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SHORT REPORT

Expanding the spectrum of *EEF1D* neurodevelopmental disorders: Biallelic variants in the guanine exchange domain

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Abstract

Protein translation is an essential cellular process and dysfunctional protein translation causes various neurodevelopmental disorders. The eukaryotic translation elongation factor 1A (eEF1A) delivers aminoacyl-tRNA to the ribosome, while the eEF1B complex acts as a guanine exchange factor (GEF) of GTP for GDP indirectly catalyzing the release of eEF1A from the ribosome. The gene *EEF1D* encodes the eEF1Bδ subunit of the eEF1B complex. *EEF1D* is alternatively spliced giving rise to one long and three short isoforms. Two different homozygous, truncating variants in *EEF1D* had been associated with severe intellectual disability and microcephaly in two families. The published variants only affect the long isoform of *EEF1D* that acts as a transcription factor of heat shock element proteins. By exome sequencing, we

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identified two different homozygous variants in *EEF1D* in two families with severe developmental delay, severe microcephaly, spasticity, and failure to thrive with optic atrophy, poor feeding, and recurrent aspiration pneumonia. The *EEF1D* variants reported in this study are localized in the *C*-terminal GEF domain, suggesting that a disturbed protein translation machinery might contribute to the neurodevelopmental phenotype. Pathogenic variants localized in both the alternatively spliced domain or the GEF domain of *EEF1D* cause a severe neurodevelopmental disorder with microcephaly and spasticity.

KEYWORDS

cerebral palsy, *EEF1D*, neurodevelopmental disorders, optic atrophy, protein translation, rare disease

1 | INTRODUCTION

Pathogenic variants in genes required for protein translation have been linked to neurodevelopmental disorders highlighting the importance of protein translational homeostasis for neuronal development. A few genes that function in this elongation step of protein translation have been implicated in human disease and intellectual disability (ID).[1] These include *EFTUD2* (OMIM 610536), *EEF2* (OMIM 609306), *EEF1A2* (OMIM 616309, 616 393), *EIF5A* (OMIM 619376), and *EIF4A3* (OMIM 268305). The eukaryotic translation elongation factor 1A (eEF1A) is required for the delivery of aminoacylated-tRNA to the ribosome.[2] The fast dissociation of eEF1A from the ribosome depends on GTP hydrolysis. After dissociation, the guanine exchange factor eEF1B speeds up the exchange of GDP for GTP by 1000 fold.[3] *EEF1D* codes for one long and three short isoforms of eEF1Bδ. The long isoform contains a nuclear localization signal (NLS) and functions as a transcription factor of heat shock response genes.[4]

In a large study on recessive ID, Reuter *et al* identified homozygous, truncating variants in *EEF1D* (NM_001130053:c.69delG; p.([Glu24Serfs*26])) in three siblings with severe ID and microcephaly.[5] Recently, Ugur Iseri *et al* reported the second family with three sisters presenting with ID caused by biallelic truncating variants in *EEF1D* (NM_001130053:c.948G>A; p.([Trp316*])).[6] Both reported variants are localized in the alternatively spliced exon that is only retained in the long isoform. Therefore, it was suggested that a disturbed heat shock response pathway might cause neurodevelopmental impairment.

Herein, we report four individuals from two families with severe ID and microcephaly, seizures, failure to thrive, poor feeding, recurrent aspiration pneumonia and optic atrophy with biallelic variants in the guanine exchange domain (GEF) in *EEF1D* that is retained in both, the long and the short isoforms.

2 | MATERIALS AND METHODS

2.1 | Patients recruitment

Written informed consent for participation in this study and the publication of photographs was obtained from the legal guardians. The study was performed in accordance with the Declaration of Helsinki and approved by the local institutional review boards (SQU-MREC#1362, Göttingen: #3/2/16).

2.2 | Genetic workup

After DNA isolation, DNA was barcoded and exons were enriched using hybrid capture technology (SureSelect All exons-V6, Agilent Technologies). Prepared DNA libraries of individuals #1–4 were sequenced on a Hiseq2000 (family 1) or Hiseq4000 (family 2) sequencer (200X coverage, minimal coverage 10x in >95%). Variant filtration for novel or rare variants (≤0.1%) was performed using public (1000 Genomes, Exome Variant Server, gnomAD) and in-house exome databases. Sanger sequencing was used for confirmation. Parents were tested by Sanger sequencing. For primer sequences and microarray see Supplementary text.

3 | RESULTS

3.1 | Clinical presentation

All four female individuals (Family 1: Individuals #1 and #2; Family 2: Individuals #3 and #4) presented with severe ID, spastic quadriparesis, severe microcephaly, and failure to thrive (Figure 1).

At birth, weight and body length were normal and head circumference ranged between microcephalic (individual #1) and normal (Table 1). Within the first year of life, all individuals developed severe microcephaly (−4.4 to −8.1 SD) and all were noticed to have muscular hypotonia of the trunk, stagnation of motor development, convergent strabismus and spontaneous nystagmus. After the age of 1 year, all developed spasticity of the limbs with joint contractures. Spontaneous cloni were observed. Individuals #1 and #2 had intermittent bruxism and psychomotor restlessness. Individuals #1 and #3 had a weak suck requiring nasogastric tube feeding in the neonatal period and gastric tube feeding later on. Individual #2 was able to swallow mashed food. All four individuals had absent speech, were unable to follow simple demands, sit, crawl or walk independently and all were

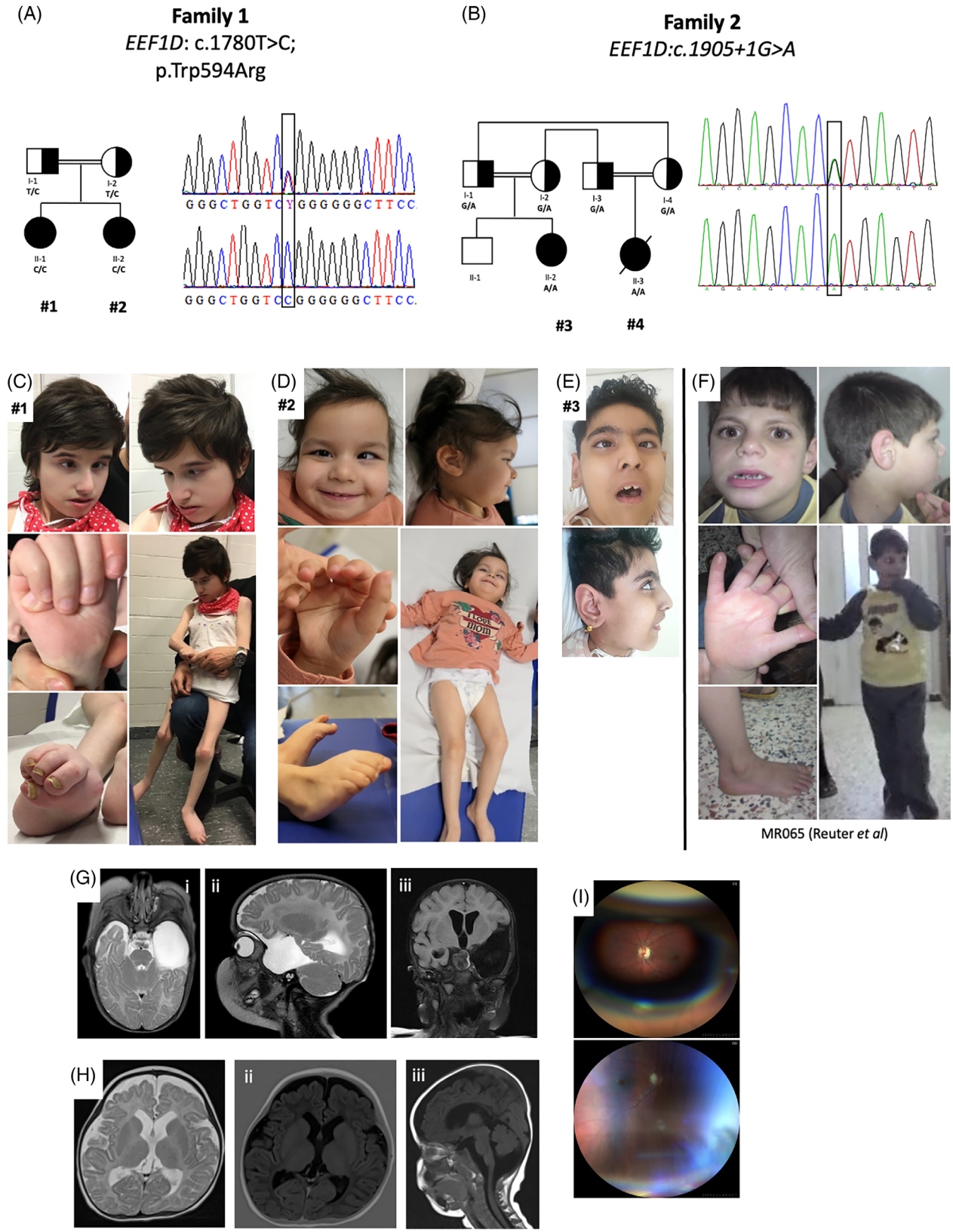


FIGURE 1 Photographs and cranial MRI. (A + B) Pedigrees (C) Photographs of #1 (15 years), (D) of #2 (3.5 years), (E) of #3 (10 years) (F) Updated photographs of one male from family MR065 (Reuter et al.[5]) (15 years). (G) Brain MRI of #2 (7 months) (i–ii) T2-weighted, (iii) T1-weighted sequences depicting a global brain atrophy, hypoplastic corpus callosum, hypomyelination (T2 hyperintense and T1 hypointense signal of the white matter), an arachnoid cyst and wide lateral ventricles. (H) Brain MRI of #3 (6 months) (i) T2-weighted, (ii-iii) T1-weighted. (I) Fundoscopy of #2: Pale optic discs on both sides. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Clinical presentation

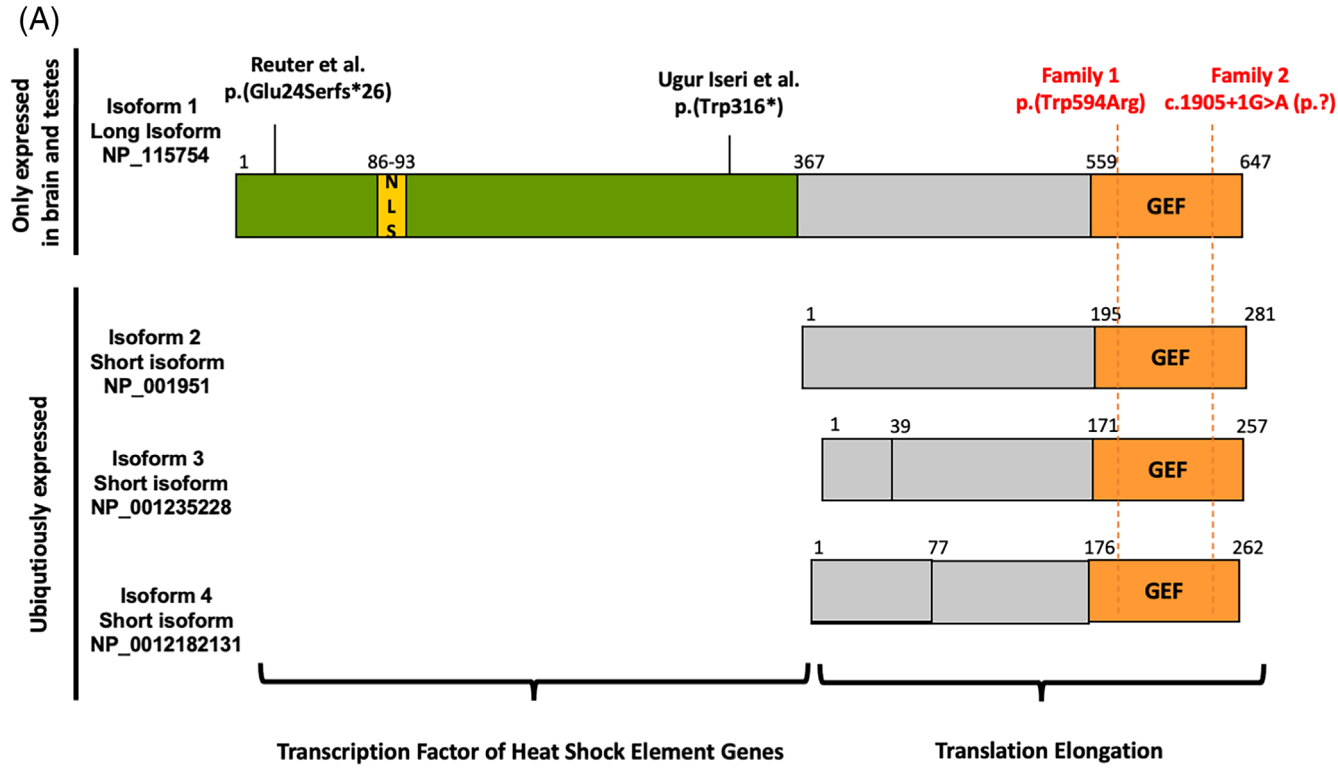
	Family 1		Family 2		Reuter et al 2017 ($N = 3$)		
	#1	#2	#3	#4	Family MR065		Ugur Iseri *et al* 2019 ($N = 3$)
EEF1D variants	c.1780T>C, p.(Trp594Arg) homozygous		c.1905+1G>A homozygous		c.69del, p.(Glu24Serfs*26) homozygous		c.948G>A; p.(Trp316*) homozygous
Consanguinity in parents	Second cousins		Double first cousins		+		+
Relation of affected individuals	Siblings		Double first cousins		Siblings		Siblings
Origin	Turkey		Oman		Syria		Turkey
Gender	F	F	F	F	1F, 1M	1M	3F
Intellectual disability	Severe	Severe	Severe	Severe	n/r	Severe	Yes, not specified
Age at last follow up	22 yr.	6 yr.	10 yr.	5 yr. (deceased)	n	n	n/r
Gestational age	42 weeks	38 weeks	39 weeks	37 weeks	Full term	Full term	Full term
Birth weight, kg, SD	2.8, −1.8	2.6, −1.4	2.7, −1.34	2.1, −1.6	n/r	n/r	n/r
Birth size, cm, SD	48, −2.0	48, −1.0	48, −0.6	48, −0.4	n/r	n/r	n/r
OFC at birth, cm, SD	32, −2.6	35, +0.5	33, −1.1	30, −1.8	n/r	n/r	n/r
Age of last follow up of body measurements	18 yr.	3.5 yr.	10 yr.	12 mo.	NA	n/r	n/r
Microcephaly	Congenital	Acquired	Acquired	Acquired	n/r	NA	N
OFC, cm, SD	44.5, − 8.1	45, −4.5	45.5, −5	37, - 6	n/r	+	3/3
Failure to thrive	+	+	+	+	n/r	n	n/r
Weight, kg, SD	17, −12	13.5, −2	13, −4	5.4, −4.5	n/r	n/r	n/r
Body length, cm, SD	112, −9	65, −3.2	n/r	64, −3	n/r	n/r	n/r
Sat/walked independently	−/−	−/−	−/−	−/−	n/r	3 yr.	−/−
First words	No speech	No speech	No speech	No speech	n/r	No speech	−/− (12, 8, 4 y)
Vision problems	Optic atrophy (pallor of optic disc)	Suspicion of optic atrophy	Mild temporal optic pallor, very poor VEP bilaterally	Severe visual impairment	n/r	n/r	n/r
Hearing	Normal	Normal	Not formally assessed	Not formally assessed	n/r	n/r	n/r
Neurological findings							
Quadriparesis	+	+	+	+	n/r	n/r	n/r
Muscular hypotonia of trunk	+	+	+	+	n/r	+	3/3
Ataxia	+	+	−	−	n/r	+	n/r

(Continues)

TABLE 1 (Continued)

	Family 1		Family 2		Reuter et al 2017 ($N = 3$)		
	#1	#2	#3	#4	Family MR065		Ugur Iseri *et al* 2019 ($N = 3$)
Nystagmus	+	+	+	+	n/r	n/r	−
Spasticity of limbs	+	+	+	+	n/r	+	3/3
Contractures of limbs	+	+	+	+ (mild)	n/r	n/	n/
Seizures	+	−	−	−	n/r	−	3/3
Seizure type	Tonic clonic	−	−	−	NA	n/	Generalized
Seizure frequency	Twice a year, last seizure at 3 yrs	−	−	−	n/r	NA	Once a month
EEG	Sporadic spike and wave complexes, left frontotemporal area	Left centroparietal slowing, focal epilleptic activity with secondary generalization during sleep	Comb-like theta rhythm over central areas	−	n/r	n/r	2/3 Generalized epileptiform discharges *
Gastrointestinal problems							
Recurrent vomiting	+	−	+	+	n/r	−	−
Gastric tube feeding	+	−	+	−	n/r	−	−
Recurrent aspiration pneumonias	−	−	−	+	n/r	−	n/r
Head MRI	Arachnoid cyst Cerebellar atrophy Hypoplastic corpus callosum, delayed myelination, reduced diameter of optic nerve	Arachnoid cyst Hypoplastic corpus callosum, delayed myelination, reduced diameter of optic nerve	Cerebral atrophy, hypoplastic corpus callosum, abnormal myelination	Cerebral atrophy, hypoplastic corpus callosum, abnormal myelination	n/r	n/r	2/2 Hypoplastic corpus callosum

Abbreviations: n/r, not reported; VEP, visual evoked potentials.



(B)

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HUMAN          VAKSSILLDVKPWDDETDMAQLEACVRSIQLDGLVWGASKLVPVGYGIRKLQIQCVVEDD 252
CHIMPANZEE     VAKSSILLDVKPWDDETDMAQLEACVRSIQLDGLVWGASKLVPVGYGIRKLQIQCVVEDD 252
MOUSE          VAKSSILLDVKPWDDETDMAQLETCVRSIQLDGLVWGASKLVPVGYGIRKLQIQCVVEDD 252
CHICKEN        IAKSSILLDVKPWDDETDMAKMEECVRSVQMDGLVWGASKLVPVGYGIKKLQIQCVVEDD 262
BOVIN          VAKSSILLDVKPWDDETDMAQLEACVRSVQLDGLVWGSSKLVPVGYGIRKLQIQCVVEDD 251
XENOPUS L:     IAKSSILLDVKPWDDETDMAKLEECVRTVQMDGLVWGSSKLVPVGYGIKKLQIQCVVEDD 236
ZEBRAFISH      IAKSSILLDVKPWDDETDMSKLEECVRSVQMDGLLWGASKLVPVGYGIKKLQINCVVEDD 134
HYDRA Vulg.    IAKSSILIDVKPWDDETDMALMEQKVRSIEMDGLLWGASKLIPLAYGIKKLQILCVVEDD 242
CAENORHAB.     IAKSSVILDVKPWDDETDLAEMEKLVRSIEMDGLVWGGGKLLPIGYGIKKLQIITVIEDL 567
DROSOPHILA     IAKSSVLLDVKPWDDETDMKDMENNVRTIEMDGLLWGASKLMPVGYGIQKLQIMCVIEDE 168
               :****:::**********:  :*  **::::***:**..**:*:.***:****  *:**
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FIGURE 2 (A) Schematic illustration of the domains and the four isoforms of eEF1Bδ. (B) Protein sequence alignment of the GEF domain of *EEF1D* orthologs in different species. eEF1Bδ(L), (long) eukaryotic elongation factor 1Bδ; NLS, nuclear localization signal [Colour figure can be viewed at wileyonlinelibrary.com]

dependent on wheelchair. Individuals #1–3 developed optic atrophy (Figure 1I). Fundoscopy of individual #4 showed retinal pigmentary changes and electroretinogram showed cone and rod dysfunction.

Individual #1 had epileptic seizures twice a year until the age of 3 years. Individuals #2 and #3 had epileptic findings on electroencephalography, but no reported seizures.

All individuals had failure to thrive. The deficit in weight and height aggravated with age (−2 SD-youngest; −12 SD-oldest).

Individual #1 suffered from an episode of acute pancreatitis. Individual #4 had recurrent aspirations and chest infections. At the age of 5 years, she died of an aspiration pneumonia. Cranial MRI showed reduced brain volume, hypoplastic corpus callosum, and abnormal, delayed myelination. Individuals #1 and #2 additionally had unilateral arachnoid cysts, but no compression of other brain structures, no midline shift indicating normal intracranial pressure. All had large, low set ears, but no distinct dysmorphic facial features (Figure 1C–E). For detailed case reports see Supplementary text.

Microarray analysis revealed normal results for family 2. Individual #2 has a heterozygous 0.5-Mb duplication of Xq28 (arr[hg19] Xq28 (154,118,619-154,560,375), hg19/GRCh37) that is not shared by the sister #1 (Figure S1). Int22h1/int22h2-mediated Xq28 duplications are associated with mild to moderate ID, increased weight, recurrent infections, and dysmorphic features in males.[7] Female carriers are

largely unaffected or show only mild cognitive impairment.[7] The healthy mother of #1 and #2 also carries the Xq28 duplication, and therefore, the duplication does not explain the severe neurodevelopmental disorder of individual #2.

3.2 | Exome sequencing and identification of homozygous variants in *EEF1D*

By exome sequencing we found that individuals #1 and #2 harbor a homozygous missense variant c.1780T>C, p.([Trp594Arg]) in *EEF1D* (NM_001130053.4, exon 9). Trp594 is highly conserved among different species and the variant resides in a highly conserved stretch in the GEF domain (Figure 2B).[8] The variant was absent from databases, and an alternative heterozygous variant at position 594 (p.[Trp594Leu]) was detected once in gnomAD. In silico tools predict a likely damaging effect (CADD 32).

In individuals #3 and #4 a homozygous canonical splicing variant c.1905+1G>A: [p.?] (NM_001130053.4) in *EEF1D* was detected. The variant was found once in a European heterozygous carrier in gnomAD. After the initial visit the family was not available for collecting a new blood sample for a transcript analysis, therefore unfortunately, a transcript analysis was not possible. This variant affects the canonical transcript, and it is located within the canonical splicing site (+1), which is considered a high-impact variant and predicted to cause aberrant splicing.[9]

Parents carrier status was confirmed by sanger sequencing (Figure 1A). According to the ACMG/AMP guidelines 2015 both variants were rated to be likely pathogenic (PM1, PM2, PP1, PP3) and disease-causing.

As the four affected individuals stem from consanguineous families, we quantified the total percentage of homozygosity (referred to the human genome size of 3,000,000,000 bp): Individuals #1: 9.5%, #2 5.7%, #3: 8.2%, #4: 5.0%. The *EEF1D* variant is located within the first 19th largest regions of homozygosity in all four individuals.

4 | DISCUSSION

EEF1D codes for the eEF1Bδ that functions as a guanine exchange factor (GEF) and is required for the efficient release of eEF1A from the ribosome during protein translation.[2,3] The long isoform (eEF1BδL) has an alternatively spliced exon that contains a nuclear localization signal (NLS).[4] In the nucleus, eEF1BδL acts as a transcription factor for heat shock element-containing genes. After heat exposure, the expression of the short, canonical eEF1Bδ isoforms is downregulated and the long eEF1BδL is upregulated indicating a role cellular stress response.[4]

While the two variants reported by Reuter and Ugur Iseri *et al* are loss-of-function variants that affect the alternatively spliced exon of eEF1BδL, this is the first study reporting homozygous variants in the highly conserved C-terminal GEF domain in association with a severe neurodevelopmental disorder.[5,6]

All published individuals and all individuals from this study have microcephaly and thinning of the corpus callosum (Table 1). All individuals of whom data were available, had short stature, muscular hypotonia and spasticity. While none of the individuals from this study or in the study by Ugur Iser *et al* were able to sit, stand or walk independently, one individual reported by Reuter *et al* walked with assistance at the age of 15 years (Figure 1F). Additional clinical signs that have not been reported to date are optic atrophy, poor feeding, and recurrent aspiration pneumonia. Of note, the progressive deficit of head circumference, weight and height over time – that is also observed in *EFF1A2* and *EFTUD2*-associated disorders - suggests a degenerative disorder, however, long-term clinical follow-up is needed to draw a final conclusion on a potentially progressive course.

Ugur Iseri *et al* proposed that an altered heat shock transcriptional response - rather than a dysfunctional protein elongation - might be the underlying disease mechanism of the *EEF1D*-associated neurodevelopmental disorders.[6] In cell culture, the overexpression of either wildtype, Lys646Ala or Lys646Arg mutant eEF1BδL upregulated the transcription of heat-shock element (HSE)-containing genes.[4] The Lys646 is one of the many highly conserved amino acids within the highly conserved GEF domain. This allows the hypothesis that the N-terminal GEF domain that includes both variants of this study might be dispensable for heat shock response.

The early neuronal development appears to be particularly sensitive to disturbed protein homeostasis. Many genes that are essential for proper protein translation have been implicated with neurodevelopmental disorders.[1] In mice, *EEF1D* short and long isoforms were expressed in the brain at all stages of development, but the expression of the short isoforms was significantly upregulated in the early fetal and neonatal stages, pointing to a pivotal role in the early infantile brain development.[10] The variants of family 1 and 2 are localized in the C-terminal GEF domain and likely affect the canonical protein translation elongation function of *EEF1D*.

Based on our clinical findings, we can only speculate on the disease mechanism, and functional studies are required to delineate the damaging effect of mutant *EEF1D* long and short isoforms. As many genes that are involved in protein translation (e.g. *YARS1*) have acquired diverse non-canonical functions during the evolution, not yet identified functions should also be considered as potential disease mechanisms.[11]

This is the first report of a neurodevelopmental disorder associated with biallelic variants in the C-terminal GEF domain of *EEF1D*. Variants in the C- and N-terminal domains cause a similar phenotype including severe ID, microcephaly, spasticity, seizures and failure to thrive.

AUTHOR CONTRIBUTIONS

Conceptualization: Luisa Averdunk, Almundher Al-Maawali, and Dagmar Wieczorek. *Clinical assessment*: Luisa Averdunk, Khalid Al-Thihli, Bassam Al Hallak, Tanja Guthoff, Michael Wallot, and Dagmar Wieczorek. *Genetic analysis*: Khalid Al-Thihli, Harald Surowy, Hermann-Josef Lüdecke, Matthias Drechsler, Gökhan Yigit, Lukasz Smorag, Yun Li, Janine Altmüller, Peter Nürnberg, Bernd Wollnik, Rami

Abou Jamra, and Almundher Al-Maawali. *Funding acquisition*: Bernd Wollnik, Dagmar Wieczorek, and Almundher Al-Maawali. *Writing-original draft and visualization*: Luisa Averdunk. *Writing-review & editing*: Khalid Al-Thihli, Almundher Al-Maawali, and Dagmar Wieczorek.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14290.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Institutional Ethical Review Boards (SQU-MREC#1362, Göttingen: #3/2/16).

PHOTO CONSENT STATEMENT

The legal guardians gave consent to the publication of photographs.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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