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RESEARCH ARTICLE

EMC10 Gene Variants May Cause Dual Molecular Effects on the Neuropsychiatric Disease Pattern

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ABSTRACT

The *EMC10* gene on chromosome 19 encodes one of the highly conserved endoplasmic reticulum membrane complexes (EMC). Specific mutations in *EMC10* cause a disorder known as neurodevelopmental disorder with dysmorphic facies and variable seizures (NEDDFAS) (OMIM #619264), characterized by global developmental delay and dysmorphic facial features, which become apparent in early childhood. This study aims to present the clinical data associated with a novel variant of a patient diagnosed with NEDDFAS (OMIM #619264), a condition rarely reported in the literature. By examining the phenotypic implications and molecular mechanisms of pathogenic variants in the *EMC10* gene, this study seeks to contribute to a better understanding of the genetic and clinical spectrum of the disease. Our case was followed up in the Child and Adolescent Psychiatry clinic with the diagnosis of intellectual disability. Initial genetic testing included karyotype analysis, *FMR1* CGG repeat analysis, and chromosomal microarray analysis. Subsequently, whole-exome sequencing (WES) was performed, and Sanger sequencing was used to confirm the identified variant and conduct familial segregation analysis. We identified a novel homozygous frameshift variant in the *EMC10* gene, NM_206538.4:c.431del, resulting in NP_996261.1:p.Asp144AlafsTer3 using WES. This variant was classified as pathogenic (P) according to ACMG criteria, which was clinically relevant to the patient's condition. Segregation analysis revealed that both the mother and the father were heterozygous carriers of this variant. To date, the phenotype associated with this variant has been reported in 31 individuals from 16 different families. To our knowledge, our case is the first reported patient in the Turkish population carrying an *EMC10* gene variant. Among reported cases, variations in symptom distribution and severity have been observed. We propose that *EMC10* gene variants may exhibit dual molecular effects. There are two types of neurodevelopmental clinical presentations: (1) a classic disease pattern with mild-to-moderate intellectual disability (ID) and no neurological findings and (2) a progressive disease pattern with severe ID, hypotonia, and abnormalities in gait.

1 | Introduction

The *EMC10* gene, located on chromosome 19, encodes one of the components of the evolutionarily conserved endoplasmic reticulum membrane complex (EMC), which plays a critical role in membrane protein biology (Shao et al. 2021). The EMC resides in the endoplasmic reticulum (ER) membrane and contributes to the regulation of cellular processes such as protein folding, ER stress, membrane protein trafficking, and degradation (Chen et al. 2024). Additionally, the EMC has been shown to facilitate interactions between the mitochondria and ER, thereby regulating the processing and folding of various proteins (Lahiri et al. 2014).

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Recent studies have revealed diverse biological functions of *EMC10*. Research using animal models has demonstrated the effects of *EMC10* on reproductive functions, energy homeostasis, and neurological processes. It has been reported that *EMC10* -/- mice exhibit normal survival rates and an overall healthy phenotype; however, males are completely infertile, while females show reduced fertility (Zhou et al. 2018). Studies on the role of *EMC10* in energy metabolism suggest that this protein may be associated with obesity and metabolic diseases (Chen et al. 2024). Furthermore, *EMC10-null* mice have been shown to display neurological and behavioral abnormalities, including abnormal vocalization, gait disturbances, increased anxiety, and deficits in memory and learning (Shao et al. 2021).

Genetic studies have identified pathogenic variants in the *EMC10* gene associated with neurodevelopmental disorders. Specific mutations in *EMC10* have been found to disrupt unfolded protein response (UPR) homeostasis, leading to a novel neurodevelopmental disorder characterized by intellectual disability, language impairment, seizures, and dysmorphic facial features (Chen et al. 2024). This disorder, termed neurodevelopmental disorder with dysmorphic facies and variable seizures (NEDDFAS) (OMIM #619264), follows an autosomal recessive inheritance pattern and is characterized by global developmental delay and dysmorphic facial features that become apparent in early childhood. Additional features such as seizures, brain imaging abnormalities, mild skeletal defects, and renal anomalies have also been described (Shao et al. 2021).

This study aims to present the clinical data and a novel variant associated with a patient diagnosed with NEDDFAS (OMIM #619264), a condition rarely reported in the literature. By addressing the phenotypic manifestations and molecular mechanisms of pathogenic *EMC10* variants, this study seeks to contribute to a better understanding of the genetic and clinical spectrum of the disease.

2 | Materials and Methods

2.1 | Patient

For this study, ethical approval was obtained from the Balıkesir University Ethics Committee on March 25, 2025, with decision number 2025/154. Written informed consent was obtained from the patient's legal guardians.

The case, which was followed up in the Child and Adolescent Mental Health and Diseases clinic with diagnoses of speech delay and intellectual disability, was referred to our department for the investigation of a genetic etiology. The patient's file, findings, physical examination results, and family pedigree were evaluated. The clinical evaluation of the case was conducted jointly by a clinical geneticist and a child psychiatrist.

2.2 | Genetic Testing

Genomic DNA was isolated from leukocytes in the peripheral blood of the patient and their parents. The first step of the genetic analyses included karyotype analysis, FMR1 CGG repeat analysis, and chromosomal microarray analysis. Subsequently, whole-exome sequencing (WES) analysis was performed on the patient. The detected variant was validated, and segregation analysis within the family was conducted using the Sanger sequencing method.

Genomic DNA was automatically isolated using the HiPurA pre-filled clinical multi-purpose nucleic acid purification kit and HIMEDIA InstaN Mag-96. DNA concentration analysis was performed using Qubit (Thermo Fisher Scientific, USA). WES was conducted using the Roche KAPA HyperExome 96 rxn kit with MGI DNBSEQ-G400. FastQ files were analyzed using the Genomize SEQ platform, version 8.7.0.

2.3 | Variant Analysis and Classification

Raw data were analyzed using the Genomize (https://seq.genomize.com) data analysis platform. Two main filtering steps were applied to identify pathogenic variants associated with clinical features: (1) filtering out all nonsense, missense, frameshift, splice site, indel, in-frame, and synonymous variants and (2) selecting variants with a minor allele frequency <1.0% in population studies (1000 Genome [1000G], ESP, ExAC, and Genome Aggregation Database [gnomAD]).

The Genome Integrative Viewer was used to visualize sequencing data. Novel variants were queried in the HGMD and ClinVar (http://ncbi.nlm.nih.gov/clinvar) databases for validation, and their pathogenicity was assessed using in silico analysis tools (Mutation Taster, Combined Annotation Dependent Depletion [CADD]).

Variant pathogenicity classification was performed according to the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al.2015). Finally, segregation analysis was conducted using DNA samples obtained from available family members.

3 | Results

Our case was an 8-year-old male child who was referred to our clinic from the child psychiatry department for the evaluation of delayed speech etiology. Prenatal follow-ups revealed no complications, and he was born via cesarean section at 41 weeks of gestation, weighing 3600 g (0.17 SD) and measuring 50 cm (−0.53 SD) in length. His developmental stages were as follows: he established eye contact at 2 months, sat unsupported at 8 months, walked independently at 17 months, spoke his first word at 10 months, formed two-word phrases at 6 years, and had not yet developed fluent speech. Toilet training was completed at 3 years of age. He had been receiving special education since the age of 2.5 years.

Due to delays in speech and walking, he was evaluated in the pediatric neurology clinic. Although he had no history of seizures, an EEG performed due to neuromotor developmental delay revealed epileptiform activity, while brain MRI findings were normal. He had been on levetiracetam (200 mg) for the past 2 years.

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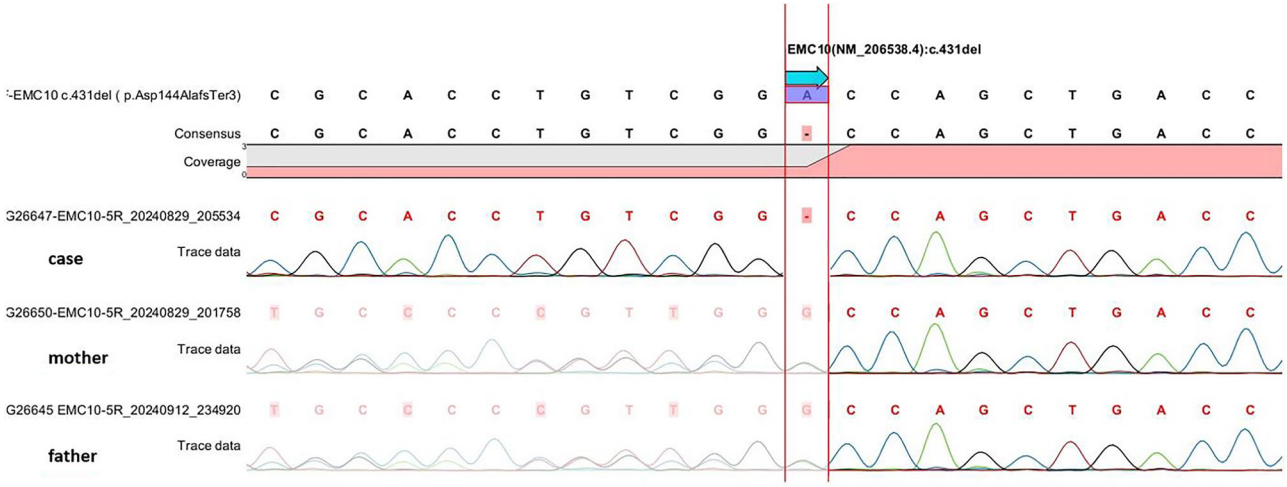

FIGURE 1 | Results of the segregation analysis of the entire family.

Psychiatric evaluation revealed that the patient was diagnosed with mild intellectual disability. Also, worsened expressive language skills were detected compared to receptive language skills. Clinical findings of our case and previous reports associated with *EMC10* gene variants are presented in Table 1.

3.1 | Genetic Results

Genetic analyses, karyotype, FMR1 CGG repeat analysis, and microarray analysis were evaluated as usual. We identified a novel homozygous frameshift variant in the *EMC10* gene, NM_206538.4:c.431del, resulting in NP_996261.1:p.Asp144AlafsTer3 using WES. This variant was classified as pathogenic (P) according to the ACMG criteria. Evolutionary conservation analysis showed that the affected locus is highly conserved, with phyloP100way: 4.229 and PhastCons100way: 1.0. As of March 2025, this variant had not been reported in the gnomAD population database or ClinVar database. Segregation analysis in the family revealed that both parents were heterozygous carriers of the variant (Figure 1). Exon locations of the *EMC10* gene variants for our case and the previous reports are presented in Figure 2.

4 | Discussion

In this study, we presented a homozygous frameshift variant of the *EMC10* gene, NM_206538.4:c.431del (NP_996261.1:p.Asp144AlafsTer3) identified by the WES analysis. This variant is not listed in the gnomAD or ClinVar databases and has not been previously reported in the literature. To date, 19 pathogenic and six likely pathogenic variants have been reported for the *EMC10* gene in the ClinVar database.

An *EMC10* gene variant was associated with neurodevelopmental disorder in 2020 in a male and female sibling born to consanguineous Saudi Arabian parents (Umair et al. 2020). Two other studies reported 13 patients from seven unrelated families of Middle Eastern descent and 10 affected individuals from six unrelated families in 2021 and 2022, respectively (Kaiyrzhanov et al. 2022; Shao et al. 2021). To date, the *EMC10*-related phenotype has been described in 31 individuals from 16 families (Haddad-Eid et al. 2022; Kaiyrzhanov et al. 2022; Shao et al. 2021; Umair et al. 2020). To the best of our knowledge, our case represents the first reported individual carrying an *EMC10* gene variant in the Turkish population.

The severity and distribution of symptoms vary among reported cases. We presented detailed clinical findings of our case and a comparison with the previous literature in Table 1. About 10% of cases in the literature present with a moderate-to-severe intellectual disability (ID) phenotype, often accompanied by additional neurological clinical findings such as inability to walk, ataxia, and hypotonia. Furthermore, some studies reported that the disease may exhibit a progressive course. Kaiyrzhanov et al. (2022) described 10 cases from six affected families, where hypotonia and gait abnormalities were observed in four individuals. They also noted a progressive disease pattern in four cases (moderate progression pattern for three cases and slow progression for one case), suggesting a potential neurodegenerative component in the more severely affected individuals (Kaiyrzhanov et al. 2022). Our patient exhibited mild-to-moderate intellectual disability without neurological findings and did not show disease progression.

We suggest that *EMC10* gene variants may present dual molecular effects, leading to two distinct neurodevelopmental phenotypes: (1) a progressive disease course characterized by severe ID and neurological abnormalities such as hypotonia and gait disturbances and (2) a classic disease pattern presenting with mild-to-moderate ID without neurological findings. Our patient's phenotype aligns with the latter category, as he demonstrated mild-to-moderate intellectual disability with preserved motor functions and no evidence of ataxia or hypotonia. In addition, he did not present any sign of a progressive disease pattern. However, the underlying mechanisms contributing to these phenotypic variations remain unclear.

In addition to ID, *EMC10* variants have been associated with impairments in language functions (Haddad-Eid et al. 2022). Our patient exhibited significant language developmental delay, with expressive language skills markedly weaker than receptive

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TABLE 1 | *EMC10*-related neurodevelopmental disorder: Clinical and laboratory features.

			Haddad-Eid et al. (2022)	Kaiyrzhanov et al. (2022)	Shao et al. (2021)	(Umair 2023)
		CASE	Five cases from one family	Ten cases from six families	Thirteen cases from seven families	Two cases from one family
Variant	ACMG classification	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic
Epidemiological data	Ethnic group	Turkish	Bedouin	Egyptian, Bedouin, Persian, Azerbaijani, Bukharian	Saudi, Arab, Bedouin	Saudi
	Gender	M	F,M	F,M	F,M	F,M
	Current age	8	Youngest: 7 year Oldest: 18 years	Youngest: 4 years Oldest: 28 years	Youngest: 7 years Oldest: 10 years	Youngest: 13 years Oldest: 16 years
	Consanguinity/family history	−	5/5	10/10	13/13	2/2
Growth and development	Preterm birth	−	Unknown	4/10	0/13	0/2
	Low birth weight	—	Unknown	2/10	0/13	0/2
	Low weight	−1.85 SD	Unknown	7/10	0/13	0/2
	Microcephaly (congenital or acquired)	+	Unknown	5/10	0/13	0/2
	Progression type (rapid, moderate, slow)	NP	Unknown	3/10 Moderate 1/10 Slow 6/10 NP	NP	NP
	DD/ID (severity)	+ (Mild-Moderate)	5/5 (mild-moderate)	3/10 (moderate-severe) 7/10 (mild-moderate)	12/13 (Mild-Moderate)	2/2 (mild-moderate)
	Failure to thrive	—	5/5	3/10	4/13	0/2
	Developmental regression	—	0/5	3/10	0/13	0/2

(Continues)

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TABLE 1 | (Continued)

		CASE	Haddad-Eid et al. (2022) Five cases from one family	Kaiyrzhanov et al. (2022) Ten cases from six families	Shao et al. (2021) Thirteen cases from seven families	(Umair 2023) Two cases from one family
Neurological symptoms	Inability to walk	—	0/5	3/10	0/13	0/2
	Dysarthria	—	0/5	6/10	0/13	0/2
	Speech delay	+	5/5	7/10	0/13	0/2
	Axial hypotonia	—	0/5	4/10	3/13	0/2
	Peripheral hypotonia	—	0/5	5/10	0/13	0/2
	Poor head control	—	0/5	4/10	0/13	0/2
	Trunk ataxia	—	0/5	3/10	0/13	0/2
	Hyperkinetic/hypokinetic movement disorders	—	0/5	4/10	0/13	2/2
	Ataxic/uncoordinated gait	—	0/5	4/10	0/13	0/2
	Seizures/EEG findings	-/+	2/5	4/10	6/13	1/2
Other systems and investigations	Facial dysmorphism	+	5/5	10/10	13/13	2/2
	Arachnodactyly	—	0/5	8/10	3/13	0/2
	Elevated PTH	—	Unknown	2/10	3/13	0/2
	Urinary system anomalies	—	3/5	Unknown	Unknown	Unknown

Abbreviations: DD, developmental delay; F, female; ID, intellectual disability; M, male; NP, nonprogressive; PTH, parathyroid hormone; SD, standard deviation.

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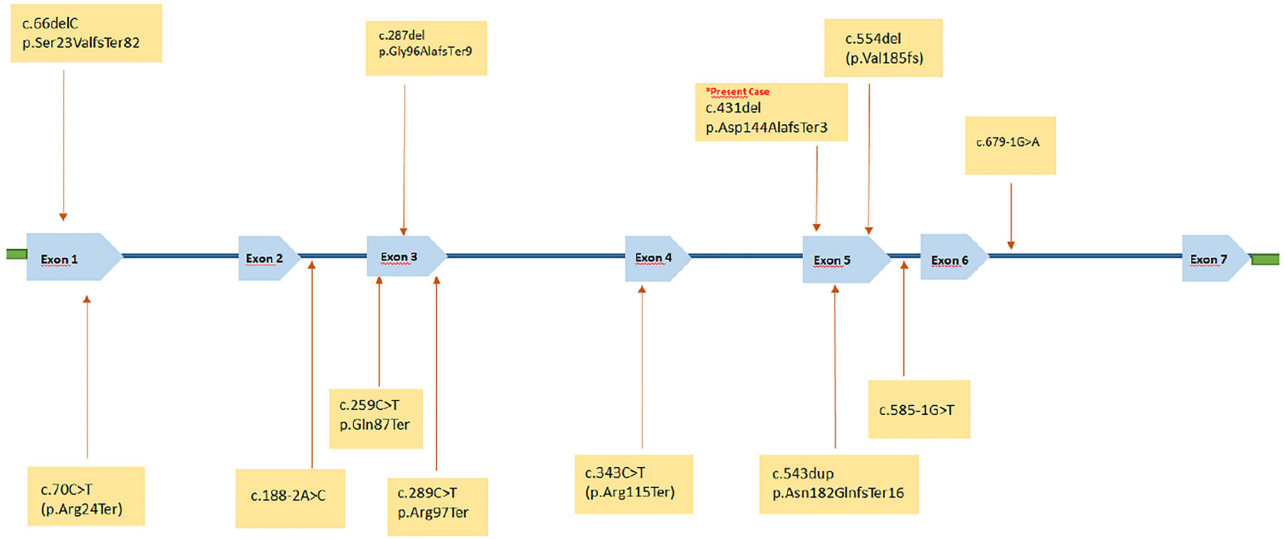

FIGURE 2 | Exon locations of the *EMC10* gene variants for our case and the previous reports.

language skills. Studies in animal models have demonstrated abnormal vocalization phenotypes, which may correspond to language deficits in humans (International Mouse Genotyping Consortium 16; www.mousephenotype.org).

Dysmorphic features have been consistently observed in all reported cases. Our patient exhibited characteristic dysmorphic findings, including a long, triangular face, tall forehead, bifrontal narrowing, narrow nasal bridge, crowded teeth, full nasal tip, and fifth finger clinodactyly. While approximately one-third of reported cases exhibit an arachnodactyly phenotype, this was not observed in our patient. Additional findings such as renal cysts, nephrocalcinosis, and elevated parathyroid hormone levels have been described in some cases; however, these were not present in our patient. Given our patient's young age, these features may not have developed yet, necessitating long-term follow-up. Similarly, *EMC10* has been linked to infertility in animal models, but this could not be assessed in our patient due to his age. Follow-up of the cases will clarify whether this situation is reflected in the human phenotype in the future. Brain magnetic resonance imaging (MRI) abnormalities have been identified in approximately one-third of reported cases; however, no neuroanatomical anomalies were observed in our patient. Additionally, while some cases in the literature present with seizures, our patient did not exhibit clinical seizures, although epileptiform activity was detected on EEG.

In conclusion, this study expands the genetic and clinical spectrum of *EMC10* deficiency, providing valuable insights into the phenotypic variability of rare *EMC10*-related NEDDFAS (OMIM #619264). The findings support the critical role of *EMC10* in human neurodevelopment and offer a detailed clinical characterization that may guide future research. The prognosis of *EMC10*-related NEDDFAS (OMIM #619264) disorders appears to be variable, highlighting the need for further genetic and clinical data to enhance our understanding of disease progression and to provide appropriate genetic counseling. Therefore, additional reports on *EMC10* variants with detailed clinical documentation are required to improve our knowledge of the disorder's natural history and its long-term outcomes.

In recent years, gene therapy has emerged as a promising treatment modality for rare monogenic disorders, offering hope for previously untreatable conditions. As advances in molecular diagnostics continue to reveal novel pathogenic variants, the precise identification and characterization of such rare diseases have become increasingly important. In this context, our contribution to the expanding clinical and genetic spectrum of *EMC10*-related neurodevelopmental disorders may have significant implications for future therapeutic strategies. Since the advance of the exome or genome sequencing platforms, the detection of rare genetic variants in neurodevelopmental disorders has improved significantly (Bolat et al. 2022; Gerik-Celebi et al. 2023). Early and accurate molecular diagnosis not only facilitates appropriate genetic counseling but may also pave the way for the development of targeted gene-based therapies as translational research in this field progresses.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors are very thankful to the family for kindly participating in this study.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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