Mitochondrial aminoacyl-tRNA synthetases deficiency: report of five cases with genotypic and phenotypic expansion

Thitiporn Fangsaad[#1], Chupong Ittiwut[#2,3], Vitchayaporn Emarach Saengow[5], Natrujee Wiwattanadittakul[6], Chinnuwat Sanguansermsri[6], Kamornwan Katanyuwong[6], Sirorat Suwannachote[7], Wuttichart Kamolvisit[2,3], Adjima Assawapitaksakul[2,3], Rungnapa Ittiwut[2,3], Tanitnun Paprad[4], Navarat Rungteeranon[8], Suda Jirasakuldej[4,9], Ponghatai Boonsimma[2,3], Tayard Desudchit[4], Kanya Suphapeetiporn[2,3],Vorasuk Shotelersuk[2,3]

[1]Division of Neurology, Department of Pediatrics, Bhumibol Adulyadej Hospital, Bangkok, Thailand
[2]Center of Excellence for Medical Genetics, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[3]Excellence Center for Medical Genetics, King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand
[4]Division of Neurology, Department of Pediatrics, Faculty of Medicine,Chulalongkorn University, Bangkok, Thailand
[5]Division of Neurology, Department of Pediatrics, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand
[6]Division of Neurology, Department of Pediatrics, Maharaj Nakorn Chiang Mai, Chiang Mai
[7]Division of Neurology, Department of Pediatrics, Faculty of Medicine, Queen Sirikit National Institute of Child Health, Bangkok, Thailand
[8]Division of Neurology, Department of Pediatrics, Samitivej Srinakarin Hospital, Bangkok, Thailand
[9]Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Thailand;
Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC), The Thai Red Cross Society, Thailand
[#]These authors contributed equally to this work.

ABSTRACT

Background: Mitochondrial aminoacyl-tRNA synthetases (mt-aaRSs), which play a vital role in mitochondrial protein synthesis by attaching amino acids to the tRNA tails, have increasingly been associated with various neurological disorders, including epilepsy.

Methods: We conducted a study involving patients with mt-aaRSs disorders who presented with epilepsy. We selected epilepsy patients who underwent genetic testing at our center. We reviewed the clinical characteristics and genetic findings of patients with mt-aaRSs disorders.

Results: From January 2016 to December 2022, 3,777 patients underwent exome sequencing at our center. One hundred and thirty-three patients were diagnosed with epilepsy. Five patients from four families harbored pathogenic or likely pathogenic variants in genes encoding mitochondrial aminoacyl-tRNA synthetases (mt-aaRSs), including one case of *AARS*, three cases of *FARS2*, and one case of *RARS2*. All patients presented with drug-resistant epilepsy. The seizure onset ranged from one month to twelve years. All patients exhibited myoclonic seizures. The siblings with an *FARS2* gene mutation represent the first reported cases of this gene causing childhood-onset progressive myoclonic epilepsy. Neuroimaging revealed brain atrophy in four patients. The outcomes for our patients ranged from mild to severe developmental delay. Two of our patients passed away. The clinical and biochemical laboratory data, including EEG and MRI, of mt-aaRSs disorders in our report were variable and did not distinguish them from other genetic developmental epileptic encephalopathies (DEEs). Genetic testing should be considered to establish the diagnosis of mt-aaRSs disorders.

Conclusion: This study expands the phenotype of genetic defects in the mt-aaRSs genes, with an emphasis on the wide range of epilepsy onset.

Keywords: mitochondrial disorder, mitochondrial tRNA synthetase, *AARS, FARS2, RARS2,* developmental and epileptic encephalopathy

OBJECTIVES

Reviewed the clinical characteristics and genetic findings of patients with mt-aaRSs disorders.

MATERIAL &METHODS

This study received approval from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand (IRB No. 264/62). Written informed consent was obtained from the parents or legal guardians of the participants. We conducted a retrospective review of genetic consultations and genetic testing, whole exome sequencing, requests at our center, King Chulalongkorn Memorial Hospital, covering the period from January 2016 to December 2022. Our study focused on cases with suspected genetic epilepsy, and we recruited patients who had identified pathogenic or likely pathogenic variants in genes encoding mitochondrial aminoacyl-tRNA.

RESULTS

From January 2016 to December 2022, 3,777 patients underwent exome sequencing at our center. One hundred and thirty-three patients were diagnosed with epilepsy. Five patients from four families harbored pathogenic or likely pathogenic variants in genes encoding mitochondrial aminoacyl-tRNA synthetases (mt-aaRSs), including one case of *AARS*, three cases of *FARS2*, and one case of *RARS2* (Table 1). All patients presented with drug-resistant epilepsy. The seizure onset ranged from one month to twelve years. All patients exhibited myoclonic seizures. The siblings with an *FARS2* gene mutation represent the first reported cases of this gene causing childhood-onset progressive myoclonic epilepsy. Neuroimaging revealed brain atrophy in four patients. The outcomes for our patients ranged from mild to severe developmental delay. Two of our patients passed away. The clinical and biochemical laboratory data, including EEG and MRI, of mt-aaRSs disorders in our report were variable and did not distinguish them from other genetic developmental epileptic encephalopathies (DEEs). Genetic testing should be considered to establish the diagnosis of mt-aaRSs disorders.

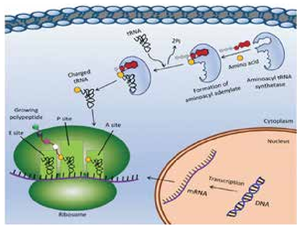

Fig 1. Mitochondrial aminoacyl-tRNA synthetases (mt-aaRSs) play a vital role in mitochondrial protein synthesis by attaching amino acids to the tRNA tails. (Modified from *ACS Omega* 2023, 8, 17, 14884–14899, Publication Date: April 10, 2023)

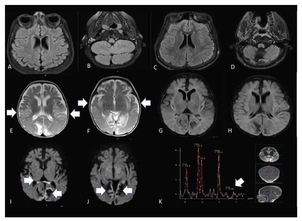

Fig. 2: A-B; MRI shows cerebral and cerebellar atrophy in Family II(1). C-D; MRI reveals mild cerebral atrophy and moderate to severe cerebellar atrophy in Family II(2). E-J; MRI indicates mild cerebral atrophy with abnormal signals at biparieto-occipital and insular lesions in Family III. K; MRS demonstrates a high lactate peak in Family III.

Table 1. Clinical data in patients with mitochondrial aminoacyl-tRNA synthetases deficiency

Family	Family I	Family II		Family III	Family IV
Gene	*AARS*	*FARS2*	*FARS2*	*FAR2*	*RARS2*
Demographic:					
Gender	F	F	M	F	M
Age at onset of epilepsy	1 month	8 years	12 years	2 months	1 year
Consanguinity	No	No	No	No	No
Age at last visit	12 Y	14 Y	23 Y	5 months	11 Y
Clinical features:					
Presenting symptoms	Epilepsy	Progressive myoclonic epilepsy	Progressive myoclonic epilepsy	Epilepsy	Epilepsy
Seizure semiologies	myoclonic	myoclonic	myoclonic, GTC	focal clonic, myoclonic	myoclonic, GTC focal clonic, eye blinking, tonic, hemiclonic
Status epilepticus	No	Yes	No	Yes	Yes
Developmental status prior to seizure onset	GDD	normal	normal	GDD	GDD
ASMs used	PB, LEV	VPA, perampanel	VPA, PHT, TPM, LEV, perampanel	PHT, TPM, PB, LEV	LEV, VPA, LCS
Seizure outcome	Controlled	controlled	Controlled	Intractable	Intractable
Physical examination					
Failure to thrive	Yes	Yes	Yes	Yes	No
Microcephaly	Yes	No	No	No	No
Dysmorphism	No	No	No	No	No
Heart/Lung	Normal	Normal	Normal	Normal	Normal
Hepatomegaly	No	No	No	No	No
Abnormal Neuro sign	abnormal eye rolling	tremor, myoclonic jerk movement, ataxia, wide base gait	No	No	myoclonic jerk, paroxysmal dyskinesia
Tone	Normal	Normal	Normal	Hypotonia	Hypotonia
Laboratory					
CBC	Normal	Normal	Normal	Normal	Normal
Metabolic Acidosis	No	No	No	Severe	Mild
SGOT/SGPT(U/L)	21/27	62/25	10/4	150/105 (high)	37/22
BUN/Cr(mg/dL)	12.5/0.32	13/0.5	8/0.76	4.7/0.21	16.09/0.17
CK	N/A	N/A	N/A	143	54
Lactate (serum/CSF)	NA	1.7/NA	1.5/NA	14.7/10.9 (High)	NA
Imaging					
Brain CT/MRI/MRS	CT: normal	MRI:Mild cerebral and cerebellar atrophy (Fig2, A-B)	MRI:Mild cerebral atrophy, moderate to severe cerebellar atrophy (Fig2, C-D)	MRI:mild cerebral atrophy with abnormal signal at biparieto-occipital and insular lesions with high lactate peak on MRS (Fig2, E-K)	MRI:suspected cerebellar atrophy with atrophy or hypoplasia of the inferior vermis
EEG	Electrical discharges associated with abnormal eye movement, slow background	Frequent bilateral frontal spike-slow waves, photoparoxysmal response reproducible with 4 Hz photic stimulation	Intermittent sharp waves at frontotemporal area, diffused encephalopathy, photoparoxysmal response	Multifocal spike, slow background	Normal awake*
Clinical at last visit					
Development	GDD, wheelchair	Mild developmental delay; attending school	No verbal communication, wheelchair	GDD	GDD, dystonia

ASMs, antiseizure medications; CNV, copy number variation; D, damaging/deleterious/disease-causing; EEG, electroencephalography; ID, identification; P, possibly damaging; PMID, pubmed identification number; Pt, patient; M, male; F, female; MRI, magnetic resonance imaging; T, tolerant;; VUS, variant of uncertain significance; SIFT, sorting intolerant from tolerant (http://sift.jcvi.org/); Polyphen-2, prediction of functional effects of human SNPs (http://genetics.bwh.harvard.edu/pph2/);M–CAP, Mendelian clinically applicable pathogenicity score (http://bejerano.stanford.edu/mcap/); MutationTaster (http://mutationtaster.org/); CADD, combined annotation dependent depletion (https://cadd.gs.washington.edu/; recommended pathogenicity threshold greater than 20); dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/); gnomAD, aAccording to the American College of Medical Genetics and Genomics (ACMG) interpretations guidelines (Richards et al., 2015).b No homozygotes found in the gnomAD (https://gnomad.broadinstitute.org/)*Normal EEG in the first two EEGs, the following EEGs showed multifocal spike and slow background

GTC; generalized tonic clonic seizures, LEV; levetiracetam, PB; phenobarbital, PHT; phenytoin, TPM; topiramate, VPA; valproic acid, WES; whole exome sequencing, LCS; Lacosamide, GDD; Global developmental delay, NA; not applicable

CONCLUSION

In summary, our study delineates the spectrum of diseases involving mt-aaRSs deficiency, characterized by variations in the age of epilepsy onset, developmental delay, and epileptic encephalopathy. Clinical features such as the type of seizures, microcephaly, EEG patterns, and MRI findings may not be specific enough to distinguish these cases from other genetic developmental epileptic encephalopathies (DEE). While clinical clues like metabolic acidosis, elevated lactate levels, and family history are not exclusive to mitochondrial diseases, they can raise suspicion and guide further diagnostic investigations. Genetic testing should be considered to confirm the diagnosis in affected individuals.

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CONFLICT OF INTEREST

During the time of submission, Ponghatai Boonsimma is an employee at F.Hoffman La Roche research and early development center

The other authors declare that they have no conflict of interest.