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New case with the recurrent c.625G>A pathogenic variant in the *PACS2* gene: expanding the phenotype☆

Nuevo caso con la variante patogénica recurrente c.625G>A en el gen *PACS2*: expansión del fenotipo

Dear Editor:

The recurrent c.625G>A (p.Glu209Lys) pathogenic variant of the *PACS2* gene has recently been reported to be the causal agent of developmental and epileptic encephalopathy 66 (DEE66; MIM #610423) in 15 patients with predominantly neonatal-onset epilepsy, facial dysmorphism, and cerebellar dysgenesis, which may also be associated with such developmental disorders as intellectual disability, autistic spectrum disorders, haematological alterations, and/or distal limb abnormalities.[1,2] Since the condition was first described, only one case with a similar phenotype and a different *PACS2* variant has been reported.[3] In 2012, 2 cases were reported of intellectual disability due to a recurrent mutation in the *PACS1* gene sharing clinical characteristics with the previously reported cases (hypotonia, epilepsy, facial dysmorphism).[4]

The *PACS2* gene is expressed in different tissues and encodes the multifunctional PACS2 protein, which plays a major role in the interaction between the endoplasmic reticulum membrane and the mitochondria. It acts as a metabolic switch involved in trafficking and signalling between these membranes, as well as nuclear gene expression in response to catabolic or anabolic signals.[5,6] We present a new case of the recurrent variant of *PACS2*, detected in 15 of the 16 cases of DEE66 reported worldwide.

Our patient was a 3-year-old girl with no relevant medical history; she was the second child of healthy, non-consanguineous parents of Bolivian descent. She was referred to our hospital's medical genetics department by the paediatric neurology department at the age of 16 months due to polydactyly, facial dysmorphism, and epilepsy. The patient was born after a spontaneous, uneventful, full-term pregnancy. Birth weight was 4000 g; resuscitation was not required and the neonatal period was normal. The blood spot and otoacoustic emission tests yielded normal results. She underwent surgery to treat postaxial polydactyly in both feet, with no complications. Developmentally, she presents no feeding problems and shows normal growth at 3 years of age: weight, 13.9 kg (p63); height, 89 cm (p36); head circumference, 47 cm (p10). Her dysmorphic features overlap with those previously described (Fig. 1).

At 3 months of age, our patient began to present seizures, consisting of right-sided deviation of the head and eyes, generalised hypertonia, and dystonic posturing of the limbs; levetiracetam achieved no response and valproic acid exacerbated symptoms. An emergency head CT scan revealed no alterations; the patient was admitted to the intensive care unit due to status epilepticus. We started perfusion with midazolam and phenytoin; after seizure control, phenytoin was switched for zonisamide, which the patient continues receiving at present. EEG at admission revealed diffuse background slowing, with no focal abnormalities or any other type of epileptiform activity. EEG findings at 24 hours were similar but less marked; a month later, the EEG trace was completely normal. However, at 5 months of age she was readmitted due to exacerbation of seizures; she presented additional episodes at ages 24 and 30 months. The patient has remained seizure-free since then, with all interictal EEG studies showing normal results.

Our patient presented psychomotor retardation; at age 3 years and 6 months, she presented a developmental age of 15-18 months in the areas assessed, according to the modified Vaughan scale. Expressive language was the most severely affected area, with the patient also presenting occasional episodes of self- and hetero-aggression. She is currently being followed up at an early childhood special needs centre and attends mainstream school, where she receives tailored support. Table 1 compares the clinical features of our case against those from previously reported cases.

The paediatric neurology department conducted the following complementary tests during follow-up: brain MRI and abdominal ultrasound (neonatal period), with no pathological findings; cardiology and ophthalmology examinations, with normal results (no signs of retinopathy); 60 K array-CGH analysis; and blood and urine metabolic screening including asialotransferrin, sterols, amino acids, organic acids, lactate/pyruvate, acylcarnitines, sulfites, and purine metabolism, with normal results. The patient was assessed by the genetics department due to suspicion of a genetic disorder, possibly a ciliopathy, due to

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Table 1 Clinical characteristics of our patient and the previously published cases.

Clinical manifestations	Frequency described by Olson et al.,[1] Dentici et al.,[2] and Terrone et al.[3]	Our patient
Neurological symptoms		
Seizures	16/16	+
Neonatal seizures	15/16	—
Mean age of epilepsy onset	7 days	90 days
Mean age at seizure control (5/16)	11 months	30 months
Psychomotor retardation/intellectual disability	16/16	+
Hypotonia	7/16	—
Language delay	16/16	+
Behavioural alterations	10/16	—
Ataxia	2/16	—
CNS alterations		
Cerebellar dysgenesis (folia)	10/16	—
Other (megacisterna magna, ventriculomegaly, abnormal fusion of the hypothalamus, etc)	14/16	—
Haematologic alterations	5/16	—
Distal limb abnormalities	8/16	+
Clinodactyly	4/16	—
Brachydactyly	1/16	+
Single palmar crease	3/16	—
Polydactyly	0/16	+
Other major and minor structural alterations		
Heart alterations (dextrocardia, atrial/ventricular septal defects)	3/16	—
Ophthalmological alterations (strabismus, refractive errors, anisocoria)	6/16	—
Genital abnormalities (cryptorchidism, ectopic testicle, micropenis)	4/16	—
Other	Nystagmus (3), café-au-lait spots (1), increased reflexes (2), dysphasia (2)	Café-au-lait spot
Characteristic facial features		
Synophrys	6/16	+
Hypertelorism	8/16	+
Slanting palpebral fissures	9/16	—
Wide nose bridge	11/16	+
Anteverted nares	No data	+
Macrostomia with downward oral commissures	10/16	+
Other	Arched eyebrows, prominent incisors, widely spaced teeth, everted lower lip	Arched eyebrows, prominent ears, retrognathia

the combination of psychomotor retardation, polydactyly, brachydactyly, and facial dysmorphism. A next-generation sequencing analysis of the associated genes found no candidate variants, and hearing tests (brainstem auditory evoked potentials and audiometry test) detected no alterations. Clinical exome sequencing identified the previously described pathogenic variant in *PACS2*. Our patient's parents could not undergo genetic studies since they were not registered as residents of the region where our centre is located.

We present a new case of DEE66 due to *PACS2* pathogenic variant c.625G>A, manifesting with milder symptoms than reported in most cases due to later onset of epilepsy and lack of cerebellar dysgenesis. Our case expands the phenotype of the condition, as the patient presented polydactyly. The clinical worsening observed after onset of

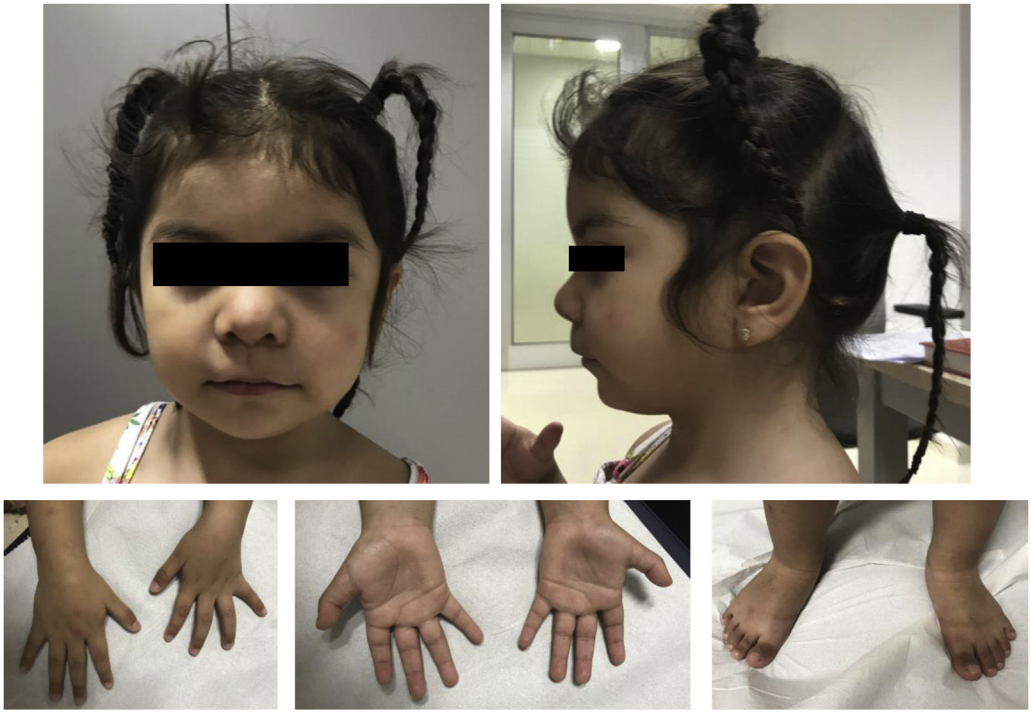

Figure 1 Phenotype of our patient at the age of 3 years. Coarse facial features, mild hypertelorism, arched eyebrows with mild synophrys, low nasal bridge, short nose, anteverted nares, thin upper lip with downward oral commissures, mild retrognathia, mild brachydactyly, and surgically corrected postaxial polydactyly in both feet.

treatment with valproic acid may be linked to the function of the PACS2 protein; use of this drug should therefore be questioned.

Our case confirms the involvement of *PACS2* in the pathogenesis of intellectual disability and epileptic encephalopathy, and underscores the usefulness of clinical exome sequencing for the diagnosis of recently-described, and probably underdiagnosed, rare, complex phenotypes.

Our patient presented the same variant as 15 of the 16 reported cases of DEE66, which confirms that this is a recurrent variant.

The *PACS2* gene should be included in panels for epileptic encephalopathy and cerebellar dysgenesis, and in patients with suspected ciliopathies and/or alterations in the *PACS1* gene.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Meningoencephalitis caused by *Cryptococcus neoformans* and varicella[16_TD$DIFF]-zoster virus in a patient with systemic lupus erythematosus☆

Meningoencefalitis por *Cryptococcus neoformans* y virus varicela-zoster en paciente con lupus eritematoso sistémico

Dear Editor:

Infectious processes are one of the most frequent causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE). This is due both to the immunological dysfunction caused by the disease itself and the immunosuppressive treatment[18_TD$DIFF].[1] Most of these infections are of bacterial origin[19_TD$DIFF],[2] although infection with parvovirus or viruses from the herpesvirus family, including varicella-zoster virus (VZV), is not infrequent[20_TD$DIFF].[3] In turn, case series of systemic infections with such fungi as *Cryptococcus neoformans* have also been reported[21_TD$DIFF].[4]

Most cases of *C. neoformans* meningoencephalitis occur in patients with AIDS with CD4 counts below 100 [22_TD$DIFF]cells/μL,[5] but it also manifests in seronegative patients, especially those who are immunocompromised for other reasons, including patients with SLE[23_TD$DIFF].[6,7] Cases of meningoencephalitis due to VZV infection in patients with SLE are scarce in the literature[24_TD$DIFF].[8]

The aim of this article is to report the first case in the literature of central nervous system co-infection with *C. neoformans* and VZV in a patient with SLE and treated with mycophenolate mofetil (MMF) and corticosteroids.

Our patient was an 18-year-old woman with SLE with haematological (autoimmune haemolytic anaemia treated with decreasing doses of prednisone from the previous year) and pulmonary involvement (bronchiectasis and recurring infections treated with antibiotics and cycles of prophylactic azithromycin), as well as positive antiphospholipid antibodies, treated with prednisone (5 [25_TD$DIFF]mg/24 h), MMF (1 g/12 h), and hydroxychloroquine.

The patient initially presented persistent severe headache and vomiting after manifesting symptoms compatible with respiratory infection in the previous week, which were treated with antibiotics. An eczema-like lesion without vesicles was observed on the outer ear. Several days later, she manifested behavioural alterations and irritability, as well as decreased level of consciousness, and finally an episode compatible with seizure. The patient did not present fever during the episodes.

An emergency head CT scan revealed a slight left occipital cortical hypodensity. She subsequently underwent a lumbar puncture, obtaining clear cerebrospinal fluid (CSF), which revealed slight, predominantly mononuclear pleocytosis (100 cells) and high protein levels. Opening pressure was not measured at that time.

Due to the possibility of autoimmune encephalitis, the patient received a megadose of methylprednisolone. She was also treated with aciclovir and antibiotics (as we could not rule out meningoencephalitis that resolved due to the recent antibiotic treatment), and MMF was suspended due to the possibility of posterior reversible encephalopathy syndrome.

We requested a CSF microbiological study, including Gram and India ink staining, bacterial and fungal cultures, and a PCR assay panel (FilmArray®). The PCR assay detected *Cryptococcus*[26_TD$DIFF] and VZV, and India ink staining showed presence of fungi. The culture was also positive for *C. neoformans*. We started treatment with amphotericin B and flucytosine and suspended antibiotic treatment and high-dose corticosteroids, but maintained aciclovir.

A brain MRI scan confirmed that the hypodensity observed in the head CT scan corresponded to vasogenic oedema, which is compatible with an encephalitis-like inflammatory process in this clinical context. We also observed diffuse leptomeningeal enhancement [27_TD$DIFF]and 2 dilated Virchow-Robin spaces with minimal contrast enhancement (Fig. 1). Dilated Virchow[15_TD$DIFF]-Robin spaces in the basal ganglia constitute one characteristic of brain cryptococcosis, and may merge and form what are known as gelatinous pseudocysts.

In the subsequent hours, the patient developed vesicles in the eczema previously observed on the outer ear. Reduced level of consciousness and intense headache persisted, in association with bilateral limitation of gaze abduction. Due to these symptoms, we suspected intracranial hyperten-

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