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Severe short stature in two siblings as the presenting sign of *ACP5* deficiency

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Abstract

Background—*ACP5* deficiency is known to cause spondyloenchondrodysplasia (SPENCD), which is characterized by various auto-immune and neurological symptoms in addition to short stature.

Methods—Two siblings from a consanguineous Turkish family, a girl age 13 (P1) and a boy age 8 (P2), presented to their endocrinologist with progressive growth failure and severe short stature (−5 SDS). They had no comorbid conditions and on physical exam there were no signs of an overt skeletal dysplasia with normal appearance of extremities. Sitting height ratio (SHR) was mildy decreased in P1 (−2.5 SD) and normal in P2. Extensive laboratory work-up, including growth hormone stimulation and IGF-1 generation tests, were normal. Exome sequencing was performed.

Results—Exome sequencing identified the presence of a homozygous frameshift mutation (p.Ser258Trpfs*39) in *ACP5* in both siblings, which was confirmed by Sanger sequencing. This specific mutation has previously been described in patients with spondyloenchondrodysplasia (SPENCD). Additional work-up in the two siblings showed distinct features of skeletal dysplasia on X-rays consistent with SPENCD, but none of the common auto-immune or neurological abnormalities associated with this condition.

Conclusion—Severe short stature can be the only presenting sign of *ACP5* deficiency and could therefore be considered as a rare cause in the differential diagnosis of severe, proportionate growth failure.

Keywords

ACP5 deficiency; SPENCD; short stature; skeletal dysplasia; exome sequencing

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Introduction

Short stature can be caused by many different diseases and conditions, as well as by primary growth disorders affecting growth plate physiology, GH/IGF-1 axis signaling, cell cycle control and centriole functions. In cases of severe idopathic short stature, whole exome sequencing can be used for diagnostic purposes with a reasonable chance of identifying the underlying genetic defect [1]. In this study, exome sequencing led to the identification of a homozygous mutation in *ACP5* in two siblings who presented with isolated extreme short stature but without the typical autoimmune features seen in the rare form of spondyloenchondrodysplasia caused by *ACP5* mutations.

Patient description

A 13-year old girl (P1) and her 8-year old brother (P2) from a consanguineous Turkish family presented to their pediatric endocrinologist for the evaluation of severe short stature (~−5 SDS). Both children were born full term after uncomplicated pregnancies and deliveries. Exact birth weight of P1 was unknown, P2 had a birth weight of 3000 grams. Neonatal course and overall health during infancy and childhood had been excellent for both siblings other than the onset of progressive post-natal growth failure with a gradual decline in height to below −5 SDS. Neither of the siblings had a history of frequent childhood infections, recurrent fevers, skin or joint problems, or chronic gastro-intestinal complaints, and their weight relative to height had been normal throughout childhood. Neurological review of symptoms was negative, other than a slight delay in onset of walking (2 years of age) in both siblings. School performance was noted to be moderate in both of them. The father's height was 153 cm (−3.2 SDS) and the mother's height was 150 cm (−1.7 SDS), which translated into a female mid-parental height (MPH) of 145 cm (−2.5 SDS, for P1) and a male MPH of 158 cm (−2.5 SDS, for P2). The parents are second degree cousins and both were asymptomatic with no significant past medical history. The parents have two other healthy children: a 15 year old female with a height of 151 cm (−1.4 SDS) and an 11 year old male with a height of 126 cm (−2.7 SD). Timing of puberty had been age-appropriate in both parents and the 15 year old sister.

On physical exam it was noted that both children had severe short-stature (P1: height 123cm; −5.5 SD; P2: height 98 cm, −5.1 SD) with a mild decrease in sitting height ratio in P1 and a normal ratio in P2 (P1: 0.50, −2.5 SD, P2: 0.54, −0.5 SD [2]), no facial dysmorphisms without any midline defects and normal hands and nails. BMI and head circumference were normal for age (Table 1). Cognitive and verbal skills were appropriate for age, there were no joint or skin abnormalities and neurological exam including gait was normal. Endocrine work-up was normal, except for low baseline IGF-1 levels in both siblings and a low IGFBP3 in P2. However, a clonidine-levodopa growth hormone stimulation test and an IGF-1 generation test were normal in both siblings (Table 1).

Written informed consent for research testing was obtained for all family members. Whole exome sequencing of the two affected siblings was performed at Cincinnati Children’s Hospital Medical Center as previously described [3]. Given the consanguinity of the parents and the severity of the growth phenotype, we filtered the exome data looking for non-

synonymous, homozygous variants present in both siblings with a minor allele frequency of <0.001 in the 1000 Genomes and ExAC Browser databases (http://browser.1000genomes.org/, http://exac.broadinstitute.org/). This identified 10 different candidate genes (Supplemental Table 1), only one of which (*ACP5*), harbored a previously reported, pathogenic homozygous frameshift mutation (p.Ser258Trpfs*39) associated with severe growth failure [4]. The other nine candidate genes had no apparent connections to any known growth disorders or biological pathways affecting human growth. Sanger sequencing confirmed the presence of the homozygous p.Ser258Trpfs*39 mutation in both siblings. Mutations in the *ACP5* gene are known to cause spondyloenchondrodysplasia (SPENCD), characterized by short stature due to skeletal dysplasia in addition to various auto-immune and neurological abnormalities [4, 5]. Subsequent to our exome analysis, we performed skeletal surveys on both siblings, which revealed characteristic findings of spondyloenchondrodysplasia with flattening of the vertebral bodies (platyspondyly), widening of the epiphyses of the upper and lower distal extremities (fibula/tibia/ulna/radius), cupping of the ulna and dense thickening of the radioulnar ligament without the presence of a Madelung deformity (Figure 1). Additional laboratory and radiological evaluation demonstrated no evidence of subclinical autoimmune or neurological dysfunction (Table 1).

Discussion

The *ACP5* gene encodes the tartrate-resistant acid phosphatase (TRAP), a protein thought to play a major role in immune regulation and bone physiology. TRAP deficiency was first described in 1976 in a report of two brothers with severe platyspondyly [6]. TRAP-deficient mice have metaphyseal changes with increased bone density and immunological impairments including impaired dendritic function [7, 8].

The *ACP5* mutation identified in our two siblings (p.Ser258Trpfs*39) was previously reported as one of a number of *ACP5* mutations causal of SPENCD [4]. A concurrent study by Lausch et al. independently confirmed the causality of *ACP5* mutations in this syndrome, which is characterized by a mild skeletal dysplasia phenotype and a high prevalence of auto-immune symptoms, including thrombocytopenia, hemolytic anemia, hypothyroidism and lupus-like nephropathy and vasculopathy [5]. Elevated serum interferon-alfa (IFNα) activity and a "type 1 interferon expression signature" was found on whole-transcriptome microarray expression which could contribute to the auto-immune phenotype in many of these patients [4]. In addition, a significant subset of SPENCD patients has overt neurological abnormalities including developmental delays, spasticity, ataxia and intracranial calcifications on MRI [5].

Prior to the reports by Briggs et al. and Lausch et al., several other studies had already reported on the variable degree of auto-immune cytopenias and lupus-like symptoms in SPENCD patients, as well as various neurological abnormalities [9, 10]. Although not a primary focus, height data provided indicate that the majority of SPENCD patients display significant short stature with a median height around −3 SDS, ranging from −1.8 to −6.5 SD [4, 5]. A variable but significant degree of short stature therefore seems to be an integral part of the SPENCD syndrome.

The presentation of our patients with isolated severe short stature (−5 SDS) as the cardinal feature in the absence of immune-related or neurodevelopmental symptoms, is striking, but not unique: one of the patients described by Briggs et al. also presented with unexplained, isolated short stature and was diagnosed with SPENCD due to an affected brother [4]. They both carried a c.266C>T variant. While she did not demonstrate significant immunological disease (other than Raynoud phenomenon) or neurological disease, her affected brother, interestingly, suffered from spasticity, elevated anti-dsDNA and ANA antibodies and a vasculitic skin rash, underlining the poor genotype-phenotype correlation. Both siblings were −3 SDS in height and had platyspondyly on X-rays. Subtle disproportion was present in P1 but not in the younger sibling. Additionally, Briggs et al reported a patient with the same (p.Ser258Trpfs*39) mutation as identified in our siblings [4]. The reported patient presented at the age of 4 years with leg pain and was also found to have significant short stature (−3 SDS), although not to the degree as we observed in our patients. Similar to our patients, X-rays showed metaphyseal dysplasia and platyspondyly, but she also had documented spasticity, mildly elevated anti-dsDNA (33, ref <20) and ANA (1:640), microglobulinemia, rheumatic fever with hypogammaglobulinemia, increased bone mineral density (+1.5 SDS) and an elevated IGF-1 (+2.5 SD), none of which our two patients had, again stressing the variability of the phenotype even in patients with the same mutation. In Table 2, aggregate patient characteristics of the two major SPENCD studies with reported *ACP5* mutations are depicted and compared to our two study patients.

It is important to note that the father and the 11 year old brother of our patients had moderate short stature as well, however, not nearly as severe as in the two affected siblings. Unfortunately, DNA was unavailable from the father and the brother for exome sequencing. We therefore cannot exclude the possibility that an additional genetic variant is partially contributing to the short stature seen in this family. However, as noted above, there are other reported patients with ACP5 deficiency with the same degree of severity of short stature as seen in our patients.

Performing a skeletal survey in cases of idiopathic short stature (ISS) may be of additional diagnostic benefit as shown by a recent French study [11]. In that study, the authors found an underlying skeletal dysplasia in 20% of ISS cases, most notably so when at least one of the parents had an adult height <−2 SD [11]. The etiological diagnosis of SPENCD in these two patients with previously presumed ISS has important clinical implications in terms of screening for subclinical comorbid auto-immune or neurological disease, as well as more accurate counseling for future health in both siblings.

In summary, *ACP5* mutation should be considered as a rare genetic cause of severe short stature in the setting of typical radiological findings of skeletal metaphyseal dysplasia, even in the absence of overt immunological or neurological disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Established Facts

- *ACP5* mutations are known to cause spondyloenchondrodysplasia (SPENCD)

Novel insights

- *ACP5* deficiency can present as isolated, severe short stature in the absence of any of the auto-immune and neurological abnormalities commonly found in SPENCD.
- *ACP5* deficiency should be considered as a rare cause of severe, proportionate short stature.

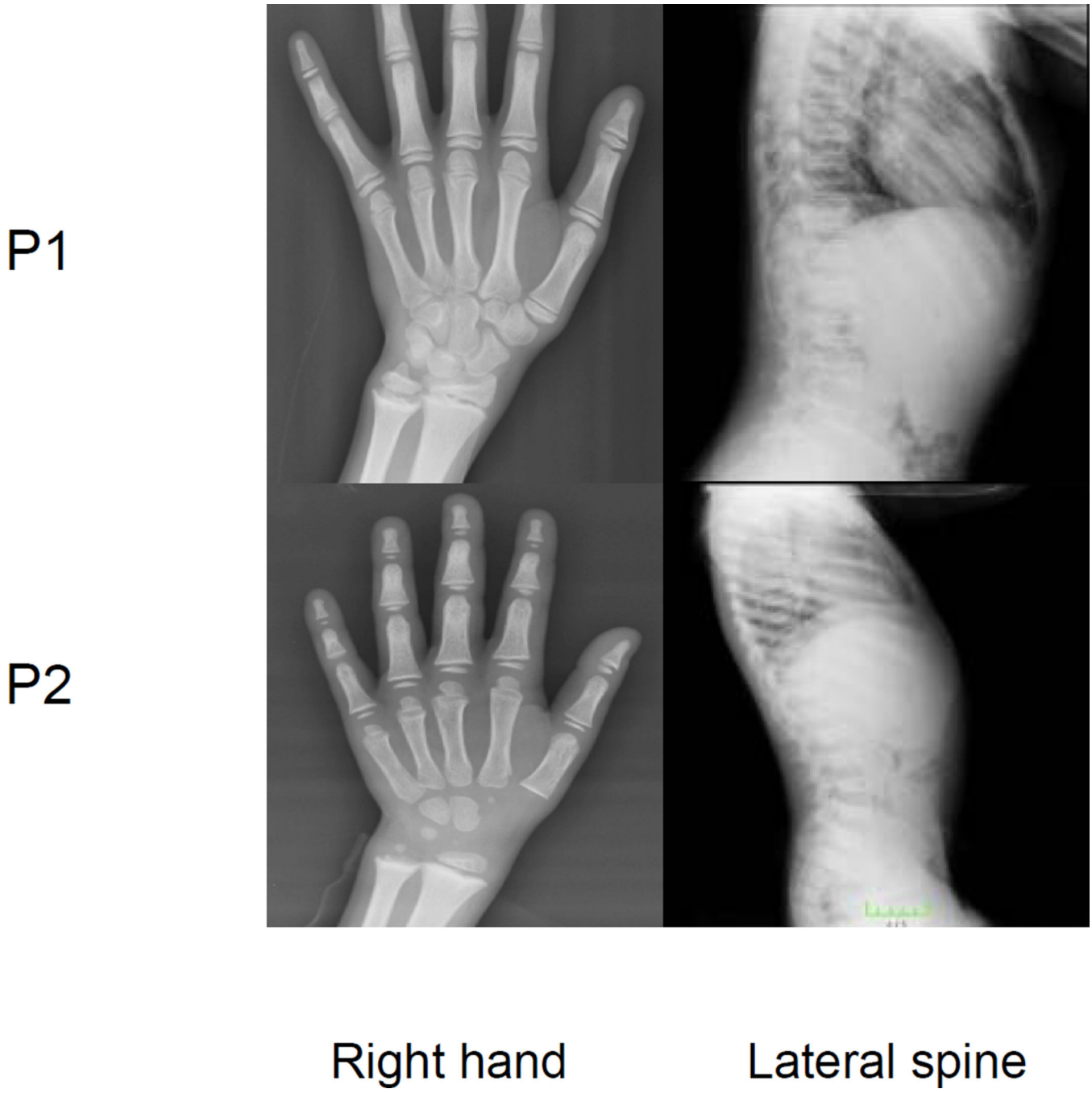

Figure 1.
Conventional radiographs as part of skeletal survey in P1 (top panel) and P2 (bottom panel): On x-rays of the right hand, there is visible widening of the epiphyses of the ulna and radius in both siblings with cupping of the ulna and dense thickening of the radioulnar ligament without the presence of a Madelung deformity. The lateral spine film shows flattening of the vertebral bodies (platyspondyly).

Table 1

Anthropometric and laboratory data

	Reference Range	P1	P2
Initial work-up			
Age (yr)		13	8
Height (cm)		123	98
Height - SDS		−5.5	−5.1
Sitting Height/Height		0.50	0.54
Sitting Height/Height(SDS)		−2.5	−0.5
Weight(kg)		25	14
BMI (kg/m^2)		16.5	14.6
BMI - SDS		−0.9	−0.8
Head Circumference (cm)		52	51
Head Circumference - SDS		−1.3	−1.2
Hemoglobin (g/dl)	11.5–14.0	12.4	12.0
Leucocytes(1000/mm^3)	4.5–13.5	5.6	8.1
Thrombocytes (1000/mm^3)	150–450	290	260
Sed rate (mm/hr)	5–20	22	25
Creatinine (mg/dl)	0.3–0.7	0.4	0.4
Urinalysis		normal	normal
Free T4 (ng/dl)	0.8–2.2	1.2	1.08
TSH (mcIU/ml)	0.6–5.5	1.05	4.73
IGF-1 (ng/ml)	13y: 192–640 8y:113–261	104	<25
IGFBP3 (ng/ml)	13y: 2.1–6.2 8y:2.1–4.2	4.04	1.75
GH peak stim (ng/ml)	> 10	23.9	11.4
IGF-1 Gen Test (pre>post ng/ml)		140>267	25>62
Additional work-up *(after Exome Seq)*			
Anti-ds DNA (U/ml)	0–20	0	0
ANA		neg	neg
C3 (g/l)	0.9–1.8	1.03	0.99
C4 (g/l)	0.1–0.4	0.19	0.22
IgA (g/l)	13y: 0.9–4.65 8y: 0.7–3.0	1.6	2.9
IgG (g/l)	13y: 9.1–19.6 8y: 7.6–21.3	19.2	14.5
IgM (g/l)	13y: 0.8–2.8 8y: 0.7–3.8	1.17	0.90
CK (U/l)	<190	189	182

	Reference Range	**P1**	**P2**
Coombs		Negative	Negative
Reticulocytes (%)	1–2%	1.5%	1.5%
Bilirubin (mg/dl)	<1.2	0.18	0.25
LDH (U/l)	120–330	214	272
Skeletalsurvey		Fig 1A	Fig 1B
MRI brain		Normal	Normal

Table 2

Overview of clinical characteristics of P1, P2 and the SPENCD patients described in the studies by Briggs et al and Lausch et al.

Parameter	P1	P2	Briggs (n=10)**	Lausch (n=14)**
Age*	13	8	7	3
Height SDS (range)	−5.4	−5.1	−3.4 (−1 to −6.5)	−2.7 (−1.8 to −4.2)
Thrombocytopenia	no	no	5/10	5/13
Hemolytic anemia	no	no	2/10	2/13
Leukopenia	no	no	n.a.	4/13
Hypothyroidism	no	no	3/10	1/13
Elevated anti-DNA or anti-ANA titers	no	no	8/10	6/13
Lupus-like symptoms (ACR)	no	no	4/10	6/13
Lupus nephritis	no	no	3/10	3/13
Spasticity	no***	no	4/10	4/13
Developmental delays	minimal	minimal***	2/10	4/13
Intracranial calcifications	no	no	4/6	6/13

Legend:

* Median age is depicted for study population in Briggs and Lausch studies

** Proportions are depicted for the patients in Briggs and Lausch studies on whom detailed clinical information was reported in the supplementary methods of both papers.

*** Slight delay in start of walking (around age 2), otherwise unremarkable neurodevelopment

n.a. = not assessed