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De novo *ARHGEF9* missense variants associated with neurodevelopmental disorder in females: expanding the genotypic and phenotypic spectrum of *ARHGEF9* disease in females

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Abstract

Individuals harboring pathogenic variants in *ARHGEF9*, encoding an essential submembrane protein for gamma-aminobutyric acid (GABA)–ergic synapses named collybistin, show intellectual disability (ID), facial dysmorphism, behavioral disorders, and epilepsy. Only few affected females carrying large chromosomal rearrangements involving *ARHGEF9* have been reported so far. Through next-generation sequencing (NGS)–based panels, we identified two single nucleotide variants (SNVs) in *ARHGEF9* in two females with neurodevelopmental features. Sanger sequencing revealed that these variants were de novo. The X-inactivation pattern in peripheral blood cells was random. We report the first affected females harboring de novo SNVs in *ARHGEF9*, expanding the genotypic and phenotypic spectrum of *ARHGEF9*–related neurodevelopmental disorder in females.

Keywords *ARHGEF9* · De novo · Neurodevelopmental disorder · Autism spectrum disorder · Epilepsy · X-inactivation

Introduction

ARHGEF9 (OMIM *300429) maps to Xq11.1 and encodes collybistin, a submembrane protein involved in the formation of inhibitory gamma-aminobutyric acid (GABA)–ergic synapses.¹ *Arhgef9* knockout mice exhibit deficient hippocampal

synaptic plasticity, behavioral disturbances, cognitive defects, and seizures [1, 2]. In humans, *ARHGEF9* pathogenic variants cause a recognizable neurologic disorder characterized by the variable association of intellectual disability (ID), dysmorphic features, hyperekplexia, anxiety, and epilepsy [3–5]. The large phenotypic spectrum encompasses non-epileptic mildly

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affected individuals and patients with severe epileptic encephalopathy (early infantile epileptic encephalopathy 8 - EIEE8, OMIM #300607) [6].

Females are usually healthy carriers and only few affected subjects have been described so far, harboring genomic imbalances involving *ARHGEF9* and showing a variable neurodevelopmental phenotype (psychomotor delay, behavioral disorders, and seizures) [7–9]. Here, we report two affected females harboring de novo missense variants in *ARHGEF9* and showing a random X-inactivation pattern in peripheral blood cells.

Materials and methods

Patients were recruited from the Epilepsy Center of San Paolo Hospital (Milan, Italy), Università degli Studi di Milano (Milan, Italy), and University Medical Center Groningen (Groningen, The Netherlands). Enrolment was approved by the ethics committee of the involved Institutions. The study was designed in compliance with the tenets of the Helsinki Declaration. Written informed consent was obtained from the parents of the patients. The subjects were examined by expert pediatric neurologists and clinical geneticists, and studied through electroencephalogram (EEG) and brain magnetic resonance imaging (MRI).

Genetic testing was performed on DNA extracted from peripheral blood with standard techniques. Patients underwent chromosomal microarray with an average resolution of 40 kb and two distinct next-generation sequencing (NGS) panels, encompassing 85 and 1000 genes associated with neurodevelopmental disorders in patients 1 and 2, respectively (Supplementary Material). The identified variants were filtered according to frequency databases, including gnomAD (<https://gnomad.broadinstitute.org>), dbSNP (<https://www.ncbi.nlm.nih.gov/snp/>), and Exome Aggregation Consortium – Exac (<http://exac.broadinstitute.org>). ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/>) and pertinent literature were also screened. The predicted impact on protein function was assessed through several in silico tools, including PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2/>), DANN (https://cbcl.ics.uci.edu/public_data/DANN/), Mutation Taster (<http://www.mutationtaster.org/>), Combined Annotation Dependent Depletion (CADD) (<https://cadd.gs.washington.edu/snv>), and Genomic Evolutionary Rate Profiling (GERP) (<http://mendel.stanford.edu/SidowLab/downloads/gerp/>). Candidate variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines [10]. Sanger sequencing was performed for parental segregation using standard methods. X-inactivation studies were performed on DNA extracted from peripheral blood cells through the analysis of the

polymorphic regions in exon 1 of *AR* (CAG repeats) and at the 5' UTR of *ZNF261* (GA repeats).

Results

Case reports

Patient 1 is a 5-year-old girl of Italian ancestry with developmental delay (DD) and seizures (Table 1). She was the only child of unrelated parents with an unremarkable family history. She was born at term after a regular pregnancy and neonatal course was uneventful. At 13 months, she was unable to sit without support and showed generalized hypotonia. She could stand at 20 months and walk unassisted at 26 months. Her speech was limited to few words but later regressed. At 2.5 years, the girl experienced sudden left side paralysis followed by a focal seizure during sleep with fixed gaze, wheezes, and drooling. She had clonus on her left side and transient post-ictal paralysis. EEG showed slow activity over the right regions and right central-temporal spike waves. Seizures were controlled by valproate (500 mg/day). Six months later, clonic movements in the left upper limb were observed. Ictal EEG showed a poly-spike waves discharge spreading from the right central area to both hemispheres (Fig. 1a). Sleep-deprived EEG revealed bilateral rhythmic theta activity and spikes over the right central-temporal region (Fig. 1b, c). The addition of oxcarbazepine (300 mg/day) to valproate resulted effective in controlling seizures. Physical examination at 5.5 years showed non-dysmorphic minor facial features, gross motor impairment, oral dyspraxia, hypotonia, and wide-based gait. She was nonverbal, but could babble and point to communicate. Brain MRI showed corpus callosum hypoplasia (CCH) (see supplementary Figure S1).

Patient 2 is a 25-year-old female of Dutch ancestry with psychomotor delay and behavioral disturbances (Table 1). She was born at term after a triplet pregnancy complicated by one fetal miscarriage. Family history revealed mild autism spectrum disorder (ASD) in her dizygotic twin sister and mother, and mild ID and hearing loss on the paternal side. Neonatal course was characterized by feeding difficulties due to wet lung syndrome and poor sucking. She had generalized hypotonia and minor dysmorphic features (thick eyebrows, narrow nasal base, hypoplastic alae nasi, crowded teeth, and low-set ears). The girl was diagnosed with DD in the first months of life, as she had evident head lag. She could sit without support at 8 months and walk independently at 36 months. Her speech was delayed. ASD and mild-to-moderate ID were diagnosed when she was 7 years old. She had severe sleeping difficulties responding to promethazine and lorazepam. At the age of 24 years, the patient experienced a sudden psychotic episode after sleep deprivation. She developed schizotypal

Table 1 Genetic and clinical features of *ARHGEF9* female patients

Case	ARHGEF9 variant	Inheritance	X-inactivation pattern	Phenotype	EEG findings
Alber (2017), P1	46, X, t(X;20) (q12;p13) [^]	De novo	Skewed (100)	DD/ID (severe), nonverbal, ASD, seizures (GTC) partially responding to VPA, PHT, PGB	Generalized spikes and waves
Alber (2017), P2	46, X, t(X;18) (q11.1;q11.21) [^]	De novo	Skewed (100)	DD/ID (severe), nonverbal, aggressive, dysmorphic features, seizures (GTC), OSAS	Slow background
Alber (2017), P3	Xq11.1 deletion of 27 kb (62,838,630-62,865,334)	De novo	Skewed (95:5)	DD/ID (moderate), aggressive, hypotonia, facial dysmorphism	-
Alber (2017), P4	Xq11.1 deletion of 7.5 kb (62,854,862-62,862,403)	De novo	Skewed (90:10)	DD/ID (moderate), self-resolving seizures (F, GTC), dysmorphic features	Normal
Alber (2017), P5	46, X, inv.(X) (q11.1q27.3)	De novo	Skewed (100)	DD/ID (moderate), facial dysmorphism, sensory hyperarousal	-
Aarabi (2018), P1	Xq11.1 deletion of 23.9 kb (62,874,590-62,900,823)	De novo	Random	DD/ID (moderate), ASD, speech delay, short stature, dysmorphic features	-
Aarabi (2018), P2	Xq11.1 deletion of 56.5 kb (62,872,539-62,929,093)	De novo	Random	DD/ID (mild), ASD, facial dysmorphism, small foci of gliosis on MRI	Normal
Bhat (2016)	Xq11.1-11.2 deletion of 82 kb (62,970,571-63,052,696)	De novo	Random (80:20)	DD/ID (mild), ASD, ADHD, temper tantrums	-
Holman (2013), P1	Deletion encompassing <i>ARHGEF9</i> , <i>WTX</i> , and <i>MTMR8</i>	De novo	Random (49:51)	DD/ID (severe), macrocephaly, dysmorphic features, seizures (complex partial), multiple congenital anomalies (OSCS)	-
Holman (2013), P2	Deletion encompassing <i>ARHGEF9</i> , <i>WTX</i> , and <i>MTMR8</i>	De novo	Random (38:62)	DD/ID (severe), dysmorphic features, hyperactivity, deafness, multiple congenital anomalies (OSCS)	-
Kalscheuer (2009)	46, X, t(X;18) (q11.1;q11.21)	De novo	Skewed (100)	DD/ID (severe), ADHD, seizures (GTC), dysmorphic features, microcephaly, self-aggressive, hyperactivity, OSAS	-
Marco (2007)	46, X, inv.(X) (q11.1;q27.3) ^{^^}	De novo	Skewed (100)	DD/ID (severe), sensory hyperarousal, ADHD, poor coordination, hyperekplexia	-
Current study					
Patient 1	c.311G>A (p.Arg104Gln) [NM_015185.2]	De novo	Random (36:64)	DD/ID (severe), language regression, hypotonia, seizures (F), dysmorphic features, corpus callosum hypoplasia	Unilateral slow activity and spike/poly-spike waves
Patient 2	c.535G>A, p.(Glu179Lys) [NM_015185.2]	De novo	Random	DD/ID (moderate), speech delay, hypotonia, dysmorphism, ASD, psychotic episode	-

[^] Balanced translocation^{^^} Paracentric inversion

All chromosomal rearrangements refer to hg19 coordinates

ADHD, attention deficit hyperactivity disorder; *ASD*, autism spectrum disorder; *DD*, developmental delay; *EEG*, electroencephalogram; *F*, focal; *ID*, intellectual disability; *GTC*, generalized tonic-clonic; *ID*, intellectual disability; *MRI*, magnetic resonance imaging; *OSCS*, osteopathia striata congenita with cranial sclerosis; *OXC*, oxcarbazepine; *P*, patient; *PGB*, pregabalin; *PHT*, phenytoin; *VPA*, valproic acid

features and started to suffer from delusions and visual and acoustic hallucinations. Aripiprazole effectively controlled these symptoms, leading to a complete resolution in 2 years.

Genetic analysis

In patient 1, the de novo NM_015185.2:c.311G>A; p.(Arg104Gln) variant in *ARHGEF9* was identified. It is absent

◀ **Fig. 1** Serial EEG recordings of from patient 1 at 3 years of age during awake, falling asleep, and in sleep, respectively. **a** Ictal EEG recording showing diffuse, high-voltage rhythmic theta activity prominent over the posterior brain regions. Poly-spike wave discharge originating in the right central area and spreading to both cerebral hemispheres. **b, c** Sleep EEG shows bilateral rhythmic theta activity prevalent over the anterior and midline regions (**b**) and interictal sharp wave-slow wave complexes in over the central-temporal regions frontotemporal area (reversal phase on F4/F8) (**c**). EEG details: system 10e20, bipolar longitudinal montage, sens 10 mV, HF 50 RP Hz, LF 0.1, 20 s/page (the bar indicates 1 s))

in population databases (e.g., gnomAD, Exac, dbSNP) and results in a semi-conservative amino acid substitution of a conserved residue in the DH domain of Collybistin (GERP score 5.73). This variant is predicted pathogenic by several bioinformatic tools (Table 2) and is described as pathogenic in ClinVar (ID 432195). X-inactivation studies showed random inactivation at the AR locus (36:64 ratio).

The heterozygous missense variant NM_015185.2:c.535G>A; p.(Glu179Lys) in *ARHGEF9* was instead identified in patient 2. This variant occurred de novo in the proband and was absent in her twin sister. It is absent in gnomAD and affects a distinct conserved residue in the DH domain (GERP score 5.65). This variant is predicted pathogenic by several in silico tools (Table 2) and has been observed in an affected male from Invitae (ClinVar, ID SCV000943659.1). A random X-inactivation pattern was observed, with an AR-locus methylation of 57% and 63% in two separate calculations, respectively.

Discussion

Collybistin is involved in the post-synaptic clustering and stabilization of gephyrin-dependent glycine and GABA type A (GABA_A) receptors at inhibitory synaptic sites [3]. Loss-of-function *ARHGEF9* variants cause an inhibitory imbalance leading to post-synaptic hyperexcitability with seizure predisposition and negative impact on synaptic plasticity [3, 5, 11]. Collybistin also contributes to the inhibition of mTORC1 signaling, which is crucial for neuronal development and synaptic formation and plasticity. The disinhibition of mTORC1 has been associated with several neurodevelopmental disorders and might significantly contribute to the ID and ASD observed in *ARHGEF9* patients [1].

Twelve female *ARHGEF9* patients have been reported so far [7–9, 12–14]. All subjects carried genomic imbalances involving *ARHGEF9* (Fig. 2a) and showed a variable phenotype mainly characterized by DD/ID, ASD, and seizures (Table 1). This variability is likely explained by a dosage effect resulting from the X chromosome inactivation pattern. Indeed, the proportion of the post-synaptic neurons in which the defective chromosome is active determines the extent of GABA signaling abnormality and excitatory-inhibitory un-

Table 2 Frequency and predicted effect of the identified de novo *ARHGEF9* variants

ARHGEF9 variant [NM_015185.3]	g. (hg19)	ExAC/ gnomAD	Ensembl	ClinVar	DANN	Polyphen-2	Mutation Taster	FATHMM- MKL	GERP score	CADD score (v1.6)	ACMG class
c.311G>A; p.(Arg104Gln)	g.62926208C>T -	-	rs1556401714	Pathogenic (ID 432195)	Damaging (0.9996)	Probably damaging (1)	Disease causing (1)	Damaging (0.9772)	5.73	29.4	Likely pathogenic (PM2, PM5, PM6, PP2, PP3, PP5)
c.535G>A; p.(Glu179Lys)	g.62917031C>T -	-	-	Likely pathogenic (ID SCV000943659.1)	Damaging (0.9992)	Probably damaging (0.997)	Disease causing (1)	Damaging (0.9816)	5.65	24.9	Likely pathogenic (PM2, PM6, PP2, PP3)

Abbreviations: CADD, combined annotation dependent depletion; GERP, genomic evolutionary rate profiling; gnomAD, genome aggregation database; MVP, missense variant pathogenicity prediction; PS, pathogenic strong; PM, pathogenic moderate; PP, pathogenic supporting; SIFT, Sorting Intolerant From Tolerant

Fig. 2 Genotype-phenotype spectrum in female *ARHGEF9* patients. **a** Pie chart showing the percentage distribution of *ARHGEF9* genetic alterations in affected females. **b** Schematic, not-in scale cartoon of the human collybistin protein (NM_015185.2, NP_056000.1), composed of a regulatory Src homology 3 (SH3) domain, a catalytic Dbl homology (DH) domain, and a pleckstrin homology (PH) domain. The de novo missense variants identified in the reported female patients are reported above (in red) with the relative conservation of the affected residues. Previously reported missense variants in affected males are reported below (in black). **c** Bar graph showing the cardinal features of *ARHGEF9*-related disorder in the female population. Protein data available at <https://prosite.expasy.org/cgi-bin/prosite/>. Abbreviations: ASD, autism spectrum disorder; DD, developmental delay; ID, intellectual disability; mod, moderate; HA, hyperarousal; HK, hyperekplexia; SNV, single nucleotide variant

balance in the cortical network [7]. Accordingly, skewed inactivation was found in 7 females [7, 12]. A random X-inactivation was instead identified in the remaining 6 cases, as well as in the two patients reported in our study. This finding does not contradict the previous pathogenic model, since the inactivation pattern in post-synaptic inhibitory neurons might not be reflected by the ascertainment in peripheral blood [7].

Here we report the first affected females harboring a de novo missense variant in *ARHGEF9*. Interestingly, missense variants have only been reported in apparently healthy mothers of male patients so far [7]. The c.311G>A; p.(Arg104Gln) identified in patient 1 was previously reported in a male patient with DD, seizures, and ASD [12]. Similarly, the c.535G>A; p.(Glu179Lys) variant detected in patient 2 that lies very close to the c.530T>C; (p.Leu177Pro) variant has been identified in an affected male with DD, mild dysmorphic features, and seizures [12]. Both these variants affect conserved residues in the Dbl homology (DH) domain of collybistin (Fig. 2b), which primarily mediates the guanyl nucleotide exchange function, possibly leading to impaired GDP-GTP exchange [3].

In line with previously reported female cases, our patients showed DD/ID, speech impairment, dysmorphic features, behavioral abnormalities, and epilepsy (Table 1). All affected females show mild-to-severe ID (Fig. 2c). Dysmorphic features are variable, without a recognizable facial gestalt. Most epileptic patients suffer from generalized tonic-clonic seizures, whereas focal seizures had only been observed once before this report (patient 1) [12]. EEG findings are not specific and some patients have normal EEGs [12]. Common behavioral abnormalities include attention deficit hyperactivity disorder (ADHD), ASD, sensory hyperarousal, and aggressive behavior [7–9, 13]. Although the mTOR disinhibition might result in malformation of cortical development, only minor neuroimaging abnormalities have been reported (e.g., frontal lobes hypoplasia and unilateral polymicrogyria) [12]. Of note, isolated CCH was observed in patient 1.

In summary, we reported the first *ARHGEF9* female patients harboring de novo missense variants, expanding the genotypic and phenotypic spectrum of *ARHGEF9*-related disorder. Our observations support the idea that *ARHGEF9* variants may be disease-causing in females and that X-inactivation phenotype in blood does not necessarily exclude their pathogenicity. Functional studies on brain tissues in animal models and the report of further cases will be fundamental to clarify the pathogenic mechanisms underlying the neurocognitive phenotype in these patients.

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Authors' contributions MS analyzed genetic data, conceived the target, and drafted the manuscript. EZ, MB, OM, AV, EZ, KT, AP, and AV investigated the patients and collected clinical and genetic data. FZ and PS critically reviewed the manuscript and coordinated genetic analysis.

Data availability All data generated or analyzed during this study are included in this published article and its supplementary information files.

Compliance with ethical standards

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

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki and approved by the Ethics Committees of San Paolo Hospital (Milan, Italy), Università degli Studi di Milano (Milan, Italy), and University Medical Center Groningen (Groningen, The Netherlands).

Consent to participate Written informed consent was obtained from the parents of the studied individuals.

Consent for publication The parents of the reported subjects signed informed consent regarding the publication of clinical data and photographs.

Code availability Not applicable.

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