Mutation of *PACS1*: the milder end of the spectrum

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List of Key features

Macrocephaly
Overgrowth
Tall stature
Long palm
Long feet
Talipes equinovarus
Camptodactyly

Introduction

Schuurs-Hoeijmakers syndrome (SHS; MIM#615009) is frequently caused by a recurrent mutation in phosphofurin acidic cluster sorting protein 1 (*PACS1*). It is characterized by intellectual disability, severe speech difficulties and facial dysmorphism, and fewer than 40 patients have been described. It may also cause seizures, behaviour disturbances, congenital malformations, short stature and feeding difficulties (Scott *et al*., 2006; Schuurs-Hoeijmakers *et al*., 2012, 2016; Gadzicki *et al*., 2015; Miyake *et al*., 2017).

PACS1 (OMIM* 607492) is responsible for trafficking proteins in the trans-Golgi network (Scott *et al*., 2006). The recurrent missense mutation c.607C > T (NM_018026; p.Arg203Trp) is present in most of the patients described so far (Schuurs-Hoeijmakers *et al*., 2012, 2016; Gadzicki *et al*., 2015), although a further novel mutation (c.608G > A) has been described (Miyake *et al*., 2017). It is suggested that the common missense variant could disrupt regulation, leading to mislocalization of protein variants, and act through dominant-negative or gain-of-function effects (Schuurs-Hoeijmakers *et al*., 2012, 2016; Gadzicki *et al*., 2015). Other *PACS1* variants may not induce a recognizable phenotype. Furthermore, different deletions or duplications in *PACS1* are reported in association with variable phenotypes, some of them with nonsyndromic neurodevelopmental disorder (Gadzicki *et al*., 2015).

A detailed phenotypic description of rare disorders using Human Phenotype Ontology or other phenotypic classifications can help to clarify the pathogenicity of mutations and to reach a diagnosis through analysis of complex Next Generation Sequencing data. We describe a girl with the recurrent c.607C > T *PACS1* mutation, expanding upon the already known phenotype and including some unexpected findings that may help to identify other atypical patients and to broaden the phenotype.

Case report

A 12-year-old girl, the first child of healthy nonconsanguineous parents, was followed up because of developmental delay. She showed an overgrowth phenotype from birth involving tall stature (height > p97), macrocephaly (head circumference > p97) and large, broad hands and feet (hand and foot length > p99). The parents' growth parameters were within the normal range. She also had clinodactyly and camptodactyly of the fifth finger, high plantar arches without evidence of a neuropathy and dysmorphic facies (Fig. 1). The facial features included hypertelorism, downslanting palpebral fissures, eversion of the lateral third of lower eyelids, a bulbous nasal tip, long philtrum, thin upper vermilion, a wide mouth with downturned corners and low-set ears. At the age of 3, she underwent surgery for a persistent ductus arteriosus. She has a patent foramen ovale and bicuspid aortic valve without haemodynamic consequences.

She never showed feeding or gastrointestinal dysfunction, and despite a delay in speech, she has a broad vocabulary. She achieved independent walking at the age of 2 years; at present, she shows some clumsiness. She attends a special school. She has undergone three MRI scans, showing a structural normal brain and cerebellum. She has been treated with carbamazepine because of partial seizures since the age of 3. In terms of her behavioural phenotype, she is a kind girl, she normally uses language to request and ask, she does not present with tantrums and there are no aggressive spells. From the age of 10, she has presented with laughing episodes not explained by electroencephalographic findings. These have interfered with her normal activities and have been controlled with aripiprazol. During the last year, she has had three episodes of a few hours' duration of ataxia occurring during periods when she had recurrent mycoplasma respiratory tract infections affecting the right upper lobe of the lung. The ataxia resolved spontaneously, and cerebrospinal

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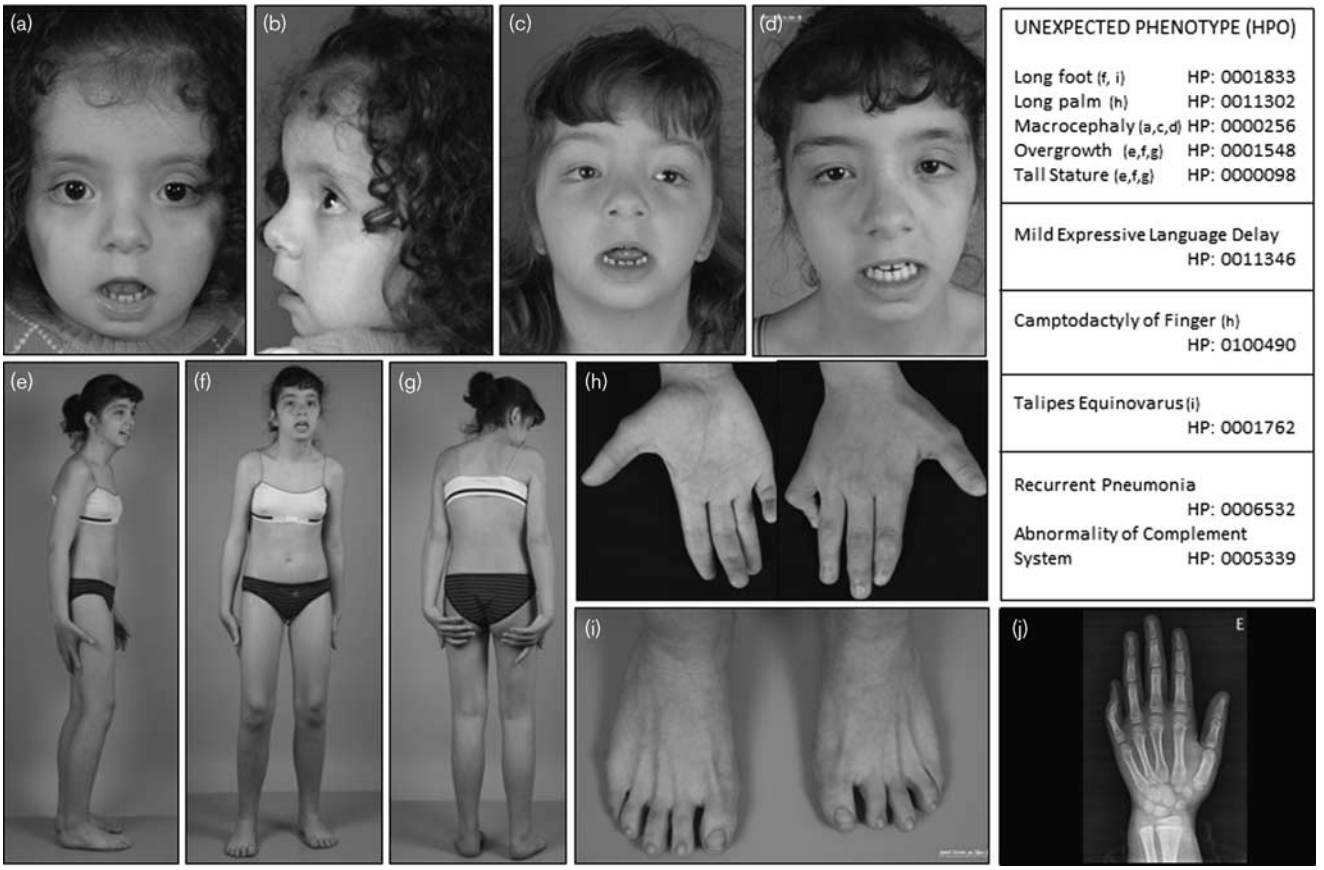
Fig. 1



Photographs of the patient at different ages and unexpected features encoded by Human Phenotype Ontoloy (HPO). (a, b) Frontal and lateral facial view of patient at the age of 2 years. (c) Frontal facial view at the age of 6 years. (d) Frontal facial view at the age of 12 years. (e–g) Frontal, lateral and posterior body views at the age of 12 years. (h, i) Hands and feet views at the age of 12 years. (j) Hand radiograph showing an advanced bone age of 1 year at the age of 5 years.

fluid analysis and neuroimaging were normal. A bronchoscopy and complete laboratory test were performed, yielding normal results, except for a maintained decrease in complement factor C3 (< 110 U/ml, normal: 890–1950). Interestingly, she had not developed recurrent infections before.

Through trio-based whole-exome sequencing and Sanger sequencing, a de novo missense *PACS1* mutation, already reported in other affected individuals, was identified and confirmed (c.607G > A). No other plausible mutations were found.

Discussion

SHS is a recently described syndrome with a consistent phenotype among reports. Some features such as facial dysmorphic features and variable intellectual disability with language difficulties seemed to be constant. In contrast to other described patients, our patient has overgrowth, normal feeding and only mild compromise of communication skills, thus showing a milder presentation of the PACS1-related spectrum. Facial gestalt in classical patients includes hypertelorism, downslanting palpebral fissures, mild ectropion, a bulbous nasal tip, long philtrum, thin upper vermilion, downturned corners and low-set ears. Currently, SHS is likely to be an under-reported phenotype, with patients at the milder end of the spectrum remaining unrecognized despite the recurrent mutation being found in most patients.

In terms of the clinical picture in our patient, four characteristics in particular should be highlighted: (i) overgrowth phenotype, (ii) absence of digestive and feeding disturbances, (iii) only mild impairment of communication skills and (iv) unexplained immunological issues.

In terms of this last finding, previous reports do not include any remarkable immunological symptoms related to the *PACS1* mutation. However, *PACS1* has been linked to cellular immunological response as it is a membrane trafficking protein that may be implicated in many cellular processes. Whether the recurrent infections in our patient are because of *PACS1* dysfunction is

difficult to conclude on the basis of a single patient report and this could be coincidental. This observation needs to be explored further in other patients.

Describing patients with atypical rare disease phenotypes should be a priority, particularly for extremely rare and newly identified syndromes. Otherwise, expectations that all patients should fit the classical phenotype may bias bioinformatics analysis and the clinician's search for molecular causes.

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Conflicts of interest

There are no conflicts of interest.

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