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SHORT REPORT

Serpentine fibula polycystic kidney syndrome is part of the phenotypic spectrum of Hajdu–Cheney syndrome

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Serpentine fibula polycystic kidney syndrome (SFPKS; MIM600330) is a rare skeletal dysplasia that has polycystic kidneys and dysmorphic facies as additional defining phenotypic components. The nosological classification of this disease has been debated as the condition shares features common to other skeletal dysplasias such as Melnick Needles syndrome (MNS; MIM309350) and Hajdu–Cheney Syndrome (HCS; MIM102500). Here, two previously reported cases of SFPKS are presented with emphasis on their phenotypic evolution. With the recent discovery that HCS is caused by mutations in *NOTCH2*, DNA from the both cases was examined and both were found to have truncating mutations in exon 34 of *NOTCH2*. The phenotypic evolution of SFPKS and this molecular analysis strongly suggest that SFPKS is part of the phenotypic spectrum of HCS and should no longer be classified as a distinct disease entity.
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INTRODUCTION

Serpentine fibula polycystic kidney syndrome (SFPKS) is a rare skeletal dysplasia that primarily affects bone and kidney development. SFPKS was first described in a 5-year-old female with a distinct facial appearance, proportional short stature, hirsutism, polycystic kidneys, vertebral abnormalities, elongated 'serpentine' fibulae,[1] acro-osteolysis of the terminal phalanges and toes,[2] bilateral cystic kidneys, progressive hearing loss, epilepsy and hypertension.[3] She died at 21 years of age from grand-mal seizures and renal failure.[3] A second case of SFPKS was reported in 1993 in another female patient who had a more extreme skeletal manifestation of the disease.[4] The only reported familial case of SFPKS consisted of an unequivocally affected female and her two deceased brothers who may have had some manifestations of the disorder. Only the female proband had serpentine fibulae.[5] The pronounced bowing of the long bones in SFPKS evoked comparisons with Melnick Needles syndrome in one report[5] and forms the basis of the current classification of the condition alongside the filaminopathy disorders in the 2010 Nosology and Classification of Genetic Skeletal Disorders.[6] Mutations in *FLNA*, the locus mutated in Melnick Needles syndrome, have been excluded in one individual with SFPCKS.[7]

In the report of the familial instance of SFPKS, it was noted that the three siblings had significant phenotypic overlap with the autosomal dominant condition known as Hajdu-Cheney syndrome (HCS).[5] The presentation of HCS is variable but typically includes acro-osteolysis of the distal phalanges, generalised osteoporosis, craniofacial anomalies, short stature, premature tooth loss and cystic kidneys.[8] Simpson *et al*[9] and Isidor *et al*[10] have recently identified truncating mutations in exon 34 of *NOTCH2* in several families and sporadic individuals with HCS. All individuals were heterozygous for these mutations, consistent with the established autosomal dominant inheritance pattern for this disease. Here data are presented to show that mutations in exon 34 of *NOTCH2* also underlie some instances of SFPKS and that some individuals with this condition evolve a phenotype over time that closely approximates that of HCS.

CLINICAL REPORTS

Case one

Case one has been described previously at the age of 4 months as the only survivor of three affected siblings.[5] She had persistent ductus arteriosus and intestinal malrotation (which were repaired), an atrial septal defect, splenomegaly, bilateral sensorineural hearing loss, recurrent respiratory infections and corneal diameters of 11–12 mm without glaucoma. Facial dysmorphism was evident with high-arched eyebrows, hypertelorism, full checks, left ptosis and micrognathia. Radiological findings included short terminal phalanges, short bowed humeri, short dysplastic radii and metacarpal heads, subluxed elbows, bowed femora and serpentine fibulae.

On follow-up at the age of 8 years mild developmental delay was evident, as well as short stature, dental malocclusion, a narrow hirsute forehead, low-set posteriorly rotated ears, bilateral epicanthic folds and reduced supination at the elbow (Figure 1). At 9 years of age her lung function had deteriorated so that she required supplemental oxygen, and radiographs confirmed acro-osteolysis of the terminal phalanges. By 10 years of age she required corticosteroid treatment for her pulmonary disease, which had also necessitated a partial lobectomy. Her height was 123.3 cm (0.4th–2nd centile), weight 33.6 kg (50th centile) and OFC 53.5 cm (>50th centile). Her facial dysmorphism resembled HCS with a hirsute forehead, low posterior

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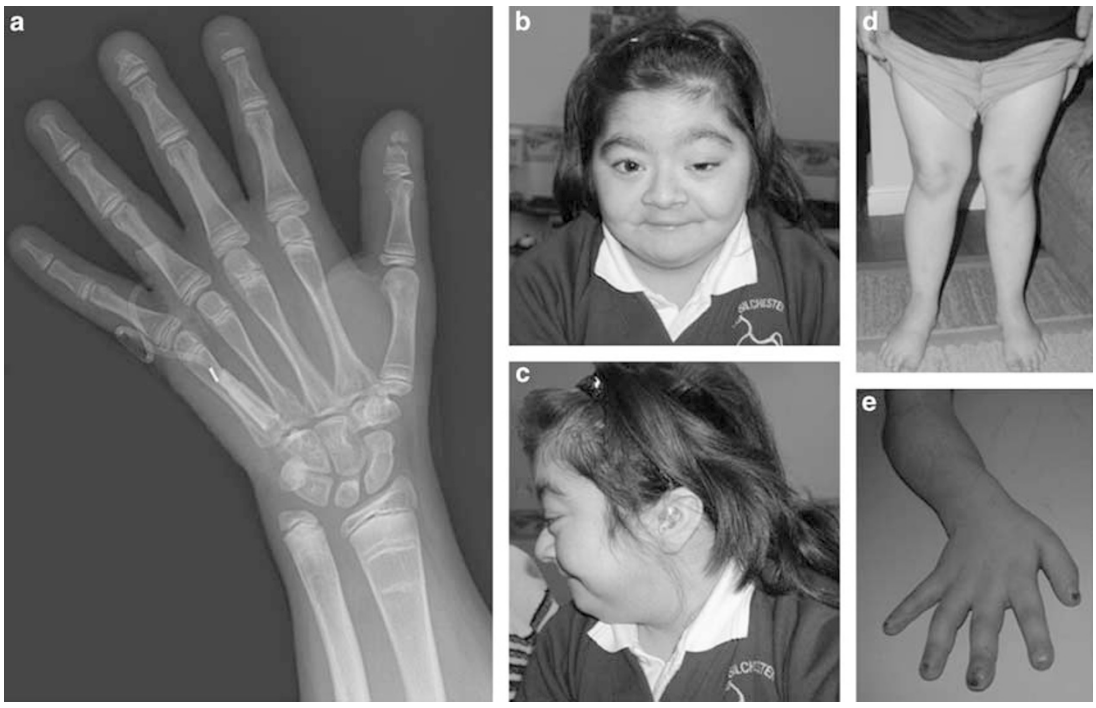

Figure 1 Radiograph of the hand and clinical appearance of case one. (**a**) Significant osteolysis of the distal phalanges of digits I, II and III has developed and thinning of the corticies is evident. (**b**, **c**) Facial appearance typical of that seen in individuals with HCS with a hirsute forehead, low posterior hairline, shallow supra-orbital ridges, left-sided ptosis, a pinched nasal bridge with a widened nasal tip, a small mouth, low-set posteriorly rotated ears and prominent maxillae. (**d**) Moderate genu valgum and (**e**) shortening of the distal phalanges.

hairline, shallow supra-orbital ridges, horizontal palpebral fissures, a convergent squint, a pinched nasal bridge with a wide nose, a small mouth, low-set posteriorly rotated ears and prominent maxillae. Her acro-osteolysis had progressed. At 12 years of age she had osteoporosis and had sustained stress fractures of the metatarsals bilaterally. She is negative for a mutation in *FLNA*.

Case two

Case two (Figure 2) was described at 8 years of age as a white female with a persistent ductus arteriosus, ventricular septal defect and dysmorphism, which consisted of a thin upper lip, downturned mouth, wide nasal tip, long and flat philtrum, dysplastic and posteriorly rotated ears.[7] She had bilateral sensorineural hearing loss. Radiographs of the patient showed wormian bones, vertebral abnormalities and serpentine fibulae. Ultrasound examination demonstrated polycystic kidneys, but she had normal renal function. At 18 years of age she weighs 51 kg (25th centile) and has a height of 151.5 cm ($<$5th centile). Since her previous review she had developed hypothyroidism, bathrocephaly and irregular tooth positioning. Radiographs of her hands and feet did not show significant acro-osteolysis, but mild thinning of the distal phalanges was observed (Figure 2b). MRI scan of her head and neck showed basilar invagination and abnormal curvature of the cervical spine without cord compression (Figure 2c). Her intelligence was unimpaired.

Molecular analysis

NOTCH2 exon 34 was amplified by PCR as described[9] from genomic DNA. Automated sequencing was performed on the 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA). All traces were analysed in Sequencher v4.9 (GeneCodes, Ann Arbor, MI, USA). Both patients with SFPKS were heterozygous for truncating mutations in *NOTCH2* exon 34. Case one, as reported,[9] was heterozygous for c.6895G$>$T (p.Glu2299X) and case two has a novel truncating mutation, c.7165C$>$T (Gln2389X). Despite parental samples not being available for either case, the truncating nature of these variants and their predicted functional consequences were identical to previously reported *NOTCH2* mutations causative of HCS. Consequently, these mutations are highly likely to be causative of the observed phenotypes.

DISCUSSION

Both individuals described here demonstrate phenotypic features that are shared between SFPKS and HCS. Previously the delineation of these two disorders has primarily been through the presence of serpentine fibulae in SFPKS, while individuals with HCS have acro-osteolysis and coarse hirsute facial features. However, both conditions have cystic renal disease as a phenotypic feature and serpentine fibulae have also been documented in HCS cases[8,11] casting doubt on these conditions being distinct. Case one[5] was originally reported as an example of familial SFPKS, but her phenotype has evolved into a more typical HCS presentation complete with acrosteolysis. Case two[7] presented with marked serpentine fibulae and lacks acro-osteolysis, but many of her other phenotypic features were typical of the HCS phenotype. The phenotypic overlap between HCS and SFPKS was first noted in a description of a cohort of individuals with HCS and polycystic kidney syndrome.[12] Ramos *et al*[11] compared the phenotype of SFPKS with HCS and concluded that ascertainment bias had led to the delineation of SFPKS as a distinct condition. Two additional cases of SFPKS were subsequently reported in female patients[7,13] and both authors concluded that HCS and SFPKS are likely to be allelic. Both individuals described here are heterozygous for truncating mutations in exon 34 of *NOTCH2*, similar to those identified in individuals with HCS.[9,10] The truncating mutations in these two SFPKS patients are located in the same region of the gene where mutations causative of

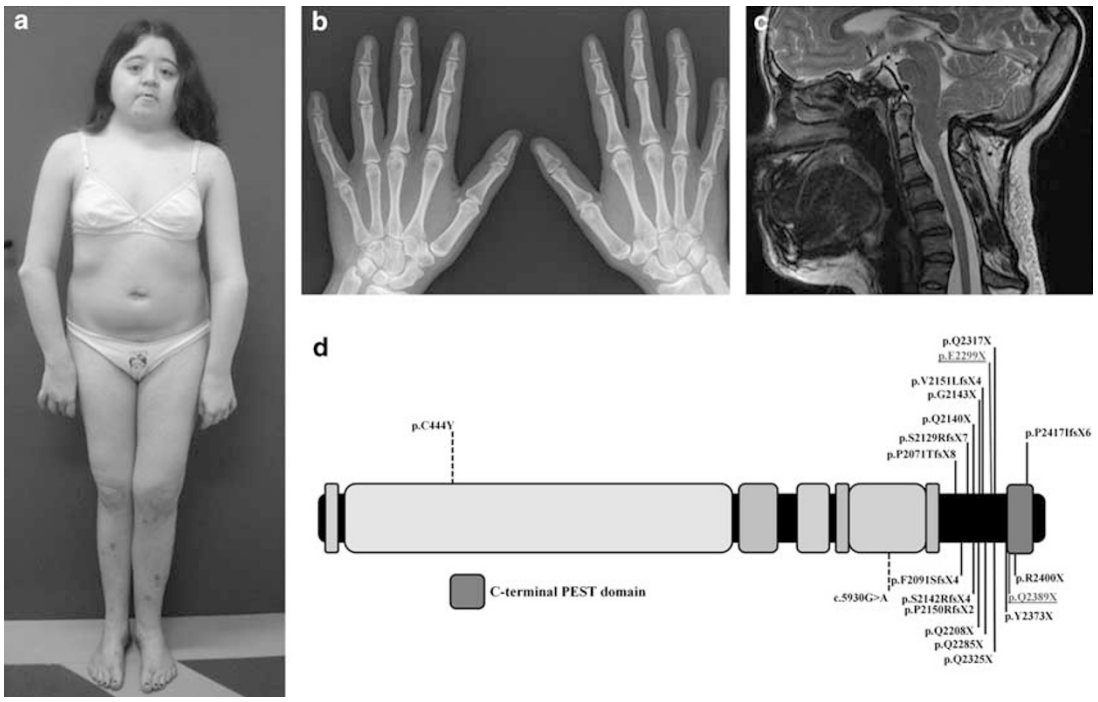

Figure 2 Case two. (**a**) Clinical presentation of case two showing characteristic facial dysmorphism, flexion contractures at the elbows and metatarsus varus. (**b**) Radiograph of the hands showing thinning of the cortices of the phalanges but no acro-osteolysis. (**c**) MRI scan showing basilar invagination with impression of the anterior surface of pons by the odontoid process, a small posterior fossa with cerebellar tonsillar herniation, and a kyphosis of the cervical spine but no abnormal spinal cord signal or evidence of compression. (**d**) Schematic of the NOTCH2 protein with the locations of the previously identified mutations causative of HCS[9,10] and Alagille syndrome[14] (dashed line). The two mutations found in the individuals described in this report are underlined and in bold.

HCS are found. The recently identified HCS mutations lead to truncation of the terminal exon of *NOTCH2*, which produces a protein product missing the proteolytic proline–glutamate–serine–threonine-rich (PEST) domain. PEST domains mediate the internalisation and recycling of proteins in which they reside and therefore the absence of a PEST sequence in this protein is proposed to lead to an elevated level of NOTCH signalling activity in multiple tissues, an observation that highlights its essential role in skeletal development and homeostasis.[9] Two cases of Alagille syndrome (MIM#118450) have been reported with mutations in *NOTCH2*, one of which is a splice acceptor mutation of exon 33 that not only leads to the loss of the PEST domain but also the nuclear localisation sequence and three ankyrin repeats[14] (Figure 2d). The ankyrin repeat domains facilitate protein–protein interactions and are required for NOTCH signalling.[15] In contrast, the gain-of-function mutations that cause HCS are restricted to the terminal exon that encodes the PEST domain only.

Given the strong phenotypic overlap between SFPKS and HCS and the observation that the two current cases have mutations in *NOTCH2*, there is strong evidence that SFPKS is not only allelic to HCS but also should be considered one end of the spectrum of the disorder. On the basis of these observations the diagnosis of SFPCKS appears to be redundant, and patients falling into this phenotypic category are best considered to have HCS.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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