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# Characteristics of epilepsy secondary to mutations in the *PNKP* gene☆

## Características de la epilepsia secundaria a alteraciones en el gen *PNKP*

*Dear Editor:*

*PNKP* gene mutations cause neurodevelopmental disorders with varying degrees of epilepsy, psychomotor retardation, cerebellar atrophy, and peripheral neuropathy[1]. Different phenotypes have been described in the literature:

1 Microcephaly, seizures, and developmental delay (MIM #613402). The condition, first described by Shen et al. in 2010, follows an autosomal recessive inheritance pattern. Patients present congenital microcephaly, early-onset epilepsy rapidly progressing to developmental and epileptic encephalopathy, and intellectual disability.[1—4]
2 Ataxia-oculomotor apraxia 4 (MIM #616267). First described by Bras et al. in 2015, it is characterised by ataxia and oculomotor apraxia secondary to cerebellar atrophy. Patients frequently present axonal sensorimotor polyneuropathy, but do not present microcephaly or epilepsy.[3,5,6]
3 In recent years, cases have been reported of patients with intermediate phenotypes[3,4,7—10]:

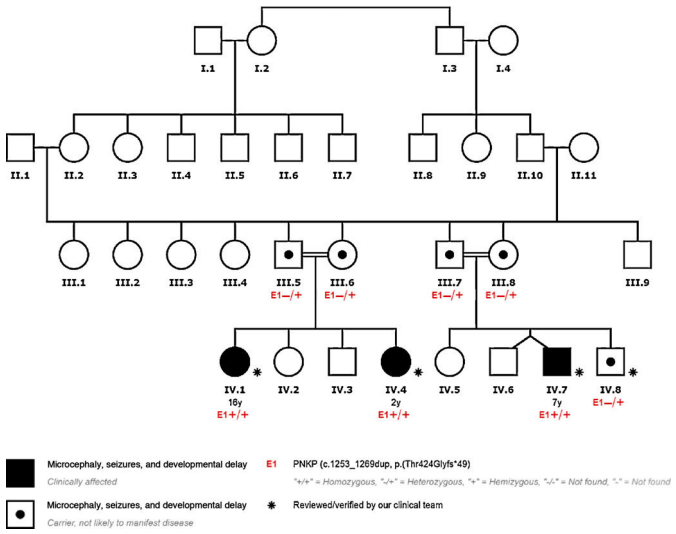


**Figure 1** Pedigree chart of our patients' family.

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**Table 1** Characteristics of our patients.

| | *PNKP* mutation | Epilepsy | Brain MRI | Initial EEG | Congenital microcephaly | CP | Intellectual disability | Other | Diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Patient 1 | *PNKP*: c.1253_1269dup; p.Thr424Glyfs*49 (homozygosis) | Age at onset: 3 months<br>First seizure: GTCS<br>Progression: GTCS<br>Controlled at age 4 years with VPA and TPM | Cerebral and cerebellar atrophy | Onset: multifocal<br>Progression: EE, normal | Yes | Severe spastic quadriplegia | Severe intellectual disability | Mixed sensorimotor polyneuropathy | MSDD or MNP |
| Patient 2 | *PNKP*: c.1253_1269dup; p.Thr424Glyfs*49 (homozygosis) | Age at onset: 8 months<br>First seizure: GTS<br>Progression: GTS, FS with clonic movements of RUL<br>Controlled at age 12 months with VPA and LEV | Brain atrophy | Onset: multifocal<br>Progression: normal | Yes | Mild spastic diplegia | Severe intellectual disability | | MSDD |
| Patient 3 | *PNKP*: c.1253_1269dup; p.Thr424Glyfs*49 (homozygosis) | Age at onset: 3 months<br>First seizure: GTS<br>Progression: GTS and FS with clonic movements in the right hemibody<br>Controlled at age 2 years with VPA, LEV, and TPM | Brain atrophy, thinning of the corpus callosum | Onset: multifocal<br>Progression: multifocal, normal | Yes | Severe spastic-dystonic quadriplegia | Severe intellectual disability | | MSDD |
| Patient 4 | *PNKP*: c.1253_1269dup; p.Thr424Glyfs*49 (heterozygosis) | Age at onset: 2 years<br>First and subsequent seizures: no data<br>Controlled with VPA | Normal | Onset: focal<br>Progression: normal | No | No | Normal intellectual function | ADHD | Epilepsy not linked to *PNKP* mutation |

CP: cerebral palsy; EE: epileptic encephalopathy; EEG: electroencephalography; FS: focal seizure; GTCS: generalised tonic-clonic seizure; GTS: generalised tonic seizure; LEV: levetiracetam; MNP: microcephaly with neurodegeneration and polyneuropathy; MRI: magnetic resonance imaging; MSDD: microcephaly, seizures, and developmental delay; RUL: right upper limb; TPM: topiramate; VPA: valproic acid.

Microcephaly with neurodegeneration and polyneuropathy. This phenotype is a combination of the 2 phenotypes previously mentioned. The syndrome is caused by presence of the p.Thr424Glyfs*48 frameshift variant in homozygosis, and was described by Poulton et al. in 2013, in 2 siblings with congenital microcephaly, epilepsy, ataxia, and progressive cerebellar degeneration.[2,4,7]

Charcot-Marie-Tooth—like disease. Characterised by pes cavus, sensorimotor polyneuropathy, and progressive ataxia. These patients do not present oculomotor apraxia, epilepsy, or intellectual disability.[8,9]

We present the cases of 4 patients from a single family with *PNKP* pathogenic variant NM_007254.3:c.1253_1269dup;p.Thr424Glyfs*49, detected by clinical exome sequencing. This variant has previously been described as pathogenic (Table 1, Fig. 1).

*Patient 1:* 16-year-old girl who presented epilepsy at 3 months of age in the form of status epilepticus. Epilepsy was controlled at 4 years of age. She also presented congenital microcephaly, spastic quadriplegia, and intellectual disability. A brain MRI scan revealed cerebellar atrophy and diffuse thickening of the diploë. The patient presents calf atrophy and absent patellar and Achilles reflexes. The EMG study revealed predominantly axonal mixed sensorimotor neuropathy.

*Patient 2:* 2-year-old girl who presented epilepsy at 8 months of age, and status epilepticus at one year of age. She also presented congenital microcephaly, cerebral palsy, and severe intellectual disability. A brain MRI scan revealed diffuse cerebral atrophy.

*Patient 3:* 7-year-old boy, presenting epilepsy at 3 months of age, with several episodes of status epilepticus. Epilepsy was controlled at 2 years of age. He also presented microcephaly, cerebral palsy, and severe intellectual disability. A brain MRI scan revealed diffuse cerebral atrophy and thinning of the corpus callosum.

*PNKP* pathogenic variant c.1253_1269dup;p.Thr424Glyfs*49 was detected in homozygosis in patients 1, 2, and 3.

*Patient 4:* 8-year-old boy, who began to present frontal lobe seizures at the age of 2 years. He did not present microcephaly, intellectual disability, or cerebral palsy. Neuroimaging studies revealed normal results. He only presented attention deficit—hyperactivity disorder, with normal intellectual function.

We detected *PNKP* variant c.1253_1269dup;p.Thr424Glyfs*49 in heterozygosis; this patient was therefore considered to be an asymptomatic carrier of the mutation. His epilepsy is a phenocopy, meaning that while it presents similar phenotypic traits to those of patients with the homozygous mutation, these cannot be attributed to the mutation.

All the parents of our patients were heterozygous carriers of the mutation.

## Discussion

The patients carrying the mutation in homozygosis (patients 1, 2, and 3) present early-onset epilepsy, developmental and epileptic encephalopathy, congenital microcephaly, cerebral palsy, and brain atrophy. They may be classified as having microcephaly, seizures, and developmental delay (MIM #613402), although patient 1 also presented neuropathy, which suggests the phenotype microcephaly with neurodegeneration and polyneuropathy.

In patient 4, epilepsy is a phenocopy, as it cannot be attributed to *PNKP* variant c.1253_1269dup;p.Thr424Glyfs*49 in heterozygosis.

Furthermore, all our patients' parents presented the mutation in heterozygosis, and were asymptomatic carriers.

Several clinical presentations of *PNKP* mutations have been reported, some of which include epilepsy.

The reason why a single *PNKP* mutation may cause different phenotypes is unknown; this phenomenon, known as variable expressivity, may involve other genetic, epigenetic, and/or environmental factors[3].

The appearance of intermediate phenotypes in recent years suggests that all phenotypes lie on a spectrum of the same disease. Genetic studies should be performed in patients with complex genotypes.

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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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