The recurrent PACS1 variant disrupting trans-Golgi-membrane trafficking: A recognizable phenotype

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Introduction and aim

PACS1 is a trans-golgi-membrane traffic regulator directing protein cargo. A de novo missense variant in the *PACS1* gene first identified in individuals with intellectual disability and dysmorphism in 2012 and designated as Schuurs-Hoeijmakers syndrome. Epilepsy and multi-systemic involvement are frequent. It is reported that seizures respond well to anti-seizure medications. We aim to present unpublished six patients with very rare Schuurs-Hoeijmakers syndrome, some of whom had drug-resistant epilepsy and significant EEG abnormalities.

Methods

We retrospectively collected clinical information and molecular diagnosis data of six patients with a variant in the *PACS1* gene from multiple centers. Clinical exome or whole-exome sequencing had been performed to identify it.

Results

All patients had the same de novo c.607C>T variant in the PACS1 gene, which was classified as likely pathogenic. The age range was 5-33 years, including the oldest patient in the literature. They all had distinctive facial features characterized by hypertelorism, bulbous nasal tip, flat philtrum with thin upper lip, low set ears, and diastema (Figure 1). Some patients had cardiac, genitourinary, and ocular involvement. Ophthalmologic findings such as iris coloboma, optic nerve abnormalities, and decreased visual acuity were present in three patients. The intellectual developmental disorder was present in all, ranging from moderate to severe, with autistic features in some. Gross and fine motor delays accompanied. Five patients had epilepsy, one had drug-resistant epilepsy, and another was on polytherapy for continuous generalized spike-waves. Ethosuximide was added to valproic acid and levetiracetam for myoclonic atonic seizures, resulting in a significant reduction in seizure frequency. Another patient with focal motor seizures and frequent generalized spike-wave complexes was treated with clobazam, valproic acid, and levetiracetam. She later became seizure free with improvement in EEG showing right central epileptiform discharges with secondary generalization. Details of all patients are given in Table 1.

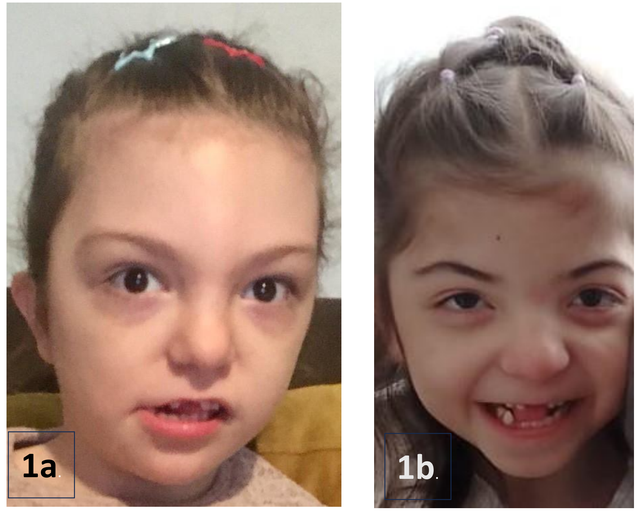

Figure 1a,b. Facial phenotypic features of the patients. arched eyebrows, hypertelorism with downslanting palpebral fissures, and long eye lashes, low set and simple ears, bulbous nasal tip, wide mouth with downturned corners and a thin upper lip with an unusual “wavy” profile, flat philtrum and diastema of the teeth.

Table 1. Details of patients with Schuurs-Hoeijmakers syndrome.

Pt	*Age (yrs)*	*Variant in the PACS1 gene*	*Epilepsy (seizure type/drugs and response to therapy)*	*EEG (Localization of epileptiform discharges)*	*Other*
1	5	c.607C>T p.Arg203Trp	Focal motor/ Valproic acid, Levetiracetam, Clobazam/ no seizures	Right central with secondary generalization	Myopia Strabismus
2	8	c.607C>T p.Arg203Trp	No	Normal	Mitral insufficiency Left double ureter
3	8	c.607C>T p.Arg203Trp	Focal motor/ Levetiracetam/ No seizures	Right central	Decreased vision
4	33	c.607C>T p.Arg203Trp	Generalized tonic-clonic/ Oxcarbazepine/ No seizures	Bilateral frontocentro-parietal	PDA-VSD Cryptorchidism Hashimoto thyroiditis
5	13	c.607C>T p.Arg203Trp	Focal motor/ Valproic acid/ No seizures	Bilateral frontal-temporal (first)/ Normal (last)	Iris coloboma, strabismus
6	7	c.607C>T p.Arg203Trp	Myoclonic-atonic/ Valproic acid, Levetiracetam, Ethosuximide/ Seizures >%50 decrease	Rare generalized	ASD, VSD Decreased Vision (optic nerve abnormality)

ASD:atrial septal defect; EEG:electroencephalography; PDA:patent ductus arteriosus; pt:patient; VSD:ventricular septal defect; yrs:years.

DISCUSSION

We have described a spectrum of patients with this rare Schuurs-Hoeijmakers syndrome with a clinically recognizable phenotype including multisystem involvement with associated epilepsy in all but one patient. Polytherapy was required to control seizures in two patients. One patient continued to have myoclonic-atonic seizures despite treatment. Epilepsy has been reported to be common and mostly well managed, but we have described some difficult to treat patients. Ethosuximide showed some response in myoclonic-atonic seizures in the patient described and later clonazepam as add-on treatment (after submission of the abstract) resulted in complete control of seizures.

All of our patients had the same variant; the recurrence of the particular variant and the absence of variants at other positions had been reported to indicate a dominant-negative effect or gain of function at the protein level.

Coloboma in one patient and decreased visual acuity in two patients were noted. Ocular coloboma is a defect of the eye caused by incomplete closure of the embryonic choroidal fissure. Thus, PACS1 is a very important gene for the development of craniofacial structures and fetal brain, involved in cargo protein trafficking in the trans-Golgi network**.**

Conclusion

Epilepsy is frequent in our case series even with drug-resistant seizures. Ophthalmological involvement may be severe, resulting in decreased vision. De novo c.607C>T variant is the major variant reported. A gain-of-function effect has been proposed as a reason for the absence of other variants in the gene.

References

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