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Tribal Founder *EMC1* Variant in 5 Kuwaiti Families Expands Phenotypic Spectrum of *EMC1*-Related Disorder

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Abstract

Background and Objectives

The endoplasmic reticulum (ER) membrane protein complex is a conserved multisubunit transmembrane complex that enables energy-independent insertion of newly synthesized membrane proteins into ER membranes, mediating protein folding, phospholipid transfer from ER to mitochondria, and elimination of misfolded proteins. The first subunit of EMC (EMC1) is encoded by *EMC1*. Both monoallelic de novo and biallelic *EMC1* variants have been identified to cause cerebellar atrophy, visual impairment, and psychomotor retardation (CAVIPMR) [OMIM #616875]. Eight families with biallelic *EMC1* variants and CAVIPMR have been reported. Here, we describe 8 individuals from 5 Kuwaiti families from the same tribe, with the previously reported homozygous pathogenic missense *EMC1* variant [c.245C>T:p.(Thr82Met)] and CAVIPMR.

Methods

Proband exome sequencing was performed in 3 families, while targeted molecular testing for *EMC1* [c.245C>T:p.(Thr82Met)] variant was performed in the other 2 families based on strong clinical suspicion and tribal origin. Sanger sequencing confirmed variant segregation with disease in all families.

Results

We identified 8 individuals from 5 Kuwaiti families with the homozygous pathogenic *EMC1* variant [c.245C>T:p.(Thr82Met)] previously reported in a Turkish family with CAVIPMR. The variant was absent from Kuwait Medical Genetic Center database, thus unlikely to represent a population founder allelic variant. The average age at symptom onset was 11 weeks, with all families reporting either visual abnormalities, hypotonia, and/or global developmental delay (GDD) as the presenting features. Shared clinical features included GDD (8/8), microcephaly (8/8), truncal hypotonia (8/8), visual impairment (7/7), and failure to thrive (7/7). Other common features included hyperreflexia (5/6; 83%), peripheral hypertonia (3/5; 60%), dysmorphism (3/6; 50%), epilepsy (4/8; 50%), and chorea (3/8; 36%). Brain imaging showed cerebellar atrophy in 4/7 (57%) and cerebral atrophy in 3/6 (50%) individuals.

Discussion

The presence of exact biallelic homozygous *EMC1* variant in 5 Kuwaiti families from the same tribe suggests a tribal founder allelic variant. The clinical features in this study are consistent

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

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Informed consent for the publication of relevant findings and clinical photographs was obtained from the legal guardians of the affected individuals from all families. The research study was approved by the Research and Ethical Committee of the Ministry of Health in Kuwait and was conducted according to the ethical principles of Declaration of Helsinki.

Glossary

AD = autosomal dominant; **AR** = autosomal recessive; **BAEP** = brainstem auditory evoked potential; **EMC** = ER membrane protein complex; **ER** = endoplasmic reticulum; **ERAD** = ER-associated degradation; **ES** = exome sequencing; **GDD** = global developmental delay; **TA** = tail-anchored; **TMH** = transmembrane helix; **VEP** = visual evoked potential.

with the phenotypic spectrum of *EMC1*-associated CAVIPMR in previous reports. The presence of chorea, first noted in this study, further expands the phenotypic spectrum. Our findings emphasize the importance of targeted *EMC1* variant [c.245C>T: p.(Thr82Met)] testing for infants from affected tribe who present with visual impairment, GDD, and hypotonia.

Introduction

The endoplasmic reticulum (ER) is responsible for the biogenesis of integral, or intrinsic, transmembrane proteins (IMPs). Mammals encode ~5,000 IMPs that play key functional roles in organelles and plasma membranes. Their biological function is highly dependent on accurate membrane integration, and precise and efficient insertion of transmembrane proteins, which is guided by ER membrane protein complex (EMC) and other ER-resident factors.[1] The EMC is an evolutionary conserved multifunctional multisubunit transmembrane protein complex.[1] Prokaryotic EMC is composed of 6 subunits while eukaryotic EMC is composed of 10 subunits, namely EMC1–EMC10.[1]

EMC, as an important chaperone for IMP biogenesis, functions as a transmembrane helix (TMH) insertase for many of these multipass IMPs into the ER membrane.[2,3] It also acts as a TMH insertase for a subset of tail-anchored (TA) proteins, which play an essential role in many cellular processes such as vesicular trafficking, apoptosis, signal transduction, and lipid biosynthesis.[4,5] In addition, EMC facilitates the transfer of lipids from the ER to mitochondria, which is necessary for the biogenesis and metabolism of lipids.[4] Furthermore, EMC is a part of the ER-associated degradation (ERAD) pathway that degrades proteins that fail to correctly fold or assemble into ER.[1] Misfolded proteins have been associated with different neurodegenerative processes.[6]

The first subunit of the EMC (EMC1) is ubiquitously expressed including all regions of the brain and has been shown to be necessary for the biosynthesis of rhodopsin in drosophila and for proper glial function.[7,8] *EMC1* was first proposed as a candidate gene for a human disease in 2013 when a family with nonsyndromic retinitis pigmentosa and a rare homozygous variant in *EMC1* was reported.[9] A 2016 study[6] later described 3 families with biallelic variants and 1 family with monoallelic de novo variant and established *EMC1* as a cause for neurodevelopmental disorder characterized by cerebellar atrophy, visual impairment, and psychomotor retardation (CAVIPMR) (OMIM #616875) with both autosomal recessive (AR) and autosomal dominant (AD) inheritance. Five additional families with biallelic variants and 3 individuals with monoallelic de novo variants and CAVIPMR have been reported since, raising the total of families reported to date with this rare disorder to 12 families with affected 17 individuals (8 families with biallelic *EMC1* variants and 4 families with de novo variants).[6,8,10-14] The mode of inheritance in CAVIPMR has been proposed to be dependent on the variant localization and region affected where the variants in all AR cases to date affect 1 of the 2 EMC1 domains, while variants in the AD cases cluster at interdomain region.[8]

In this study, we describe 8 individuals with CAVIPMR from 5 Kuwaiti families from the same tribe with the previously reported homozygous pathogenic missense *EMC1* variant [c.245C>T: p.(Thr82Met)] likely representing a tribal founder allelic variant.[6] This study reports affected individuals with *EMC1*-related disease from the Middle East and North Africa (MENA) region. Our families show the same phenotypic features previously described in association with CAVIPMR in addition to chorea, which was not previously described in CAVIPMR, thus expanding the phenotype of the disease.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents. Genetic Testing and Clinical Information

Proband exome sequencing (ES) was performed through clinical diagnostic laboratories for families 1, and 3–4, while targeted testing was performed in families 2 and 5 based on strong clinical suspicion and tribal origin. A retrospective chart review was performed to delineate the clinical features of the disease. All individuals had documented neurology and genetic assessments conducted by a child neurologist and a geneticist.

Data Availability

All data described in this study are provided within the article and supplementary material. Deidentified clinical data are available from the corresponding authors upon request.

Results

Tables 1 and 2 summarize the perinatal history and clinical features of all affected individuals with the biallelic *EMC1* variants in this study in comparison with the previously

Table 1 Demographics, Perinatal History, Presenting Features and Investigations of the 5 Families With the Founder *EMC1* Variant in This Study

Family and individual	Family 1		Family 2	Family 3		Family 4		Family 5
	Individual 1	Individual 2	Individual 3	Individual 4	Individual 5	Individual 6	Individual 7	Individual 8
Gender	Male	Female	Female	Female	Male	Female	Female	Female
Age (y)	10	5	4	Died at 8	5	8	6	1
Perinatal history								
Gestational age; birth weight	FT; 2.7 kg	FT; N/A	FT; 2.6 kg	FT; 3 kg	FT; 3.7 kg	FT; 2.6 kg	FT; 2.5 kg	FT; 2.19 kg
Mode of delivery	SVD	SVD	LSCS	SVD	SVD	LSCS	LSCS	LSCS
Age at onset	4 mo	3 mo	3 mo	3 mo	3 wk	8 mo	Since birth	1 m
Presenting feature(s)	Poor neck support	Visual inattentiveness	Visual inattentiveness; abnormal eye movements; low tone; seizures	DD; visual inattentiveness; low tone	Visual inattentiveness	DD	DD; squint	Visual inattentiveness
Feature(s) on initial examination	Hypotonia	No social smile; inability to follow light; microcephaly; hypotonia; hyperreflexia	Hypotonia; GDD; hyperlaxity; hip dislocation	N/A	Hypotonia; DD; seizures	N/A	Microcephaly camptodactyly; partial simian crease	Hypotonia; GDD; microcephaly
Growth parameters								
Age at last examination	10 y	4 y	2 y 6 mo	7 y	4 y	3 y	5 y	1 y
Height in cm (SD)	N/A	90 (−2.6)	N/A	88 (−6.4)	N/A	89.5 (−1.3)	N/A	73 (−0.26)
Weight in kg (SD)	15.7 (−3.9)	8.5 (−4.5)	N/A	10.9 (−4.4)	11.5 (−3.3)	10.5 (−2.5)	13 (−2.5)	6.8 (−3.9)
OFC in cm (SD)	46.6 (−4.9)	43 (−4.3)	N/A (<−2)	43 (−6.9)	45 (−3.6)	42 (−4)	45 (−3.8)	41 (−3.4)
Investigations								
Brainstem evoked potential (age)	N/A	Abnormal (5 mo)	Normal (11 mo)	N/A	N/A	N/A	N/A	N/A
Visual evoked potential (age)	Normal (N/A)	Normal (5 mo)	Normal (11 mo)	N/A	N/A	N/A	N/A	N/A
EEG (age)	N/A	N/A	Abnormal (2 y)	Abnormal (14 mo)	Abnormal (1 y)	Normal (8 mo)	Abnormal (3 y)	N/A
Brain MRI (age)	Abnormal (<1 y)	Normal (9 mo)	Abnormal (7 mo)	Abnormal (1 y)	Abnormal (7 mo)	Normal (8 mo)	N/A	Abnormal (7 mo)

Abbreviations: DD = developmental delay; FT = full term; GDD = global developmental delay; LSCS = lower segment Cesarean section; N/A = not available; SVD = spontaneous vaginal delivery.

published studies. Figure 1 shows the extended pedigrees and genotype. Figure 2 shows brain imaging features of selected individuals of the 5 families with *EMC1* p.(Thr82Met) variant. Detailed clinical case reports can be found in the eAppendix.

Clinical Data

All individuals were born to consanguineous marriages from different branches of the same tribe. Parents were either first-degree cousins (families 1–3) or first-degree cousins once removed (families 4 and 5) (Figure 1). Eight children were born full term, delivered by either spontaneous vaginal delivery (4/8; 50%) or by lower Cesarean section (4/8; 50%) due to either breech presentation (family 2, IV-5/S3 and family 5, V-2/S8) or fetal decelerations (family 4, V-2/S6).

The average reported age at symptom onset was 11 weeks (range: birth to 8 months). The initial parental concern at presentation was visual inattentiveness in 5 individuals (5/8:

Table 2 Summary of the Clinical Features of All Affected Individuals With the Biallelic *EMC1* Variants in This Study and all Previously Published Studies

	Biallelic cases																					Monoallelic cases					
Study[a]	This report									Harel et al., 2016						Geetha et al., 2018	Cabet et al., 2020	Wang et al., 2023		Bryen et al., 2023	Dai et al., 2024		Harel et al., 2016	Chung et al., 2022			Other reports	Total
Family	F1		F2	F3		F4		F5	Total (this report)	F6	F7			F8		F9	F10	F11		F12	F13		F14	F15	F16	F17		
Subject	S1	S2	S3	S4	S5	S6	S7	S8		S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	S24	S25		25
Age (y)	10	5	4	8	5	8	6	1		4	13	5	3	10	12	4	10	4	1.3	7	Prenatal	Prenatal	11	4	15	5		
Ethnicity/ origin	KWT									EUR	TUR			SA		IND	EUR	CHN		MOA/SAM	CHN		N/A	N/A	N/A	N/A		
Variant (c.DNA)	c.245C>T									c.2619 2622del TCCT	c.245C>T			c.2602G>A		c.1212+ 1G>A	c.1134C>A; c.2858T> C	c.765_c.777delins ATTCTACTT; c.2376G>A		c.287-1G>A; c.2588-771C>G	c.245C>T; c.1459delC		c.1411 G>C	c.1745C>A	c.1745C>G	c.1751C>A		
Zygosity	Hmz			Hmz	Hmz		Hmz	Hmz		Hmz	Hmz			Hmz		Hmz	Comp het	Comp het		Comp het	Comp het		Het (de novo)	Het (de novo)	Het (de novo)	Het (de novo)		
Amino acid change	P. Thr82Met									p.Pro874	p.Thr82 Met			p.Gly868 Arg		p.Arg404Valfs*43	p.Tyr378*; p.Phe953Ser	p.Leu256fs*10); p.Val792fs*31		p.Asp96Glyfs*45, p.Asp96Glufs*22, p.Asp96Valfs*14, p.Asp96_ Gly103del; p.Ile863Lysfs*27	p.Thr82Met; p.Arg487Alafs*49		p.Gly471 Arg	p.Pro58 2His	p.Pro582 Arg	p.Pro58 4His		
GDD/ID	+	+	+	+	+	+	+	+	8/8	+	+	+	+	+	+	+	+	+	N/A	+	N/A	N/A	+	+	+	+	14/14	22/22
Truncal hypotonia	+	+	+	+	+	+	+	+	8/8	+	+	+	+	+	−	+	+	+	+	+	N/A	N/A	+	+	+	+	14/15	22/23
Visual impairment	N/A	+	+	+	+	+	+	+	7/7	+ (C)	+ (abnormal ERG)	+ (abnormal ERG)	+ (abnormal ERG)	+	N/A	+	+	+ (RD)	N/A	+ (C)	N/A	N/A	+	+ (C)	+ (C)	+ (C)	13/13	20/20
Scoliosis	N/A	−	N/A	+	N/A	+	N/A	+	3/4	+	+	+	+	+	−	+	−	−	N/A	−	N/A	N/A	+	+	+	−	9/14	12/18
Dysmorphism	+	+	N/A	+	N/A	−	−	−	3/6	+	+	+	+	+	+	+	−	−	N/A	−	N/A	N/A	+	+	−	−	9/14	12/20
Cerebellar atrophy	+	−	+	+	−	−	N/A	+	4/7	+	+	+	+	+	N/A	+	−	−	−	+	N/A	N/A	+	+	−	+	10/14	14/21
Microcephaly	+	+	+	+	+	+	+	+	8/8	−	+	+	+	−	−	+	−	−	−	+	N/A	N/A	−	−	+	−	6/15	14/23
Cerebral atrophy	−	−	+	N/A	+	−	N/A	+	3/6	+	+	+	+	−	−	+	−	−	−	−	N/A	N/A	+	−	+	−	7/15	10/21
Peripheral hypertonia	N/A	+	N/A	+	−	+	N/A	−	3/5	+	+	+	+	−	−	−	−	N/A	N/A	N/A	N/A	N/A	−	+	+	−	6/12	9/17
Epilepsy	−	−	+	+	+	−	+	−	4/8	−	−	−	−	−	−	+	−	−	N/A	−	N/A	N/A	−	+	+	+	4/14	8/22
Hyperreflexia	N/A	+	+	+	+	+	N/A	−	5/6	−	−	−	−	N/A	N/A	−	N/A	N/A	N/A	−	N/A	N/A	−	−	−	+ (LE)	1/10	6/16
Hyporeflexia	N/A	−	−	−	−	−	N/A	−	0/6	+	+	+	+	N/A	−	+	−	N/A	N/A	+	N/A	N/A	+	+	+	+ (UE)	10/12	10/18
Dystonic posture	−	−	−	+	+	−	−	−	2/8	+	+	+	+	−	−	+	−	N/A	N/A	N/A	N/A	N/A	−	+	+	−	7/12	10/20

Continued

Table 2 Summary of the Clinical Features of All Affected Individuals With the Biallelic *EMC1* Variants in This Study and all Previously Published Studies *(continued)*

	Biallelic cases																						Monoallelic cases					
Study[a]	This report								Harel et al., 2016				Geetha et al., 2018		Cabet et al., 2020	Wang et al., 2023	Bryen et al., 2023		Dai et al., 2024		Harel et al., 2016		Chung et al., 2022			Other reports	
Family	F1		F2	F3		F4		F5	Total (this report)	F6	F7			F8		F9	F10	F11	F12		F13		F14	F15	F16	F17		
Subject	S1	S2	S3	S4	S5	S6	S7	S8		S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	S24	S25		Total
Hearing impairment	+	+	–	N/A	N/A	N/A	N/A	N/A	2/3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2/3
FTT	+	+	+	+	+	N/A	+	+	7/7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	7/7
Chorea	+	–	–	–	+	–	+	–	3/8	–	–	–	–	–	–	–	–	N/A	N/A	N/A	N/A	N/A	–	–	–	–	0/12	3/20	

Abbreviations: C = cortical; CHN = Chinese; Comp het = compound heterozygous; ERG = electroretinogram; EUR = Europe; FTT = failure to thrive; GDD = global developmental delay; HET = heterozygous; HMZ = homozygous; ID = intellectual disability; IND = India; KWT = Kuwait; LE = lower extremities; MAO = Māori; N/A = not available; RD = retinal dystrophy; SA = Saudi Arabia; SAM = Samoan; TUR = Turkish = UE = upper extremities.
[a] The study conducted by Abu Safieh et al. is not listed in Table 2 because the reported variant is considered variant of uncertain significance and not linked to the reported phenotype.

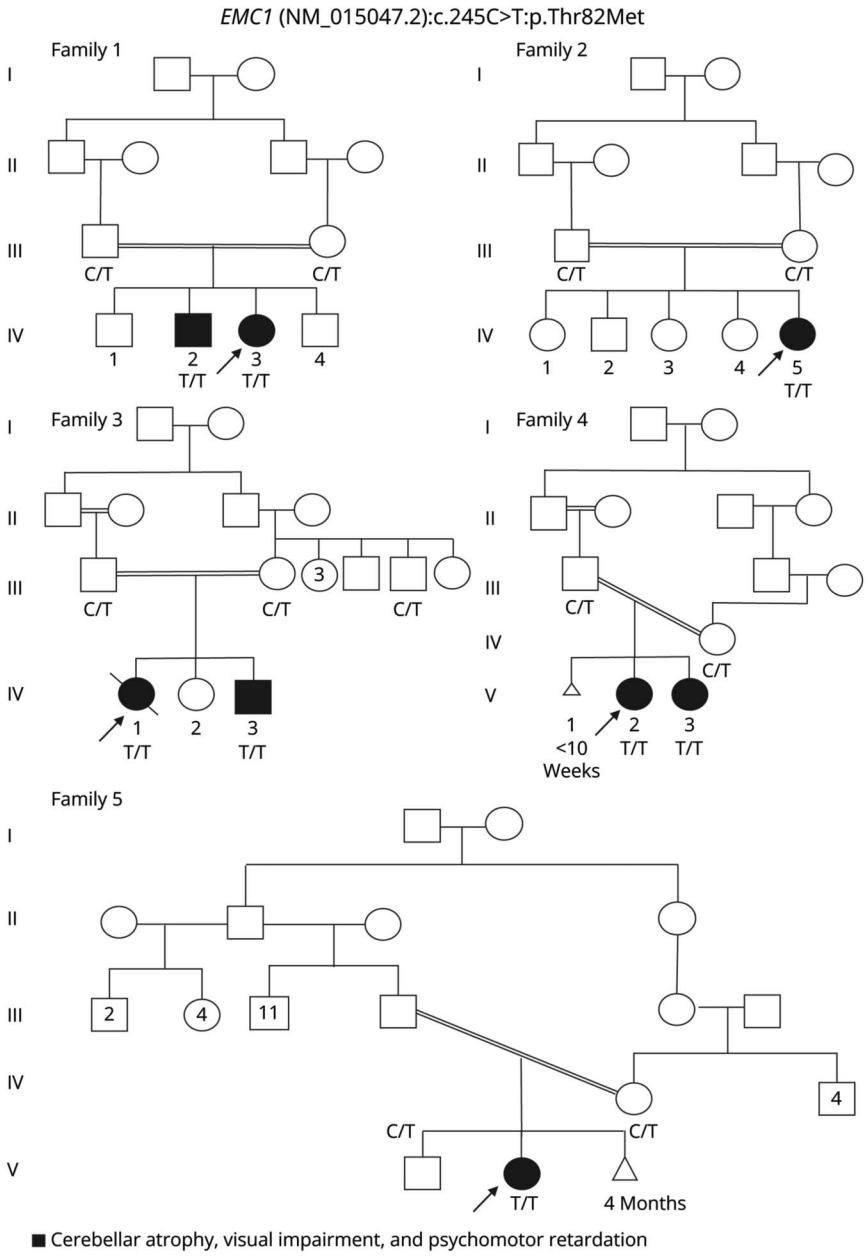
63%), low tone or poor head support in 3 individuals (3/8; 38%), and/or developmental delay compared with older siblings or peers in 3 individuals (3/8; 38%). One family (family 2, IV-5) reported seizures as one of the features at the initial presentation. Documentation of initial neurologic examination was available in 6/8 individuals. On the initial examination by a child neurologist, the most common observed features were generalized hypotonia (5/6 individuals, 83%), developmental delay (4/6 individuals; 67%), microcephaly (3/6 individuals; 50%) and GDD/DD (3/6 individuals; 50%). Less common features at initial examination were brisk reflexes (family 1, IV-3/S2) (1/6; 17%), hyperlaxity, hip dislocation (family 2, IV-5/S3) (1/6; 17%), camptodactyly, and partial simian crease (family 4, V-3/S7) (1/6; 17%).

Shared clinical features that developed over time included global developmental delay (GDD) (8/8), microcephaly (8/8), truncal hypotonia (8/8), visual impairment (7/7), and failure to thrive (7/7). Other common features included hyperreflexia (5/6; 83%), kyphoscoliosis (3/4; 75%), peripheral hypertonia (3/5; 60%), hearing impairment (2/3; 67%), dysmorphism (3/6; 50%), epilepsy (4/8; 50%), short stature (2/4; 50%), and chorea (3/8; 36%). Sequential head circumference measurements were available in only 3 individuals (individual family 1, IV-3/S2, family 3, IV-1/S4, and family 4, V-3/S7) and showed that microcephaly was progressive in nature. Less common features included gastroesophageal reflux disease (2/8, 25%), hip dislocation (2/8; 25%), and squint (2/8; 25%). Features that were seen in one individual each included pectus excavatum, first-degree heart block, nystagmus, stridor, and constipation.

Seizure types included tonic seizures in 3 individuals (family 2, IV-5/S3, family 3, IV-1/S4, and family 3, IV-3/S5) and myoclonic seizures in 2 individuals (family 2, IV-5/S3 and family 4, V-3/S7). Two individuals (family 3, IV-3/S5 and family 4, V-3/S7) were on monotherapy, while 2 others were on polytherapy (family 2, IV-5/S3 and family 3, IV-1/S4). Antiepileptic medications used include valproic acid in 3 individuals, levetiracetam in 2 individuals, and clobazam and zonisamide in one individual with variable response, and no specific antiepileptic medication being particularly effective.

EEG was performed in 5 individuals and was normal in 1 (family 4, V-2/S6). The EEG was abnormal in the other 4 individuals showing epileptiform discharges (focal or multifocal) in 3 individuals and slow background activity in 3 individuals. Visual and brainstem auditory evoked potentials (VEP and BAEP, respectively) were performed on 3 and 2 individuals, respectively. Abnormalities on brainstem evoked potential were noted in 1 individual (family 1, IV-3/S2) showing findings consistent with moderate-to-severe sensorineural hearing loss, while VEP was normal in all 3 individuals. None of our individuals had electroretinogram (ERG) performed to evaluate retinal alterations, and all our individuals were presumed to have cortical visual impairment. An electromyogram was performed in 2 individuals: normal in 1 individual (family 5, V-2/S8) and abnormal and consistent

Figure 1 Pedigrees in Families 1–5 With Biallelic *EMC1* Founder p.(Thr82Met) Variants



Pedigrees of the 5 families described. Square = male; circle = female; black filled symbol = affected individual; white symbols = unaffected individuals. Double lines indicate consanguinity. Genotype of tested individuals are indicated under the individuals.

with myopathic pattern (family 3, IV-1/S4) in the other individual. Her muscle biopsy, however, showed normal histopathology and normal muscle respiratory chain enzyme complexes I–VI analysis.

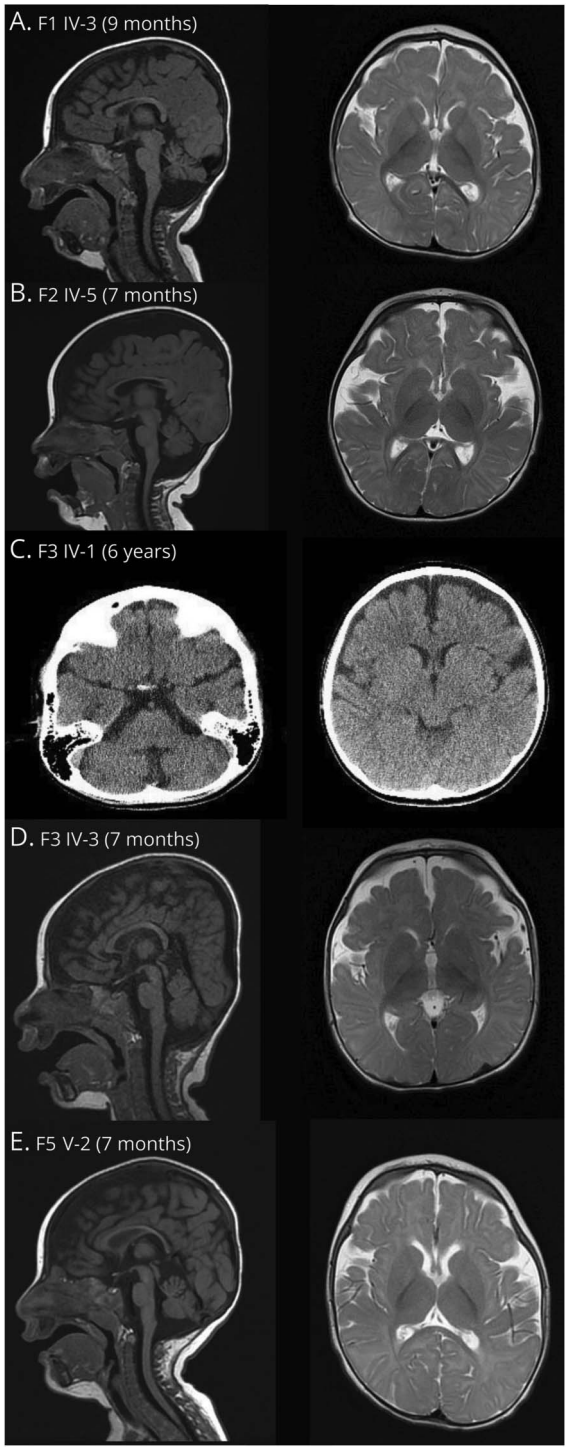
Brain MRI was obtained in 7 individuals and was abnormal in 5 individuals (5/7; 71%) (Figure 2). Four individuals had mild cerebellar atrophy (4/7, 57%) at ages 7 months to 1 year, and 3 individuals had cerebral atrophy (3/6; 50%). Benign enlargement of subarachnoid space in temporal and frontal regions was observed in 2 individuals. Other findings observed in 1 individual each were wide extra-axial spaces, subtle optic nerve and chiasm prominence, and subtle posterior plagiocephaly.

Genetic Data

ES was performed through clinical diagnostic laboratories for probands from families 1 (individual S2) and 3–4 (individuals S4 and S6, respectively), while targeted testing was performed in the proband from families 2 and 5 (individuals S3 and S8, respectively) based on strong clinical suspicion and tribal origin. Segregation study was performed on each family and confirmed that affected siblings in families 1, 3, and 4 were also homozygous for the variant, while parents in all families were heterozygous carriers conforming with Mendelian expectations.

Genealogic analysis suggested these families shared a common ancestor, as evident by their tribal affiliation and strict

Figure 2 Neuroimaging Findings in Families 1–5 With Biallelic *EMC1* Founder p.(Thr82Met) Variants



(A) Brain MRI of family 1, individual IV-3 at 9 months. T1 Mid-sagittal view (left) and T2 axial view (right) showing benign enlargement of subarachnoid space in temporal and frontal regions. (B) Brain MRI of family 2, individual IV-5 at 7 months. T1 Mid-sagittal view (left) and T2 axial view (right) showing wide extra-axial spaces, prominent cerebellar folia, and cerebellar atrophy. (C) Brain CT of family 3, individual IV-1 at 6 years showing a normal cerebellar parenchyma (left) and normal brain parenchyma (right). Note that subtle cerebellar atrophy was seen on brain MRI (not shown here). (D) Brain MRI of family 3, individual IV-3 at 7 months. T1 Mid-sagittal view (left) and T2 axial view (right) showing cerebral atrophy. (E) Brain MRI of family 5, individual V-2 at 7 months. T1 Mid-sagittal view (left) and T2 axial view (right) showing mild cerebral and cerebellar atrophy.

endogamy. Three of the families originated from the same branch of the tribe, and the other 2 families were from 2 different branches of the same tribe. Haplotype analysis was not possible because these families had their genetic testing in different laboratories, thus restricting the access to the raw data for further analysis.

Discussion

In this study, we describe 5 families from the same Kuwaiti tribe with the same *EMC1* variant p.(Thr82Met), suggesting a possible founder allelic variant. Symptoms in our participants included visual impairment, microcephaly, truncal hypotonia, peripheral hypertonia, hyperreflexia, movement disorder in the form of chorea, epilepsy, GDD, failure to thrive (FTT), dysmorphism, as well as cerebellar and cerebral atrophy shown on brain imaging. Table 2 summarizes the clinical features of our individuals in comparison with all previously published cases with *EMC1*-related disorder.

GDD and visual impairment were universal findings in all individuals identified to date with *EMC1*-related disorders (including the 8 new participants included here). However, while the retinal impairment of 4 individuals either as evident by abnormal ERG (the 3 Turkish siblings with the same variant, as in our case)[6] or by recognized retinal dystrophy,[12] none of our individuals had ERG performed when 3 of them had normal VEP to reliably determine the origin of the visual impairment, which is a limitation of our study. Truncal hypotonia was identified in all individuals assessed to date except for 1 previously published case (22/23 cases).

Other common features noted in our individuals similar to the previously published cases are microcephaly, epilepsy, peripheral hypertonia, cerebral atrophy, dysmorphism, and scoliosis. Yet, some of these clinical features were noted at different prevalence in our individuals compared with previously reported cases.

Microcephaly, for example, was noted in all 8/8 (100%) of our individuals compared with 6/15 (40%) of the previously published cases. This could be due to the type of variant, which may suggest an emerging genotype-phenotype correlation, or the age-dependent nature of microcephaly. Microcephaly was noted in the 3 Turkish siblings with the same variant described in this study, but in contrast to most of our participants who had hyperreflexia and epilepsy, the Turkish siblings had hyporeflexia and lacked the history of epilepsy. The ages of previously published cases ranged from prenatal to 15 years, closer to the age range of our participants (Table 2), although the age at which the head circumference was recorded was not always available. By examining the available serial head circumference measurements in previous reports, 1 of the 9 previously published cases without microcephaly was showing a progressive decline in their head circumference while 2 others had borderline head circumference

measurement (3–10% percentile) at 9–18 months, which is still above threshold for the diagnosis of microcephaly (~<3rd centile for age; −2 SD).[8] A progressive decline in head circumference, consistent with postnatal/progressive microcephaly, was seen in 3 of our participants who had serial measurements consistent with this observation (family 1, IV-3/S2, family 3, IV-1/S4, and family 4, V-3/S7; see eAppendix).

Similarly, cerebellar atrophy was not a common feature observed in our participants. It was identified in 4/7 (57%) of our participants in comparison with 10/14 (71%) of the previously published cases. This contrasts with cerebral atrophy, which was noted in 3/6 (50%) of our participants, closer to the previously published cases (7/15; 46%). Cerebral and cerebellar atrophy possibly develop over time, considering the progressive nature and potential neurodegenerative process accompanying *EMC1*-related disease. Chung et al.[8] have shown that EMC1 impairment leads to glial dysfunction. Glial dysfunction has been linked to several neurodegenerative diseases.[15] Our participants had their brain imaging between 7 month and 1 year, probably early before such neuroimaging features were all evident, and follow-up neuroradiologic studies were not available in any of the individuals to confirm.

In our study, we describe the early clinical signs of the disease. Most of the individuals were first brought to medical attention due to concerns for visual impairment, low tone, and developmental delay, which were often confirmed on clinical examination along with microcephaly. Such findings, when observed in individuals from same tribe in our region, should prompt targeted testing for this tribal founder variant. In addition, new clinical features that were commonly observed in our participants and not described in previously published cases with *EMC1*-related disorder were FTT (7/7; 100%), hyperreflexia (5/6; 83%), and chorea (3/8 individuals; 36%). By contrast, previously reported cases were described to have diminished deep tendon reflexes (10/12; 83%), which was not observed in our participants. Furthermore, dystonic movements were more common in the previous cases (7/12; 58%) compared with our cases in which it was observed only in 2/8 individuals (25%). Both dystonia and chorea are movement disorders that implicate the basal ganglia, possibly attributed to the ubiquitous expression of EMC1, including all regions of the brain. To gain a deeper understanding of the characteristics of this disease, it will be necessary to conduct more comprehensive studies on its natural history and follow-up patients over a long period. In addition, it is important to study diverse populations to fully comprehend the range of clinical manifestations and the impact of various variants on the development of *EMC1*-related disorder.

A total of 14 variants have been reported so far, including 11 biallelic variants and 3 monoallelic de novo variants that have been associated with CAVIPMR.[6,8,10,11] There are several examples of diseases inherited as both autosomal dominant and autosomal recessive manners.[16,17] EMC1 has 2 main domains, the quinoprotein alcohol dehydrogenase–like domain (PQQ-like) domain and an uncharacterized domain of unknown function 1620 (DUF1620).[8] The 2022 study showed that the mode of inheritance of the disease depends on EMC1 protein region to which the variant localizes. All biallelic variants (both missense and complete loss of function variants) affect 1 of the 2 main EMC1 domains and are associated with autosomal recessive inheritance, while the de novo monoallelic variants (all missense variants) cluster at interdomain region at the edge of a β-strand within a β-propellar, possibly leading to protein misfolding or affecting interaction with other proteins, and account for autosomal dominant inheritance.[8] The p.Thr82Met variant, described in this study, is 1 of the 2 variant affecting the PQQ-like domain.[8,12] This observation should be further evaluated in future allelic series.

All families described in this study were found to have the same homozygous pathogenic *EMC1* variant [c.245C>T: p.(Thr82Met)] and originate from the same large tribe, thus likely representing a founder allelic variant. Unfortunately, the unavailability of raw data from the different clinical laboratories where genetic testing was conducted for our participants posed a challenge in conducting haplotype analysis. Founder variants are disease-causing variants frequently occurring in groups or subgroups that are or were geographically and/or culturally isolated and in which a common ancestor had the variant.[18] While some disease allelic variants characterized by the ancestral population may vanish due to natural selection, alterations with weaker effect may survive for a long time and have the potential to enhance the prevalence of some rare conditions such as those causing autosomal recessive disease traits.[19,20] Several studies from Saudi Arabia showed that 30%–40% of the detected variants in genetic cases are caused by a founder variant.[21,22] Consanguinity is a common practice in Kuwait, reaching up to 56%, similar to other areas of the MENA region, thus predisposing the population to pathogenic private and founder variants and their deleterious effects.[20,23] The founder effect is further enhanced by the common occurrence of tribal unions. Founder variants in the region have contributed to several gene discoveries and improved the understanding of different diseases. For example, a founder variant in *ADAT3* in 4 unrelated Saudi families led to the discovery of a rare form of autosomal recessive intellectual disability with subsequent additional reported cases leading to an improved understanding of the disease.[24,25] Similarly, several founder variants have been reported in Kuwaiti families such as a *DNAI2* tribal founder variant associated with primary ciliary dyskinesia and *SLC19A3* Arab founder variant associated with biotin-thiamine responsive basal ganglia disease.[26,27]

In conclusion, our data expand the phenotypic spectrum of *EMC1*-related CAVIPMR and add to the global efforts to understand this rare disease. This is the first study in Kuwait and MENA region describing new cases of *EMC1*-related disorder, increasing the number of reported cases to 25. Furthermore, our study highlights the importance of targeted molecular testing for Kuwaiti individuals suspected to have

EMC1-related disorder, which could potentially be included in future national premarital screening programs. Studying additional cases from diverse populations can further enhance our knowledge of the disease's full spectrum.

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