVS1, PM2, PP2, PP3, PP4)	-	-	0	novel
	c.1304A>G	p.(Tyr435Cys)	CATD		missense	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	deleterious (score: 0, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.0025 %	dbSNP: rs143462532
5	c.1389-3C>A	p.?	CATD	compound heterozygous	splice	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	-	-	0	novel
	c.134G>T	p.(Gly45Val)	NTD		missense	**pathogenic** (PS3, PM2, PM3, PP1, PP2, PP3)	deleterious (score: 0.03, median: 3.43)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.0024 %	reported (2)
6	c.2084+2_2084+3del	p.?	ABD	compound heterozygous	splice	**likely pathogenic** (PM2, PM4, PP2, PP3, PP4)	-	-	0	reported (3)
	c.793C>T	p.(Arg265Cys)	CATD		missense	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	deleterious (score: 0.01, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0	novel
7	c.40G>A	p.(Gly14Ser)	NTD	compound heterozygous	missense	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	deleterious (score: 0, median: 3.43)	probably damaging (score 0.996, sensitivity: 0.55, specificity: 0.98)	0	novel
	c.1573C>T	p.(Arg525Trp)	CATD		missense	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	deleterious (score: 0, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0	ClinVar: RCV000623160.1
8	c.1570C>T	p.(Arg524Trp)	CATD	compound heterozygous	missense	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	deleterious (score: 0, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.0011 %	dbSNP: rs774980346, ClinVar: RCV000415807.1
	c.2068C>T	p.(Arg690Cys)	ABD		missense	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	deleterious (score: 0, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.0040 %	dbSNP: rs370934093, ClinVar: RCV000416268.1
9	c.170_171insAAA	p.(Tyr57*)	NTD	compound heterozygous	nonsense	**pathogenic** (PVS1, PM2, PP2, PP3, PP4)	-	-	0	novel
	c.170A>G	p.(Tyr57Cys)	NTD		missense	**pathogenic** (PS1, PM2, PM3, PP2, PP3, PP4	deleterious (score: 0.01, median: 3.43)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.00041 %	novel
10	c.1207C>T	p.(Arg403Trp)	CATD	compound heterozygous	missense	**pathogenic** (PS3, PM2, PM3, PP1, PP2, PP3)	deleterious (score: 0, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.00072 %	reported (2)
	c.4G>A	p.(Ala2Thr)	NTD		missense	**likely pathogenic** (PS4, PM2, PM3, PP2, PP3, PP4	tolerated (score: 0.16, median: 3.41)	possibly damaging (score 0.919, sensitivity: 0.81, specificity: 0.94)	0	novel
11, 12	c.169T>C	p.(Tyr57His)	NTD	compound heterozygous	missense	**pathogenic** (PS3, PM2, PM3, PP1, PP2, PP3)	tolerated (score: 0.24, median: 3.43)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.00041 %	reported (2, 4)
	c.1543C>T	p.(Arg515Trp)	CATD		missense	**pathogenic** (PS3, PM2, PM3, PP1, PP2, PP3)	deleterious (score: 0, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.0014 %	reported (2)
13, 14	c.134G>T	p.(Gly45Val)	NTD	compound heterozygous	missense	**pathogenic** (PS3, PM2, PM3, PP1, PP2, PP3)	deleterious (score: 0.03, median: 3.43)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.0024 %	reported(2)

Patient ID	*QARS* variants (NM_005051.2)		Domain	Zygosity	Coding effect	Classification of variants according to Richards et al. 2015 (1)	SIFT	Polyphen (PolyPhen-2 v2.2.2r398)	gnomAD 2.0.1 (Allele Frequency, ALL)	Known *QARS* variation
	c.1207C>T	p.(Arg403Trp)	CATD		missense	**pathogenic** (PS3, PM2, PM3, PP1, PP2, PP3)	deleterious (score: 0, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.00072 %	reported (2)
15	c.1387C>T	p.(Arg463*)	CATD	compound heterozygous	nonsense	**pathogenic** (PVS1, PM2, PM3, PP2, PP3, PP4)	-	-	0.0016 %	reported (5)
	c.2226G>C	p.(Gln742His)	ABD		missense	**likely pathogenic** (PM2, PM3, PP2, PP3, PP4)	deleterious (score: 0, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0	reported (5)
16, 17,18	c.1426G>A	p.(Val476Ile)	CATD	homozygous	missense	**likely pathogenic** (PS3, PS4m, PP1, PP2, PP3, PP4)	tolerated (score: 0.44, median: 3.44)	possibly damaging (score 0.701, sensitivity: 0.86, specificity: 0.92)	0.16 %	reported (6, 7)
19,20	c.169T>C	p.(Tyr57His)	NTD	compound heterozygous	missense	**pathogenic** (PS3, PS4m, PM2, PM3, PP1, PP2, PP3)	tolerated (score: 0.24, median: 3.43)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0.00041 %	reported(2, 4)
	c.1485dup	p.(Lys496*)	CATD		nonsense	**pathogenic** (PVS1, PM2, PM3, PP2, PP3, PP4)	-	-	0	reported (4)
21	c.1058G>T	p.(Gly353Val)	CATD	homozygous	missense	**likely pathogenic** (PM2, PP2, PP3, PP4, PP5)	deleterious (score: 0.01, median: 3.44)	possibly damaging (score 0.758, sensitivity: 0.85, specificity: 0.92	0	reported (8)
22	c.2084+2_2084+3del	p.?	ABD	compound heterozygous	splice	**likely pathogenic** (PM2, PM4, PP2, PP3, PP4)	-	-	0	reported (3)
	c.793C>T	p.(Arg25Cys)	NTD		missense	**likely pathogenic** (PS4, PM2, PP2, PP3, PP4)	deleterious (score: 0.01, median: 3.44)	probably damaging (score 1.000, sensitivity: 0.00, specificity: 1.00)	0	reported (3)

NTD, N-terminal domain; CATD, catalytic domain, ABD, anticodon-binding domain

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