CMT2 WITH PYRAMIDAL TRACT INVOLVEMENT DUE TO ARG329HIS MUTATION IN ALANYL-TRNA SYNTHETASE (AARS)

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Introduction

Mutations in amynoacyl tRNA synthetases (ARSs), enzymes that catalyse the covalent attachment of amino acids to their cognate tRNA, are responsible for autosomal dominant CMT2, Intermediate CMT (CMT-I) and dHMN.

Objectives

To report a case of *AARS* Arg329His mutation in a patient with CMT2 and pyramidal signs, a feature not previously reported within patients carrying Arg329His mutation.
To review current knowledge clinical features and genetic findings of CMT related ARSs mutations.

Case report

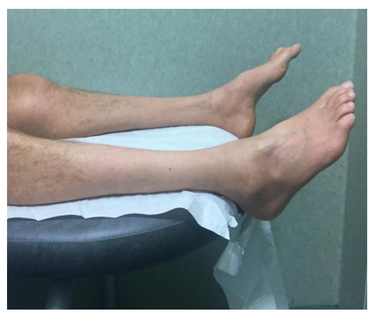
Disease onset

37y, Male
Development: bilateral clonus at 3 months of age, persisting till adolescence
chief complain: ankle instability progressive walking difficulties and distal sensory loss from the third decade
Clinical course: slowly progressive with moderate disability
PMH: uneventful
CMTES: 18

Paraclinical investigations

Brain and spinal cord MRI: normal.

	Motor				Sensory		
	CMAP (mV)	MCV (m/s)	DML (ms)	F wave latency (ms)		SAP (uV)	SCV (m/s)
ref	*>2*	*>40.6*	*<5.8*		*ref*	*>6*	*>42*
Peroneus	0,0	34,9	21,1	Not elicitable	***Suralis***	0,67/0,17	39,2/24,4
ref	*>5*	*>41*	*<5.5*				
Tibialis	0,7/0,3	32,8/19,3	9,9/11,7	NE			
ref	*>5*	*>46.8*	*<4*		*ref*	*>8*	*>46.8*
Median	5,9/5,3	36,4/39,1	10,75	45,35	***Median***	4,9/4,8	38,3/37,7



Neurologic examination

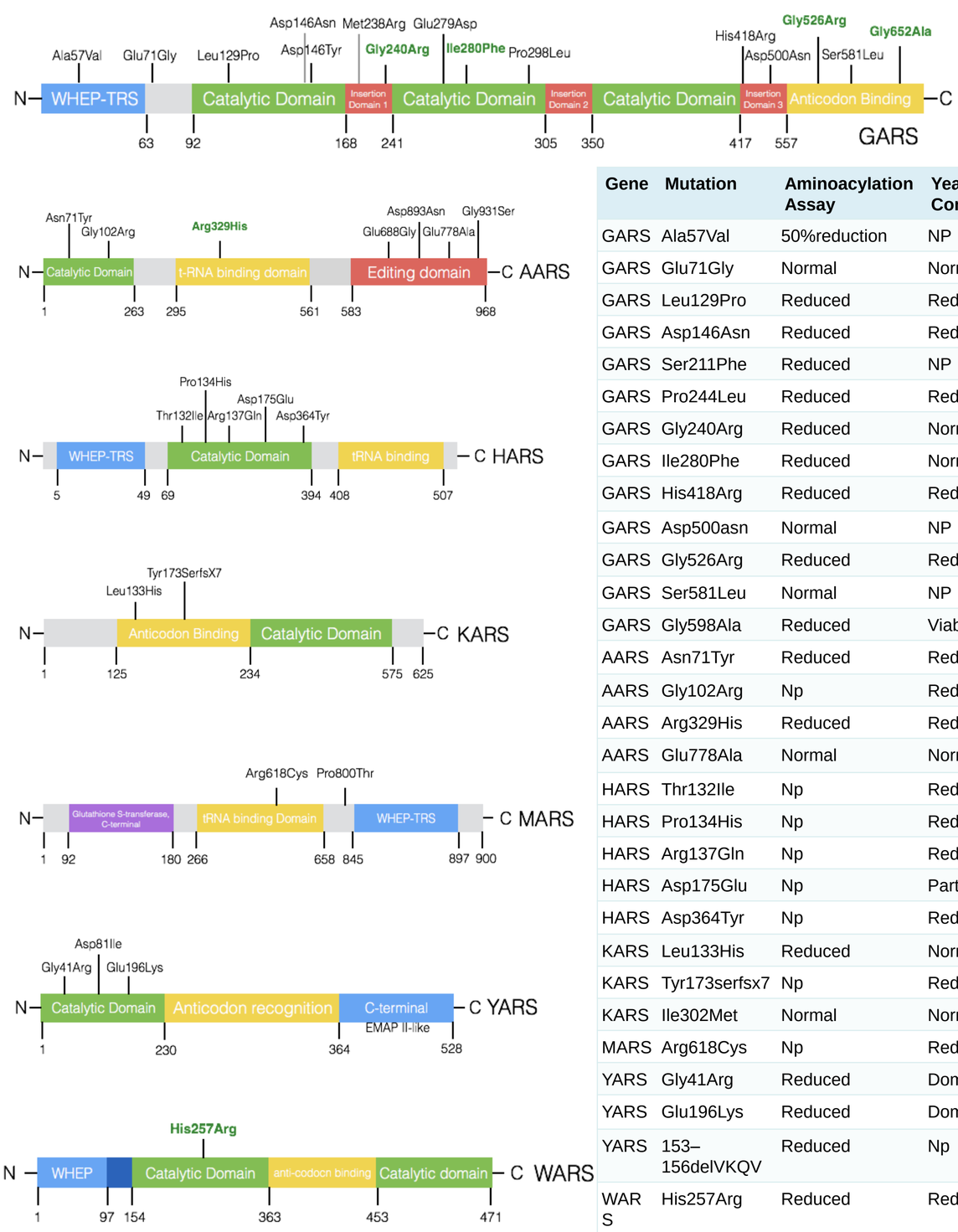
Cranial nerves: normal
Atrophy: moderate UL, marked LL
Weakness:
UL: proximal: normal; distal: mild (ABP 5-/4+)
LL: proximal: normal strength, **distal: severe**
Sensation:
Light touch and pinprick: reduced to ankles
Vibratory: I MCP reduced; hallux: absent; knee: reduced
Reflexes: **UL: brisk**; reduced at knees, absent at ankles
Bilateral Babinski
Steppage gait

Workout

Sanger sequencing of ***PMP22***, ***GJB1***, ***MPZ***, ***GDAP*** and ***MFN2***: negative.
SureSelect Focused Exome sequencing (Agilent Technologies, Santa Clara CA, USA): **c.986G>A, p.Arg329His mutation in *AARS*.**

Literature revision

	GARS	AARS	HARS	KARS	MARS	YARS	WARS
Mutations	17	6	5	1 comp het	2	3	1
Families	18	13	4	1	2	2	3
Sporadic cases, n (%)	5	0	1	-	-	1	0
Patients	43	42	23	1	4	3	7
Phenotype							
d-HMN-V	12	1	-	-	-	-	3
CMT2D	8	5	2	-	2	-	-
CMTI	-	5	1	1	-	3	-
CMT1	-	1	-	-	-	-	-
CMT2/d-HMN	3	-	2	-	-	-	-
Atypical	-	1	-	-	-	-	-
Age of Onset	0-35 16,6 ± 1,8	0-55 23,6 ± 2,8	22,05 ± 3,5	NA	45-67 44,4 ± 4,94	I-VI dec	11,7 ± 0,6
Age at first visit	37,4 ± 3,5	42,8 ± 2,88	44,7 ± 3,8	NA	51,4 ± 4,87	NA	37,7 ± 6,7
Site of onset							
UL	57%	3%	5%	NA	25%	33%	100%
LL	24%	92%	79%	NA	50%	-	-
UL + LL	16%	5%	16%	NA	25%	67%	-
Motor deficit at NE							
UL	23%	-	-	NA	-	-	-
LL	-	54%%	25%	NA	-	-	-
UL + LL	77%	46%	75%	NA	100%	100%	100%
Siensory deficit at NE							
LL	10%	58%	48%	NA	-	-	-
UL + LL	19%	27%	35%	NA	100%	100%	-
None	70%	15%	17%	NA	-	-	100%
UL predominance	40%	-	-	-	-	-	-
Cranial nerves involvement	3 cases (7%)	1 mutation (16%)	-	-	-	-	-
Pyramidal signs	Babinski 18% Brisk DTR 5%	Brisk DTR and Babinski 16%	Brisk DTR 60%	-	-	-	-
Scoliosis	6 (14%)	-	-	-	-	-	-
Other signs	Mild increase CPK (5%)	1 case mis-diagnosed as CIDP	-	Developmental delay, self-abusive behavior, dimorphism, vestibular Schwannoma	-	-	-
Median MNCV (m/s)	47,3 ± 1,2	42,4 ± 1,8	41,6 ± 1,63	39,5	52,5	29-50	55,2 ± 2,3
% ≤ 45 m/s	41%	72%	66%	-	-	-	0%



Gene	Mutation	Aminoacylation Assay	Yeast Complementation
GARS	Ala57Val	50%reduction	NP
GARS	Glu71Gly	Normal	Normal
GARS	Leu129Pro	Reduced	Reduced
GARS	Asp146Asn	Reduced	Reduced
GARS	Ser211Phe	Reduced	NP
GARS	Pro244Leu	Reduced	Reduced
GARS	Gly240Arg	Reduced	Normal
GARS	Ile280Phe	Reduced	Normal
GARS	His418Arg	Reduced	Reduced
GARS	Asp500asn	Normal	NP
GARS	Gly526Arg	Reduced	Reduced
GARS	Ser581Leu	Normal	NP
GARS	Gly598Ala	Reduced	Viable
AARS	Asn71Tyr	Reduced	Reduced
AARS	Gly102Arg	Np	Reduced
AARS	Arg329His	Reduced	Reduced
AARS	Glu778Ala	Normal	Normal
HARS	Thr132Ile	Np	Reduced
HARS	Pro134His	Np	Reduced
HARS	Arg137Gln	Np	Reduced
HARS	Asp175Glu	Np	Partially Reduced
HARS	Asp364Tyr	Np	Reduced
KARS	Leu133His	Reduced	Normal
KARS	Tyr173serfsx7	Np	Reduced
KARS	Ile302Met	Normal	Normal
MARS	Arg618Cys	Np	Reduced
YARS	Gly41Arg	Reduced	Dominant Neg
YARS	Glu196Lys	Reduced	Dominant Neg
YARS	153–156delVKQV	Reduced	Np
WARS	His257Arg	Reduced	Reduced

Conclusions

Pyramidal signs can be an early feature of CMT2N due to Arg329His mutation in AARS, further expanding the spectrum of ARSs-associated phenotypes.
ARSs mutations are increasingly recognised as a cause of CMT/d-HMN. The upper limb predominance is a distinctive sign only for *GARS*-associated neuropathies, while distinct features could not be identified for other genes
The molecular pathology, and therefore the development of a reliable assay for functional validation, of disease causing *ARSs* mutations remain elusive.