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SHORT REPORT

Expanding the clinical spectrum associated with *PACS2* mutations

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Whole exome sequencing (WES) has led to the understanding of the molecular events affecting neurodevelopment in an extremely diverse clinical context, including diseases with intellectual disability (ID) associated with variable central nervous system (CNS) malformations, and developmental and epileptic encephalopathies (DEEs). Recently, *PACS2* mutations have been causally linked to a DEE with cerebellar dysgenesis and facial dysmorphism. All known patients presented with a recurrent de novo missense mutation, c.625G>A (p.Glu209Lys). Here, we report on a 7-year-old boy with DEE, cerebellar dysgenesis, facial dysmorphism and postnatal growth delay, apparently not fitting with any recognized disorder. WES disclosed a de novo novel missense *PACS2* variant, c.631G>A (p.Glu211Lys), as the molecular cause of this complex phenotype. We provide a detailed clinical characterization of this patient, and analyse the available clinical data of individuals with *PACS2* mutations to delineate more accurately the clinical spectrum associated with this recently described syndrome. Our study expands the clinical and molecular spectrum of *PACS2* mutations. Overview of the available clinical data allow to delineate the condition associated with *PACS2* mutations as a variable trait, in which the key features are represented by moderate to severe ID, cerebellar dysgenesis and other CNS malformations, reduced growth, and facial dysmorphism.

KEYWORDS
cerebellar dysgenesis, developmental and epileptic encephalopathy, facial dysmorphism, growth deficiency, *PACS2*

1 | INTRODUCTION

Latest advances in genome analysis have significantly enabled the discovery of molecular defects underlying neurodevelopmental disorders (NDDs), a clinically heterogeneous group of rare diseases presenting with central nervous system (CNS) malformations often associated with developmental and epileptic encephalopathies (DEEs).[1–6] Among the genes that have recently been implicated in DEEs, *PACS1* (phosphofurin acid cluster sortin protein 1, OMIM 607492), encoding a *trans*-Golgi-membrane traffic regulator highly expressed during human embryonic brain development, has been implicated in Schuurs-Hoeijmakers syndrome (OMIM 615009), a dominantly inherited DEE with recognizable gestalt and brain structural abnormalities.[7] So far, all reported patients share de novo missense changes affecting the same amino acid (p.Arg203Trp; p.Arg203Gln).[7–10] Arg203 is highly conserved among orthologs, as well as in the paralog, *PACS2* (OMIM 610423). Remarkably, a recurrent de novo heterozygous missense variant in *PACS2* was more recently found in 14 unrelated individuals presenting with an NDD partially overlapping with the *PACS1*-related phenotype.[11] All patients presented with a recurrent missense mutation, c.625G>A (p.Glu209Lys), and had early-onset epilepsy with focal and generalized seizures, global developmental delay and autistic features, cerebellar dysgenesis and dysmorphic facial appearance.

Here we report on a child with DEE, in whom WES analysis disclosed a novel de novo pathogenic missense variant of *PACS2* involving

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the same functional domain that was previously reported in other affected individuals. Our findings expand the phenotypic spectrum of this novel disease and confirm the occurrence of a mutational hot-spot in PACS2-associated DEE.

2 | CASE REPORT

The 7-year-old male was the only child of non-consanguineous parents. Family history was unremarkable. Pregnancy was uneventful until the 35th week, when an ultrasound scan disclosed bilateral ventriculomegaly. Delivery was at 38 weeks, by Caesarian section because of breech presentation. Birth weight was 3040 g (25-50th centile), length 49 cm (25th centile), and occipito-frontal circumference (OFC) 35.5 cm (75th centile). At 3 days of life, respiratory distress and epilepsy were recorded, with seizures characterized by impairment of consciousness and upward rolling of the eyes. An electroencephalogram (EEG) at onset showed epileptiform abnormalities in both central regions. Phenobarbital was started with seizures remission, but reduction of drug after 1 month of treatment caused reappearance of seizures characterized by left upper limb hypertonia and blank staring followed by inconsolable crying. Therefore, vigabatrin and valproic acid were started with good control of the seizures (only one episode at age 13 months). Since no other episodes were further referred, both drugs were gradually discontinued at 6 years. Ophthalmologic evaluation and echocardiogram were normal. Brain magnetic resonance imaging (MRI), at age 27 months and at age 3 years and 10 months (Figure 1D-G), revealed an abnormal cerebellar foliation pattern along the basal and posterior portions of the right cerebellum hemisphere, quantitative reduction of the parietal region white matter in the supratentorial region, hyperintensity of the centrum semiovale in the frontal region, bilateral posterior periventricular white matter reduction and lateral ventricles asymmetry with prevalence of the right posterior horn. Global motor skills were delayed. He walked unsupported at 2 years and at 7 years, verbal speech was limited to a few words and he required assistance in hygiene and dressing. He still presented problems with chewing and dysphagia. Cognitive assessment (WISC-IV scale) revealed a total IQ of 47 (processing speed, 50; working memory, 64; perceptual reasoning, 67; verbal comprehension, 58). Because of a reduced growth velocity, growth hormone (GH) stimulation testing with clonidine and arginine was performed at 6 years, which revealed a GH peak of 4.09 and 2.40 ng/mL, respectively. Thus, GH treatment was started at 6 years because of a reduced growth velocity (Saizen, 0.5 mg for 6 days/week). At age 7, endocrinology work up revealed thyroid stimulating hormone: 2.78 μIU/mL (n.v.: 0.64-6.27), free T4: 1.12 ng/dL (n.v.: 0.89-1.76) and insulin-like growth factor 1: 63.4 ng/mL (n.v. 55-222). Brain MRI revealed no pituitary abnormalities and last EEG were normal.

At the last evaluation (7 years), growth parameters disclosed short stature (105 cm, −3.2 SD), low weight (18.5 kg, −1.9 SD), and relative macrocephaly (OFC: 51.5 cm, 50-75th centile). Physical examination disclosed a distinctive facial gestalt with features and signs that remained unchanged over the time, including synophrys, highly arched and sparse broad eyebrows, long eyelashes, low-set and posteriorly rotated ears with uplifted lobe, broad nasal tip, smooth philtrum, thin and everted upper lip vermilion, downturned corners of the mouth, widely spaced teeth, and chin with horizontal crease (Figure 1).

Metabolic screening, including urine determination of glycosaminoglycans and screening for inborn errors of amino acid metabolism, were normal. Genetic analyses, including karyotype, high resolution CGH-array (44K; Agilent Technologies, Waldbronn, Germany), and epilepsy- and cohesinopathy-related gene panels testing (Supporting Information File S1) were negative. WES workflow and analysis were performed as detailed reported in the supplemental methods.

3 | RESULTS

Written informed consents for the use of photographs and research findings were obtained from the family.

Data analysis, variant filtering and prioritization allowed to identify the de novo missense variant, c.631G>A (p.Glu211Lys) in exon 6 of *PACS2* (NM_001100913.2) as the molecular event underlying the condition. De novo occurrence of this missense change was confirmed by Sanger sequencing (Figure 2). The variant was private, being not reported in ExAC, ClinVar, and *in-house* databases. The affected residue, Glu211, is conserved in PACS2 orthologs and its paralog, PACS1 (Figure 2).

4 | DISCUSSION

Recently, a recurrent de novo missense variant, c.625G>A (p.Glu209Lys) in *PACS2* was reported in 14 unrelated individuals with epilepsy, developmental delay, cerebellar dysgenesis and dysmorphisms. Here, we report on an additional patient with a different de novo *PACS2* mutation, and revise the phenotype associated with this *PACS2* mutation (Table 1).

Differential diagnosis of cerebellar dysgenesis includes disorders associated with OPHN1 and GNAO1 mutations (MIM #300486 and MIM #617493). PACS2 is a multifunctional protein mainly expressed in the brain, including cerebellum (GTEx, https://gtexportal.org/home/, and FANTOM5, http://fantom.gsc.riken.jp/5/index.html), that acts as a traffic modulator by controlling the endoplasmic reticulum-mitochondrial communication, with nuclear gene expression.[12] Olson et al suggested that the disease-causing p.Glu209Lys substitution alters the ability of the autoregulatory domain to modulate the interaction of PACS2 with client proteins participating in processes related to neuronal development and function.[11] Of note, the Glu211 is located within the autoregulatory domain of PACS2 and is close to the residue that was previously reported to be invariantly affected in the disorder.[11] Our finding further confirms the relevance of this region in the control of PACS2 function (Figure 2).

The clinical characteristics of the affected individuals carrying the recurrent p.Glu209Lys mutation, included neonatal/early-infantile onset epilepsy, global developmental delay with or without autism, cerebellar dysgenesis and facial dysmorphisms. In the majority of these individuals, facial features suggested no specific diagnosis prior to WES. Major craniofacial findings included

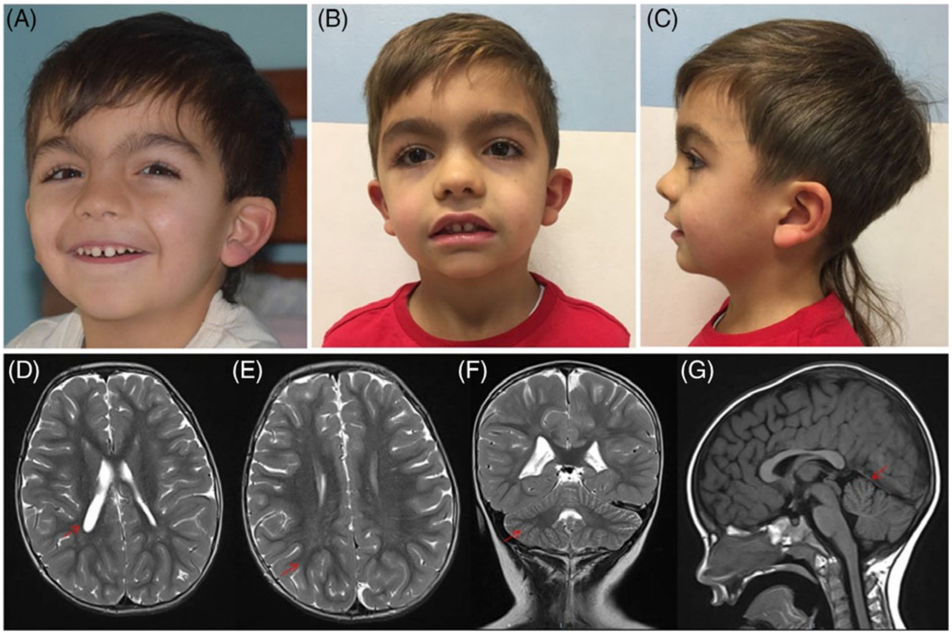

FIGURE 1 Clinical features of the patient with the novel de novo c.631G>A change in *PACS2*. Patient at age 5 years (A) and at 7 years and 6 months (B,C). Facial dysmorphisms, including synophrys, highly arched and sparse broad eyebrows, long eyelashes, low-set and posteriorly rotated ears with uplifted lobe, broad nasal tip, smooth philtrum, thin and everted upper lip vermilion, downturned corners of the mouth, widely spaced teeth, chin with horizontal crease. Brain MRI at 3 years and 10 months (D-G). Abnormal cerebellar foliation pattern along the basal and posterior portions of the right cerebellum hemisphere (F-G), a quantitative reduction of the white matter of the parietal regions (E). Lateral ventricular asymmetry is evident, with the right ventricle larger than the left (D) [Colour figure can be viewed at wileyonlinelibrary.com]

synophrys, hypertelorism, downslanting palpebral fissures, bulbous nasal tip, wide mouth with downturned corners, and thin upper lip.[11] Similar features also occurred in the present patient, who showed synophrys, highly arched and sparse broad eyebrows, long eyelashes, smooth philtrum, thin everted upper lip vermilion, reminiscent of the Cornelia de Lange facial gestalt. Of note, while this disorder was not clinically hypothesized by Olsen et al,[11] it was originally suspected in one of the two first patients affected by Schuurs-Hoeijmakers syndrome, in which WES disclosed a missense mutation in its paralog, *PACS1*. This argues for a partial overlap of facial features of *PACS*-related disorders with Cornelia de Lange syndrome.

Analysis of the clinical information available for the previously reported subjects with *PACS2* mutation indicate that growth parameters

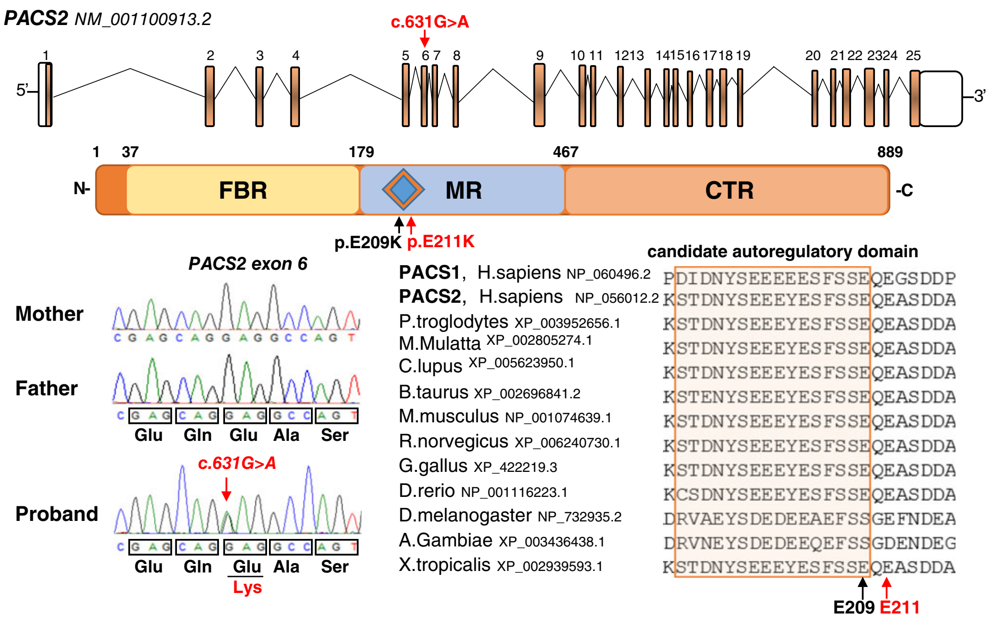

FIGURE 2 Genomic organization of *PACS2* and localization of the disease-causing mutation c.631G>A in exon 6 (NM_001100913.2). Domain structure of PACS2: FBR, furin (cargo)-binding region; candidate autoregulatory domain; MR, middle region; CTR, C-terminal region. Location of the two disease-causing missense mutations is shown. Electropherogram of the patient and his parents showing the de novo mutation c.631G>A change. Multiple alignments of PACS2 ortholog and paralogs. The candidate autoregulatory domain protein sequence of PACS2 is boxed [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Clinical features of individuals with *PACS2* p.Glu209Lys and our proband with a novel de novo missense mutation p.Glu211Lys

	Olson et al[11]														
Clinical features	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**	**P14**	**Our patient**
Sex	F	F	M	F	M	M	M	F	F	M	M	F	F	F	**M**
Gestational age (wk)	38	37	38	35	37	40	term	37	term	term	39.5	34	33	39	**38**
Birth parameters															
Weight (SD)	−0.3	Median	+2	+1.8	−1.7	+2.5SD	+1SD	-3SD	Median	NA	Median	+0.5	−0.5	+0.6	**3040**
Length (SD)	+ 0.6 SD	NA	NA	NA	−0.9 SD	+2 SD	+1SD	−1.5SD	-2SD	NA	-1SD	-1.5SD	Median	+0.9SD	**49**
OFC (SD)	+ 0.4 SD	NA	NA	NA	−2.3 SD	>3SD	median	−2.3 SD	median	NA	median	NA	median	−0-1SD	**35.5**
Growth at last evaluation/y	Normal/16 y	NR/4 y	Normal/15 y	Normal/8 y	Height,-1.8SD/19 mo	NR/8 y	Normal/16 mo	NR/5 y	NR/3 y	NR/7 y	Normal/12.5 y	NR/9 mo	NR/3.5 y	NR/5.5 y	**−3.20 SD/7 y GHD**
Facial appearance															
Synophrys	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Mildly; dysmorphic	No	No	No	No	**Yes**
Hypertelorism	Yes	Yes	Yes	Yes	No	No	No	Yes	No		No	Yes	Yes	No	**Yes**
Down slanting palpebral fissures	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No		No	No	Yes	No	**Yes**
Broad nasal root	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes		Yes	Yes	Yes	Yes	**Yes**
Thin Vermillion upper lip	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes		Yes	Yes	Yes	Yes	**Yes**
Wide mouth with downturned corners	Yes	Yes	Yes	Yes	Yes/No	No	No	Yes	No		Yes	Yes	Yes	No	**Yes**
Prominent incisors	Yes	No	Yes	Yes	NA	No	NA	No	No		No	NA	NA	No	**No**
Widely spaced teeth	Yes	No	Yes	No	NA	No	NA	No	No		Yes	NA	NA	No	**Yes**
Everted vermilion of lower lip	Yes	No	Yes	No	No	Yes	No	No	No		No	No	Yes	Yes	**Yes**
CHD		DC				VSD							ASD		**No**
Ocular	Myopia	No	No	SB	SB	SB, myopia									**No**
Genitourinary			Cryptor-chidism			Testis ectopia	Cryptor-chidism				Micropenis, cryptorchidism, CPP				**No**
Skeletal/distal limb anomalies															
	Metatarsus varus, slender fingers	No	2–3 toes syndactyly	No	V-clinodactyly, STPC	Finger pads	No	No	No	Bilateral STPC	V-finger brachy/clinodactyly	V-clinodactyly	No	STPC, V-clinodactyly	**No**
Hematologic	NA	Anaemia	NA	Anaemia	Anaemia	NA	Anaemia	NA	NA	NA	NA	NA	NA	NA	**No**
Developmental features															
Walking age	22 mo	NA	18 mo	18 mo	18 mo	22 mo	Not walking	27 mo	Not walking	24 mo	24 mo	NA	36 mo	36 mo	**24 mo**
Speech delay	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	**Yes**
DD/ID	Yes	Yes	Yes	Yes	Yes	Yes	Mild	Yes	Yes	Yes	Yes	Yes	Mild	Mild	**Moderate**

TABLE 1 (Continued)

	Olson et al[11]														
Clinical features	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**	**P14**	**Our patient**
Neurological															
Hypotonia	Yes	NA	NA	NA	No	no	axial	No	diffuse	diffuse	No	Yes	axial	diffuse	**No**
Nystagmus	No	Yes	No	No	Yes	No	No	No	No	No	transient	No	No	No	**No**
Stereotypies	No	transient	No	No	No	Yes	No	No	Yes	Yes	No	transient	Yes	No	
Behavioural features	No	Yes	No	Mild autistic	No	COD	NO	Atypical social	Atypical social	Autism spectrum disorder	Autism spectrum disorder	No	No	Selective mutism	**Transient hyperactivity**
Epilepsy															
Age of onset (d)	6 d	4 d	4 d	7 d	2 d	2 d	2 d	2 wk	2 d	1-2 mo	1 d	3 d	2 wk	3 d	**3 d**
Seizure types	Focal	GTCs	NA	GTCs	Clonic and GTC	NA	Focal with tonic stiffening and autonomic features, later clonic	Focal, later tonic	Focal, tonic-clonic and myoclonic, later GTCs and generalized tonic	Clonic seizure with eye deviation, later GTC	Focal (stopped at 2 mo), later GTCs	Focal tonic-clonic and tonic; status epilepticus	Focal tonic-clonic, later focal or generalized	Tonic, later tonic or GTCs	**Focal neonatal epilepsy stopped at 13 mo**
Age at last seizure	NA	6 mo	NA	2 y[a]	9 mo	3 mo	NA	2 y	2 y	2 y	NA	NA	NA	NA	**6 y**
EEG features	NA	Neonatal to 3.5 mo: normal background; 1 y: normal	NA	Neonatal excess multifocal sharp waves/ generalized bursts of epileptic activity	4 mo: generalized slowing with MF sharp waves and frequent focal seizures	Neonatal: left temporal spikes; 3.5 year: left paroxysmal temporal rolandic spikes, generalized slowing	6–7 wk: MF epileptiform activity; 9 mo: normal	6 wk: subtle aberration; R fronto-central and L temporal	Neonatal: excess discontinuity, excess MF sharp waves; 2 y: intermittent generalized slowing, intermittent L temporal slowing	4 months: normal; 17 months: rare generalized spikes	Neonatal: epileptic discharges, Lrolandic region	Neonatal: excess MF spikes and sharp waves, 2 mo: background; poorly organized; high amplitude; background, lack of state change, MF spikes	6 d: normal; neonatal/ infantile: MF epileptiform activity, high amplitude slow spikes bilateral temporal; 17 mo: diphasic spikes at vertex	Neonatal: excessive L and R central and temporal waves; 3 y: mild generalized slowing, frequent Left temporal epileptiform	**Focal neonatal epilepsy; 3 y sporadic focal anomalies; at 7 y: normal**
Brain MRI (age)															
	Foliar distortion of the left cerebellar hemisphere, MCM[a] (5 y)	IVH with prominent foramen Magendie and cisterna magna, severe foliar distortion of cerebellar hemispheres with centrifugal orientation, hypothalamic fusion anomaly (5 y)	Increased suba-rachnoid spaces	Mild IVH with a patulous foramen Magendie and mega cisterna magna, mild distortion of the cerebellar folia (3 wk)	Retrocerebellar arachnoidal cyst, IVH with prominent foramen Magendie, MCM, severe foliar cerebellum distortion with centrifugal orientation, hypothalamic fusion anomaly (7 d)	Normal[a] (10 d); normal[a] (4 mo)	IVH, left retrocerebellar cyst, causing distortion of the smaller left cerebellar hemisphere and thinning of the overlying bones[a] (2 mo)	Normal (birth)	Mega cisterna magna and patulous foramen Magendie, subtle cerebellar foliar distortion hypothalamic fusion anomaly (1 wk)	Mega cisterna magna, patulous foramen Magendie (1 mo)	Thick corpus callosum, inferior vermian hypoplasia[a] (12.5 y)	MCM, severe foliar distortion with centrifugal orientation (3 mo)	Moderate cerebellar foliar distortion (23 mo)	Mild scattered subarachnoid haemorrhage (2 mo); Prominent MCM and patulous foramen Magendie with subtle foilar distortion (31 mo)	**Abnormal cerebellar foliation orientation of the right cerebellum hemisphere. Iso-liquoral cyst on the right lateral ventricle**

TABLE 1 (Continued)

Clinical features	Olson et al[11]														Our patient
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	
Additional clinical features															
	Neutropenia						1mc cafè au lait spots, poor feeding, CHI	None	Dysphasia, accessory nipples	None	Hypertrophic pyloric stenosis, velopharyngeal hypotonia	Brachycephaly, inverted nipples	Sacral pit		

Abbreviations: ASD, atrial septal defect; CHI, conductive hearing impairment; CPP, central precocious puberty; DC, dextrocardia; EEG, electroencephalogram; F, female; IVH, inferior vermian hypoplasia; m, median; M, male; MCM, mega cisterna magna; MF, multifocal; NA, not available; OCD, obsessive compulsive disorder; SB, strabismus; STPC, single transverse palmar crease; VSD, ventricular septal defect.

[a] Immediate recurrence after withdrawal of valproate.

appear generally within normal ranges prenatally, as well as postnatally, notwithstanding the limited availability of data. By contrast, the present patient presented with postnatal growth delay that became evident at age 5, when GH treatment was started. WES analysis did not reveal any putative functionally relevant variant linked to processes controlling growth, suggesting that postnatal growth failure may represent part of the phenotypic spectrum of this disorder.

Six of 15 individuals, including the present case, were reported to have epilepsy. While details on the nature of epilepsy in this cohort are limited, it appears to have generally a neonatal/early-infantile onset, with 12/14 of cases having seizures during the first week of life, and often challenging to control in infancy. Consistently, our patient epilepsy manifested at 3 days of life and it was difficult to control in the first 30 days, which however was followed by a seizure-free period that still persists until now, even after the discontinuation of treatment. CNS malformations appear to be a recurrent feature of subjects with *PACS2* mutations, described in 12/14 individuals, 10/14 of which presenting with cerebellar involvement.[11] In the present case, abnormal cerebellar foliation orientation along the basal and posterior portions of the right cerebellum hemisphere was found, together with a quantitative reduction of the white matter of the parietal region and lateral ventricular asymmetry.

Other defects are less common, including congenital heart disease (3/15 patients), ocular abnormalities with myopia and strabismus, and mild distal limb anomalies, including fifth finger brachyclinodactyly.

In conclusion, the present patient confirms that de novo *PACS2* mutations underlie a complex disorder characterized by developmental and epileptic encephalopathy with mild to moderate ID, variable CNS malformations with cerebellar dysgenesis, and facial dysmorphism. Reduced postnatal growth with GH deficiency could be an additional feature. Further studies are required for delineating the natural history of this newly recognized syndrome.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Ethics approval

The study follows the principles outlined in the Helsinki Declaration and the patient's family gave written informed consent for molecular study and publication.

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SUPPORTING INFORMATION

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

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