Table e-1 Genetic and clinical data of all 22 patients with biallelic variants in *QARS*.

Reference	New patients										Zhang et al. 2014 (additional data)		Zhang et al. 2014		Salvarinova et al. 2015	Leshinsky-Silver et al. 2017			Kodera et al. 2014	Kodera et al. 2014	Alabdullatif et al. 2017	Fuchs et al. 2019	**total**
Patient ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	
Family ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**11**	**12**	**12**	**13**	**14**	**14**	**15**	**16**	**17**	**18**	**19**	
Sex	**f**	**f**	**f**	**m**	**f**	**m**	**f**	**f**	**f**	**m**	**m**	**f**	**m**	**m**	**m**	**f**	**f**	**f**	**m**	**m**	**m**	**m**	**11 f/ 11 m**
Ethnicity	European	European	Turkish	n.r.	European	n.r.	American/Hispanic	European	European	European	European	European	European american	European american	Armenian	Ashkenazi	Ashkenazi	Ashkenazi	Japanese	Japanese	n.r.	n.r.	
***QARS* variants**	c.1381delC, p.(Gln461Argfs*43); c.199C>T, p.(Arg67Trp)	c.1132C>T, p.Arg378Cys; c.1567C>T, p.(Arg523*)	c.1133G>A, p.(Arg378His); c.1133G>A, p.(Arg378His)	c.1375del, p.(Glu459Asnfs*45); c.1304A>G, p.(Tyr435Cys)	c.1389-3C>A; c.134G>T, p.(Gly45Val)	c.2084+2_2084+3del; c.793C>T, p.Arg265Cys	c.40G>A, p.(Gly14Ser); c.1573C>T, p.(Arg525Trp)	c.1570C>T, p.Arg524Trp; c.2068C>T, p.(Arg690Cys)	c.170_171insAAA, p.(Tyr57*); c.170A>G, p.(Tyr57Cys)	c.1207C>T, p.(Arg403Trp); c.4G>A, p.(Ala2Thr)	c.169T>C, p.(Tyr57His); c.1543C>T, p.(Arg515Trp)	c.169T>C, p.(Tyr57His); c.1543C>T, p.(Arg515Trp)	c.134G>T, p.(Gly45Val); c.1207C>T, p.(Arg403Trp)	c.134G>T, p.(Gly45Val); c.1207C>T, p.(Arg403Trp)	c.1387C>T, p.(R463*); c.2226G>C, p.(Gln742His)	c.1426G>A, p.(Val476Ile); c.1426G>A, p.(Val476Ile)	c.1426G>A, p.(Val476Ile); c.1426G>A, p.(Val476Ile)	c.1426G>A, p.(Val476Ile); c.1426G>A, p.(Val476Ile)	c.169T>C, p.(Tyr57His); c.1485dup, p.(Lys496*)	c.169T>C, p.(Tyr57His); c.1485dup, p.(Lys496*)	c.1058G>T, p.(Gly353Val); c.1058G>T, p.(Gly353Val)	c.2084+2_2084+3del, p.?; c.793C>T, p.(Arg25Cys)	
Measurements at birth																							
Weeks of gestation	38	38+2	38	38+2	37+6	39	36+4	36+2	38	39	41	at term	38	at term	at term	n.r.	n.r.	n.r.	39	40	n.r.	n.r.	
Weight (in g)	2200 (-2.3 SD)	2710 (-1.2 SD)	3615 (1.0 SD)	2485 (-2.0 SD)	3590 (0.7 SD)	3100 (-0.9 SD)	2050 (-1.9 SD)	1996 (-1.9 SD)	3000 (-0.4 SD)	2620 (-2.0 SD)	2722 (-2.3 SD)	2812 (-1.3 SD)	2812 (-1.1 SD)	3084 (-0.9 SD)	2466 (-2.4 SD)	2900 (-1.0 SD)	2400 (-2.0 SD)	n.r.	2975 (-1.2 SD)	3200 (-0.7 SD)	n.r.	3125	**15% (3/20) Weight <-2 SD**
Length (in cm)	46.0 (-1.9 SD)	42.5 (-3.6 SD)	53.0 (1.1 SD)	n.r.	50.5 (0.2 SD)	n.r.	40.5 (-3.5 SD)	43.0 (-2.3 SD)	50.0 (-0.2 SD)	51.0 (-0.4 SD)	51.3 (-0.8 SD)	49.0 (-1.0 SD)	50.2 (-0.4 SD)	49.5 (-1.0 SD)	n.r.	47.0 (-1.5 SD)	46.5 (-1.5 SD)	n.r.	n.r.	n.r.	n.r.	n.r.	**21% (3/14) Length <-2 SD**
OFC (in cm)	28.0 (-4.9 SD)	30.5 (-3.0 SD)	31.0 (-2.5 SD)	n.r.	33.5 (-0.9 SD)	n.r.	29.0 (-3.2 SD)	28.5 (-3.4 SD)	30.0 (-3.3 SD)	32.0 (-2.5 SD)	33.5 (-1.9 SD)	33.5 (-0.9 SD)	27.9 (-5.0 SD)	31.1 cm (-3.2 SD)	30.0 (-4.1 SD)	33.0 (-1.0 SD)	n.r.	31.0 (-2.0 SD)	32 (-2.5 SD)	33 (-1.8 SD)	n.r.	n.r.	**65% (11/17) OFC <-2 SD**
Measurements at follow-up																							
Age at follow-up	n.r.	9 4/12 years	10 6/12 years	5 1/12 years	4 6/12 years	2 6/12 years	2 6/12 years	2 2/12 years	5 months	9 years	9 years	8 years	21 months	7 months	8 years	10 years	7 6/12 years	3 years	4 6/12 years	5 years	n.r.	4 years	**mean age: 59 months**
Weight (in kg)	n.r.	27.4 (-0.8 SD)	32.0 (-0.6 SD)	11.8 (-4.3 SD)	17.5 (mean)	14.3 (0.5 SD)	16.7 (1.7 SD)	8.3 (-3.2 SD)	6.0 (-0.8 SD)	18.0 (-4.4 SD)	27.8 (-0.6 SD)	24.4 (-0.6 SD)	7.8 (-3.3 SD)	6.6 (-1.7 SD)	n.r.	17.7 (-4.3 SD)	13.6 (-4.9 SD)	n.r.	n.r.	n.r.	n.r.	n.r.	
Length (in cm)	n.r.	120.0 (-2.8 SD)	135.0 (-1.3 SD)	92.0 (-4.2 SD)	97.0 (-2.2 SD)	94.0 (0.4 SD)	93.4 (0.3 SD)	73.0 (-4.3 SD)	62.4 (-0.7 SD)	116.0 (-3.5 SD)	135.0 (-0.25 SD)	120.0 (-1.6 SD)	77.0 (-2.6 SD)	63.5 (-2.2 SD)	n.r.	107.0 (-5.1 SD)	95.0 (-5.6 SD)	96.0 (0.1 SD)	n.r.	n.r.	n.r.	n.r.	**56% (9/16) Length<-2 SD**
BMI (in kg/m²)	n.r.	19.0 (0.9 SD)	17.6 (0.2 SD)	13.9 (-1.2 SD)	18.6 (1.7 SD)	16.2 (0.3 SD)	19.1 (2.0 SD)	15.6 (-0.2 SD)	15.4 (-0.5 SD)	13,4 (-2.1 SD)	15.3 (-0.6 SD)	16.9 (0.4 SD)	13.2 (-3.0 SD)	16.4 (-0.3 SD)	n.r.	15.5 (-0.7 SD)	15.1 (-0.4 SD)	n.r.	n.r.	n.r.	n.r.	n.r.	**13% (2/15) BMI <-2 SD**
OFC (in cm)	n.r.	42.0 (-11.1 SD)	50.0 (-2.4 SD)	47.8 (-3.1 SD)	47.5 (-2.4 SD)	46.5 (-3.5 SD) at 3,5 years	40.0 (-6.4 SD) at 14 months	38.0 (-11.9 SD)	33.0 (-10.3 SD)	44.0 (-7.0 SD)	(-4.0 SD)	(-4.0 SD)	34.0 (-12.5 SD)	34.0 (-9.0 SD)	30.2 (-17.2 SD)	48.5 (-3.7 SD)	47.5 (-3.7 SD)	47.0 (-2.1 SD)	45 cm (-5.1 SD)	45 cm (-5.2 SD)	n.r.	n.r.	**100% (19/19) OFC <-2 SD**
Neurological features																							
Motor development	severe delay	severe delay	Severe delay	mild delay	mild delay	severe delay	severe delay	severe delay	severe delay	severe delay	severe delay	severe delay	severe delay	severe delay	severe delay	moderate delay	moderate delay	mild delay	severe delay	severe delay	moderate delay	severe delay	**73% (16/22) severe delay 14% (3/22) moderate delay**
Sitting (at age)	no	no	no	n.r.	10 months	21 months	no	no	too young	no	no	no	no	no	no	10 months	no	no	no	no	no	yes	**85% (17/20) no sitting**
Walking (at age)	no	no	no	2 years	4 2/12 years	no	no	no	too young	no	no	no	no	no	no	10 years	no	no	no	no	no	no	**86% (18/21) no walking**
Hypotonia	n.r.	initially hypotonia	n.r.	n.r.	no	n.r.	severe hypotonia	initially hypotonia	yes	no	severe hypotonia	severe hypotonia	yes	n.r.	diffuse hypotonia	n.r.	n.r.	n.r.	yes	yes	n.r.	n.r.	**83% (10/12) Hypotonia**
Hypertonia/ spasticity	n.r.	at 9 years spasticity	n.r.	n.r.	no	n.r.	at 2 years contractures of ankles and wrists	mixed hypotonia and hypertonia, at 2 years severe spasticity	no	hypertonia	n.r.	n.r.	mixed hypotonia and hypertonia	hypertonia	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	**75% (6/8) Hypertonia/ spasticity**
Speech development	no speech	no speech	no speech	speaks sentences, expressive speech delay	vocalizes, no words	no speech	no speech	no speech	too young	no speech	no speech	no speech	no speech	no speech	no speech	no speech	no speech	speaks short sentences	no speech	no speech	n.r.	no speech	**90% (18/20) no speach**
Stereotypies / involuntary movements	n.r.	yes	n.r.	n.r.	yes	n.r.	yes	no	no	dystonia at age 3 years	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	yes	yes	n.r.	n.r.	**75% (6/8) Stereotypies**
Episodes of irritability	intermittent irritability	intermittent irritability	n.r.	n.r.	rare	n.r.	intermittent severe irritability	intermittent severe irritability and crying	intermittent irritability	no	n.r.	n.r.	intermittent severe irritability	intermittent irritability	n.r.	n.r.	n.r.	n.r.	intermittent severe irritability	intermittent severe irritability	n.r.	n.r.	**91% (10/11) Irritability**
Visual interaction	n.r.	no	n.r.	n.r.	yes	n.r.	no	no	no	no	no	no	no	n.r.	smiling, communicating	n.r.	n.r.	n.r.	poor	n.r.	n.r.	very poor	**67% (8/12) no visual interaction**
Opthalmologic abnormalities	n.r.	astigmatism, partial horizontal nystagmus, no reaction to light	n.r.	n.r.	n.r.	n.r.	astigmatism, nystagmus, myopia, roving movements of eyes	slow pupillary light reflex	n.r.	opticus atrophy, nystagmus	n.r.	n.r.	cortical visual impairment	nystagmus	cortical visual impairment, nystagmus	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	occipital visual disturbance, nystagmus, strabismus	**(6) nystagmus**
Epilepsy																							
Onset	1 h after birth	1 h after birth	no epilepsy	n.r.	5.5 months	2.5 months	2h after birth	3 h after birth	1 h after birth	4th day of life	1 h after birth	1 month	1 h after birth	1st day of life	2nd day of life	no seizures	no seizures	no seizures	4th day of life	1st day of life	n.r.	n.r.	**60% (9/15) epilepsy onset at 1st day**
Type	myoclonus, tonic-clonic seizures, several crises per day	focal epilepsy with focal seizures, secondary generali-zation	no epilepsy, epileptic discharges in EEG	encephalo-pathy during episode of meningo-encephalitis	focal seizures and spasms, 1 seizure per 3 months at follow-up	tonic seizures, several (clusters of) seizures/day, periods of lower seizure frequency (1/week)	myoclonic seizures, 2-3 per day to 1/week	focal and generalized seizures	Myoclonic seizures, status epilepticus, hourly seizures	multifocal clonic and tonic seizures	polymorphic, long lasting, migrating partial seizures in infancy, 20-50 multifocal seizures /day at follow-up	first clonic seizures with apnoe and cyanosis, 20-50 multifocal seizures /day at follow-up	status epilepticus, generalized tonic or focal clonic seizures	frequent, recurrent, long lasting	generalized tonic clonic seizures, clusters, EEG: seizures captured from different regions, multifocal spikes and sharp waves	-	-	-	perioral twitch, tonic seizures with cyanosis, eye deviation and head turning	tonic seizures with cyanosis, eye deviation and head turning, EEG: suppression-burst, high-voltage delta and multifocal spike	febrile seizures	epileptic encephalopathy	
Antiepileptic therapy	Benzodiazepines helped to sleep a few hours	combination of Pheno-barbital, Levetiracetam, Topiramate were mild effective	n.r.	n.r.	n.r.	n.r.	Levetiracetam, Pyridoxine, Topiramate, Valproic acid, Clonazepam, Cannabidiol hemp oil, ketogenic diet	combination Topiramate, Oxcarba-zepine, Pregabalin with limited effect; response to ketogenic diet but not tolerated	n.r.	multiple combinations including Valproic acid	n.r.	n.r.	Phenobarbital, Levetir-acetam, Lorazepam, Topiramate, Oxcarba-zepine, Valproic acid, Gabapentin, Lamo-trigine, Clonazepam were ineffective	Clonazepam, Gabapentin	response to ketogenic diet	-	-	-	Phenobarbital, Phenytoin, Vitamin B6 ineffective	Combination Phenobarbital, Potassium bromide, Valproic acid, Clobazam were effective	n.r.	no response to ketogenic diet	
Effect of antiepileptic therapy	pharmacoresistant	pharmacoresistant	seizure free at follow up	seizure free at follow-up	pharmacoresistant	pharmacoresistant	pharmacoresistant	pharmacoresistant	pharmacoresistant	pharmacoresistant	pharmacoresistant	pharmacoresistant	pharmacoresistant	n.r.	pharmacoresistant	-	-	n.r.	pharmacoresistant	pharmacoresistant	seizure free	pharmacoresistant	**79% (15/19) pharmacoresistant**
Additional features																							
Constipation	n.r.	yes	n.r.	n.r.	n.r.	n.r.	yes	yes	no	yes	n.r.	n.r.	yes	no	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.		**71% (5/7) constipation**
G-tube	n.r.	G-tube	n.r.	n.r.	n.r.	n.r.	G-tube	G-tube	no	G-tube	n.r.	n.r.	G-tube	G-tube	G-tube	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	G-tube	**(8) G-tube**
Others	deceased at age 9 years	gastrooesophageal reflux	n.r.	n.r.	n.r.	n.r.	Hypothyroidism, stridor, hyporeflexia, tapering digits, koilonychias	unilateral hip dislocation	deceased at age 13 months from combination of intractable seizures and	Hepatomegaly due to Valproic acid, anemia, recurrent infections	n.r.	n.r.	Tracheomalacia	n.r.	Hydronephrosis, unilateral hydroureter, small VSD at birth; precocious puberty at 7	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	elevated liver enzymes due to antiepileptic drug introduction	

									respiratory failure						years; abnormal auditory brainstem responses							
cMRI																						
Age at cMRI	1 8/12 years	14 weeks / 9 4/12 years	10 years	n.r.	6 months / 27 months	no MRI pictures available	0 weeks / 5 weeks	1 week / 19 weeks	5 days	18 months / + follow-up	6 months / 5 4/12 years	3 7/12 years	4 3/12 years	3 1/12 years	6 days / 12 months / 5 4/12 years	n.r.	n.r.	n.r.	7 days / 7 months	11 days /7 months / 2 years	n.r.	3 months / 1 year	
Corpus callosum anomalies	no	(14 weeks) hypoplasia, (9 years) complete atrophy	hypoplasia	hypoplasia	no	hypoplasia	hypoplasia	hypoplasia	no	hypoplasia	hypoplasia	hypoplasia	hypoplasia	hypoplasia	diffues thinning at 5 years	n.r.	n.r.	n.r.	hypoplasia	hypoplasia	no	hypoplasia at 1 year	**79% (15/19) cc Hypoplasia**
Delayed myelination	no	hypomyelination	hypomyelination	hypomyelination	no	hypomyelination	too young to evaluate	hypomyelination	delayed myelination (no myelination central and subcortical)	hypomyelination	hypomyelination or delayed myelination	hypomyelination or delayed myelination	hypomyelination or delayed myelination, decreased contrast of white and gray matter	hypomyelination or delayed myelination, decreased contrast of white and gray matter	severely delayed myelination of cortex with little progression	n.r.	n.r.	n.r.	delayed myelination	delayed myelination	no	progressive delayed myelination	**88% (15/17) Hypomyelination**
Cortical anomalies	white matter atrophy, cortical dysplasia	progressive atrophy of supratentorial brain with reduced white matter bulk, pachygyria	white matter atrophy	n.r.	moderate atrophy	white matter atrophy	progressive atrophy of supratentorial brain with reduced white matter bulk, pachygyria	mild atrophy of cerebral cortex with reduced white matter bulk, pachygyria	symmetric cortical pachygyria	progressive atrophy of cerebral cortex	atrophy of cerebral cortex	atrophy of cerebral cortex	atrophy of cerebral cortex, severely simplified gyral pattern	atrophy of cerebral cortex, severely simplified gyral pattern	profound global atrophy with cerebral hypoplasia, diffuse supratentorial white matter bulk loss, pachygyria	n.r.	n.r.	n.r.	diffuse progressive cerebral atrophy with white matter volume loss, focal atrophy, signal abnormality in bilateral occipital lobes, elongation of occipital lobes	diffuse progressive cerebral atrophy with white matter volume loss, focal atrophy with signal abnormality in bilateral occipital lobes	no	gradual loss of frontal periventricular white matter	**89% (16/18) Cortical atrophy** **56% (10/18) Cortical structural anomalies**
Cerebellar anomalies	atrophy of vermis cerebelli	mild atrophy of cerebellum	no	n.r.	moderate atrophy of vermis cerebelli	atrophy of vermis cerebelli	normal	normal	normal	normal	atrophy of vermis cerebelli	atrophy of vermis cerebelli	atrophy of vermis cerebelli	atrophy of vermis cerebelli	normal	n.r.	atrophy of cerebellar hemispheres	n.r.	atrophy of cerebellum	atrophy of cerebellum	no	n.r.	**61% (11/18) Cerebellar atrophy**
Brain stem	normal	normal	normal	n.r.	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal	n.r.	n.r.	n.r.	normal	normal	n.r.	n.r.	**0 (0/16)**
Enlarged ventricles	yes	yes	yes	n.r.	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	n.r.	yes	enlarged posterior horn	no	n.r.	**95% (18/19)**