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The small patella syndrome: description of five cases from three families and examination of possible allelism with familial patella aplasia-hypoplasia and nail-patella syndrome

EDITOR—The small patella syndrome (SPS, *MIM 14789), also known as ischiopatellar dysplasia, coxopodo patellar syndrome, or Scott-Taor syndrome, is a rare autosomal dominant disorder, characterised by a/hypoplasia of the patellae and various anomalies of the pelvis and feet. This syndrome was first described by Scott and Taor[1] in 1979 in a large family with bilateral small or absent patellae accompanied by anomalies of the pelvic girdle and upper femora in most of the affected subjects. To our knowledge, 42 patients have been reported with this disorder,[1–9] comprising 35 cases from five families and seven sporadic cases. This bone dysplasia is characterised by patellar a/hypoplasia and pelvic anomalies, including bilateral absent or delayed ossification of the ischiopubic junction and infra-acetabular axe cut notches. Other major signs are a wide gap between the first and second toes, short fourth and fifth rays of the feet, and pes planus. Various other skeletal anomalies have been reported, such as elongated femoral necks, flattened and widened proximal femoral epiphyses, hypoplasia of the lesser trochanter, and tarsal anomalies. SPS should be clinically differentiated from disorders with a/hypoplastic patellae, in particular the autosomal dominant disorders isolated familial patella aplasia-hypoplasia (PTLAH) syndrome[10] and the more severe nail-patella syndrome (NPS).[11] The latter is caused by mutations of the *LMX1B* gene on chromosome 9q34. Recently, a locus for PTLAH has been identified on chromosome 17q21-22. As yet, it is unknown whether SPS and PTLAH are allelic disorders. Here we report on five cases from three families with SPS, compare their clinical and radiological anomalies with those of previously reported cases, and propose minimal diagnostic criteria for SPS. Given the clinical overlap between SPS, PTLAH, and NPS, we have studied the possible involvement of candidate regions for these syndromes on chromosome 17q21-22 and 9q34, respectively, by linkage analysis.

Family A, case 1. This male patient, aged 9 years 10 months at the time of examination, was referred because of bilateral absence of the patellae. He was the third child of non-consanguineous Dutch parents. He was born at 37 weeks' gestation after an uneventful pregnancy. Birth weight was 2750 g (10th-25th centile). At birth, talipes equinovarus was noted. Motor milestones were delayed; he sat at 13 months and walked at 24 months. Mental development was normal. At the age of 6 and 8 years, surgery for flat feet was performed, but without success. At the time of examination he complained of unstable knees, muscle weakness of the lower extremities, fatigue on moderate exertion, and inability to run or to stand up from sitting without support. At the age of 9 years 10 months, weight was 30.2 kg (10th-25th centile), height 146.5 (50th-90th centile), and head circumference 51.5 cm (10th-50th centile). The ears were low set and posteriorly angulated. He had a wide gap between the first and second toes bilaterally, short fourth and fifth rays of the feet, and pes planus (fig 1A). The patellae were not palpable. Normal

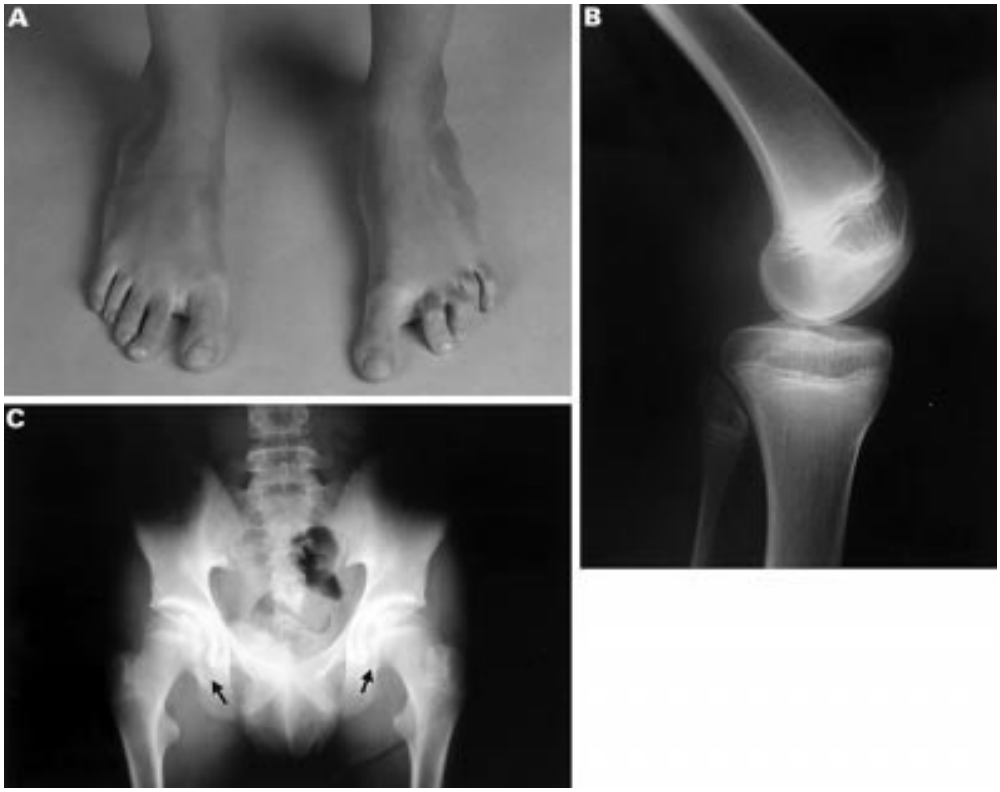

Figure 1 (A) Anterior view of the feet of the proband of family A (case 1) showing an increased space between the first and second toes and short fourth and fifth rays. (B) Radiograph of the knee at the age of 12 years 11 months. Note the absence of the patellae and dysplasia of the epiphyses of the proximal fibula. (C) Radiograph of the pelvis at the age of 12 years 11 months showing the absent ossification of the ischiopubic junction, infra-acetabular axe cut notches (arrows), and elongated femoral necks.

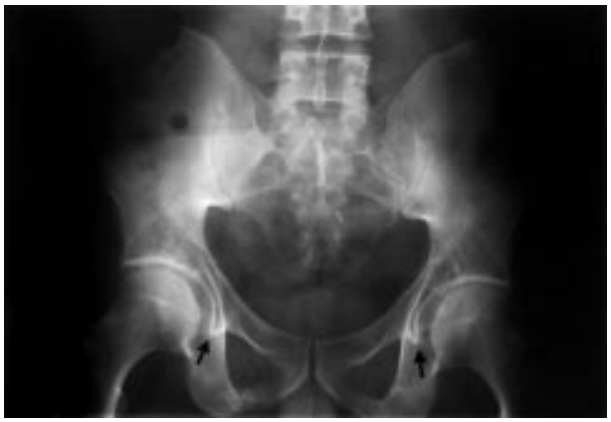

Figure 2 Radiograph of the pelvis of case 2 at the age of 53½ years showing irregular ossification of the ischiopubic junction and infra-acetabular axe cut notches (arrows).

nails and normal joint mobility were found. Radiographs of the knees confirmed the absence of the patellae and showed dysplasia of the epiphyses of the proximal fibulae (fig 1B). Radiographs of the pelvis showed delayed ossification of the ischia and inferior pubic rami, infra-acetabular axe cut notches, and elongated femoral necks (fig 1C). Short fourth and fifth rays of the feet and pes planus were confirmed on radiographs of the feet.

Family A, case 2. This male patient, aged 49 years, the father of case 1, was known to lack both patellae and to have flat feet. In addition to these abnormalities, physical examination showed a wide gap between the first and second toes, and short fourth and fifth rays of the feet. Radiographs showed patellar hypoplasia, irregular ossification of the ischiopubic junction, and infra-acetabular axe cut notches (fig 2). No abnormalities of other joints or nails were found. Chromosome analysis showed a normal male karyotype. His oldest son, daughter, and 10 sibs showed no anomalies of their elbows, knees, or feet on physical examination, except for short fourth rays of the feet in one sib. Radiological examination of this relative showed short fourth metatarsals, but because anomalies of the patellae and pelvis were not seen, he was considered not to have SPS. His parents had died. According to the patient they did not have any complaints or congenital anomalies of the knees and feet.

Family B, case 3. This male patient, aged 9 years 2 months, was referred because of bilateral small patellae and knee pain. He is the first child of non-consanguineous Dutch parents. He was born at term after an uneventful pregnancy. Birth weight was 3500 g (50th centile) and length 52 cm (50th-75th centile). Psychomotor development has been

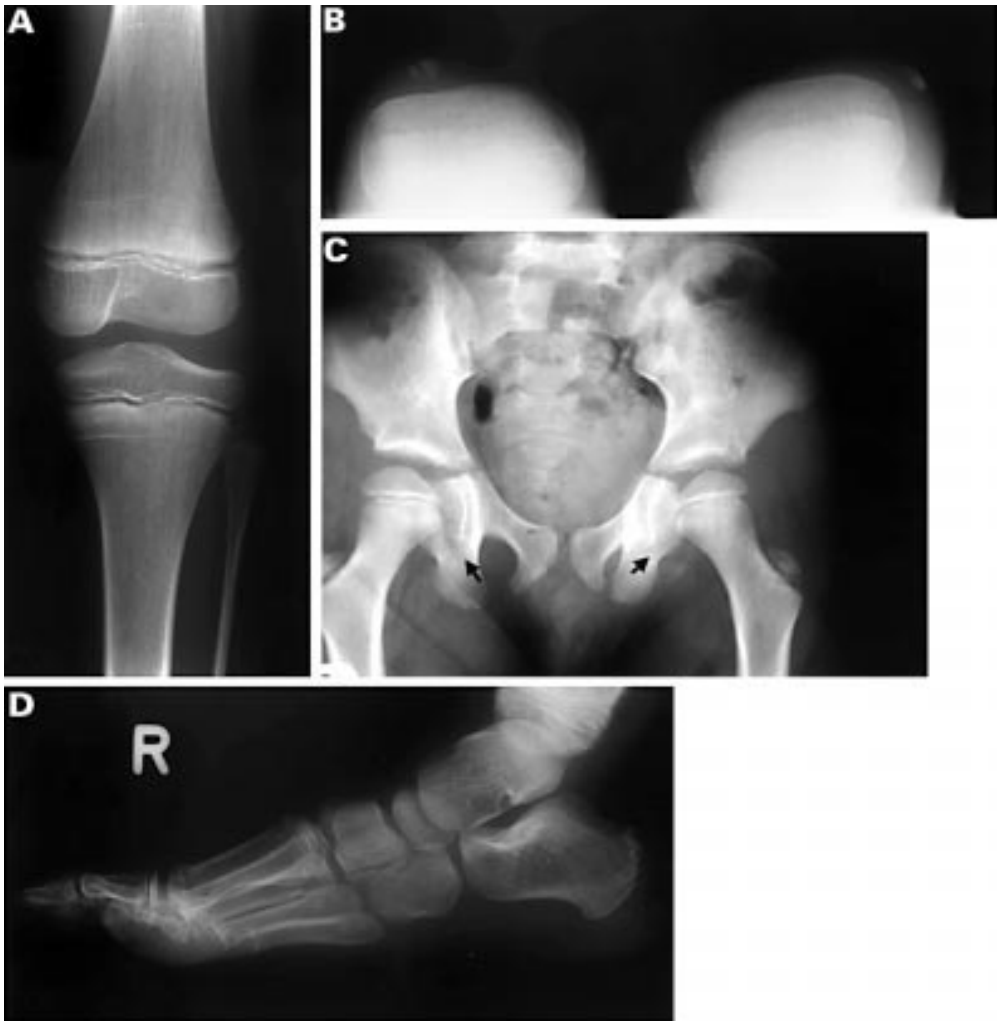

Figure 3 (A) Radiograph of the knees of the proband of family B (case 3) at the age of 9 years 2 months showing smaller medial femoral and tibial condyles compared to lateral femoral and tibial condyles. (B) Note the hypoplastic and dislocated patellae with two ossification centres on the left side, and flattened fossa intercondylares. (C) Radiograph of the pelvis at the age of 7½ years showing bilateral hypoplastic ossification of the ischia and inferior pubic rami for his age and infra-acetabular axe cut notches (arrows). (D) Radiograph of the feet showing hypertrophy of the neck of the talus.

normal except for an abnormal gait and weakness of the lower extremities. He had surgery for cryptorchidism at the age of 7½ years. At the same age, a traumatic pelvic fracture occurred with subsequent recurrent luxations of the left patella. As a consequence, running was impossible and riding a bicycle very difficult. At the age of 9 years 2 months, weight was 35.1 kg (90th centile), height 148.5 cm (>97th centile), and head circumference 53 cm (2nd centile). The face was unremarkable. The space between the first and second toes was increased, and bilateral short fourth and fifth rays of the feet were noted. There were no contractures, hypermobility of other joints, or nail anomalies. Radiographs of the knees showed small patellae and a dislocated patella on the left side, composed of two ossification centres (fig 3A, B). Radiographs of the pelvis showed bilateral hypoplasia of the ischia and inferior pubic rami, infra-acetabular axe cut notches, flattened and widened capital femoral epiphyses, elongated femoral necks, and hypoplasia of the lesser trochanter (fig 3C). The medial femoral and tibial condyles were smaller than the lateral femoral and tibial condyles. The fossae intercondylares were flattened. Hypertrophy of the neck of the talus and pes planus were seen on radiographs of the feet (fig 3D). Radiographs of the hands were normal. Chromosome analysis showed a 47,XXY karyotype.

Family B, case 4. This female patient, aged 35 years, the mother of case 3, suffered from discomfort of the knees in early childhood. On physical examination, she had bilateral small patellae and an increased space between the first and second toes bilaterally. The other joints and nails were normal. Radiographs showed bilateral small patellae, absent ossification of the ischiopubic junction bilaterally, and infra-acetabular axe cut notches. The medial femoral and

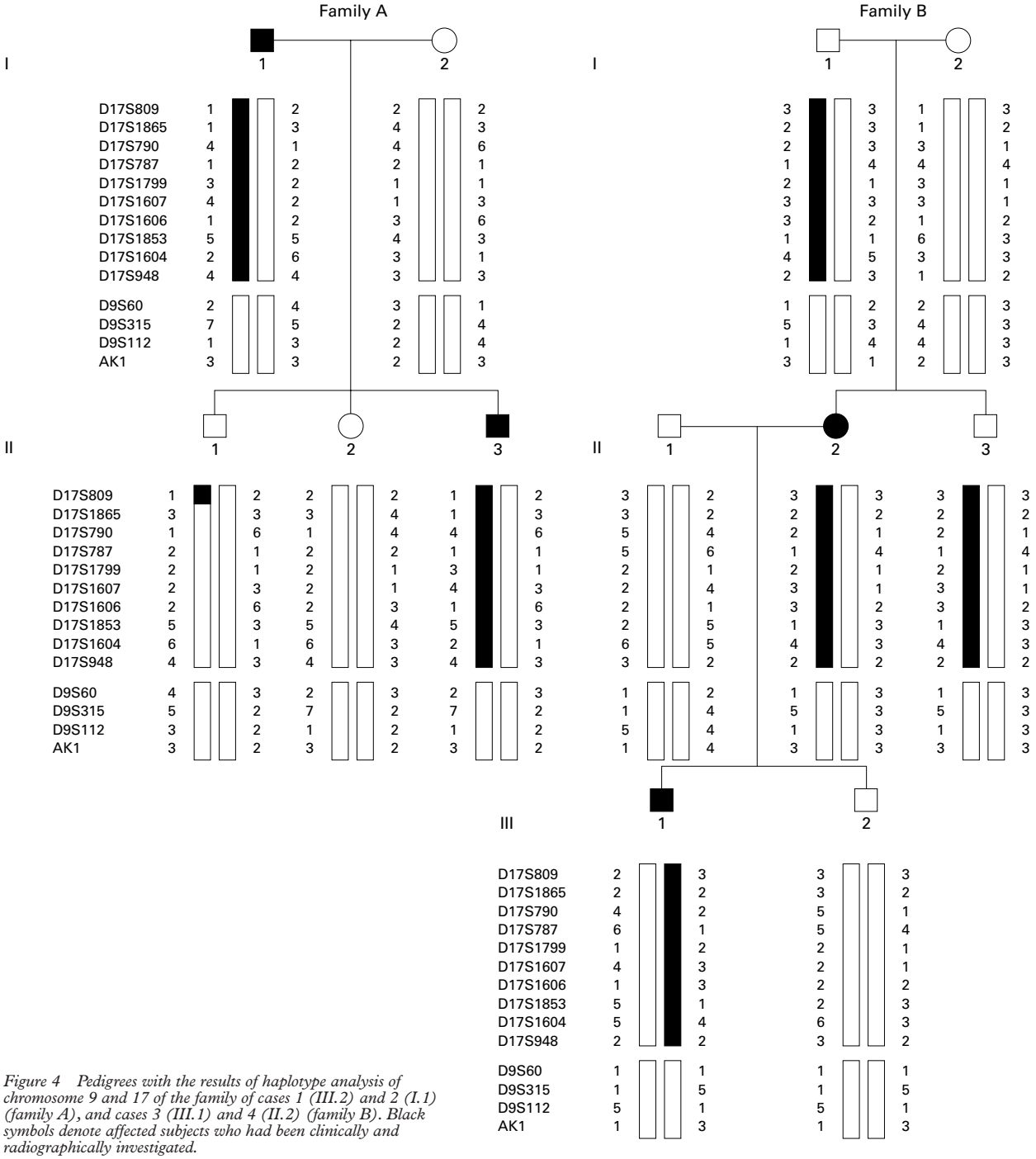

Figure 4 Pedigrees with the results of haplotype analysis of chromosome 9 and 17 of the family of cases 1 (III.2) and 2 (I.1) (family A), and cases 3 (III.1) and 4 (II.2) (family B). Black symbols denote affected subjects who had been clinically and radiographically investigated.

Table 1 Clinical and radiological features of previously published cases[1–9 12 13] and present cases with small patella syndrome

	Previously reported cases[1–9 12 13]	*Frequency (%)*	*Family A*		*Family B*		*Family C*
			Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Radiological/clinical anomalies of the patella	45/45*	100					
Patellar aplasia	14/45	32	+	−	−	−	−
Patellar hypoplasia	31/45	69	−	+	+	+	+
Radiological anomalies of the pelvis	34/35†	97					
Absence/hypoplasia/irregularity of the ischiopubic junction	24/27‡	89	+	+	+	+	+
Infra-acetabular axe cut notches	8/9	89	+	+	+	+	+
Radiological anomalies of the femora							
Hypoplasia of the lesser trochanter	3/6	50	−	−	+	+	−
Elongated femoral necks/flattened and widened proximal femoral epiphyses	8/15	53	+	−	+	+	−
Radiological/clinical anomalies of the feet							
Pes planus	9/15	60	+	+	+	+	+
Short fourth and fifth rays of feet	10/15	67	+	+	+	+	+
Clinical anomalies of the feet							
Wide gap between first and second toes	13/17	76	+	+	+	+	+

*In 45 of the 46 previously reported cases, patellar a/hypoplasia was mentioned.
†Thirty five of the 46 previously reported cases had radiological examination of the pelvis.
‡Anomalies of the ischiopubic junction were specified in 27 of the 35 previously reported cases with pelvic anomalies.

tibial condyles were smaller than the lateral femoral and tibial condyles and the fossa intercondylares were flattened. Radiographs of the feet showed hypertrophy of the neck of the talus and pes planus bilaterally. Radiographs of the hands were normal. The family history was unremarkable. Physical examination and radiographs of the knees of her father, mother, brother, and youngest son showed no abnormalities. Furthermore, radiographs of the pelvis of her youngest son at the age of 8 years 1 month showed normal ossification of the ischio-pubic junction and absence of infra-acetabular axe cut notches.

Family C, case 5. This female patient, aged 20 years, is the first child of non-consanguineous Belgian parents. She has one healthy brother. She was born at 41 weeks' gestation. Birth weight was 2500 g (<3rd centile) and length 42 cm (<3rd centile). She had surgery on her knees for recurrent luxations of the patellae in infancy. She was referred on suspicion of Marfan syndrome because of general hyperlaxity of the joints and poor wound healing at the age of 20 years. At that age, weight was 105.2 kg (>97th centile), height 174 cm (50th-90th centile), and head circumference 55.1 cm (50th centile). She had a high nasal bridge, high arched palate, and micrognathia. Furthermore, clinodactyly of the fifth fingers, short fifth fingers, bilateral small patellae, flat feet, a wide gap between the first and second toes bilaterally, short fourth and fifth toes, and joint hyperlaxity were noted. The other joints and nails were normal. Radiographs showed hypoplastic patellae, absent ossification of the ischiopubic joint bilaterally, infra-acetabular axe cut notches, and small medial femoral and tibial condyles as compared to the lateral femoral and tibial condyles. Radiographs of the skull, thorax, vertebral column, upper limbs, wrists, hands, and feet showed no abnormalities, except for pes planus. Echocardiography and ophthalmological examination were normal, excluding Marfan syndrome. Chromosome analysis showed a 46,XX,t(1;X)(q12;q27) karyotype which was also found in her mother. Her mother was said to be healthy and was not known to have had knee or foot anomalies. Her father was known to have had scoliosis and pes planus and he had surgery on his knees. Her paternal grandmother was also known to have had knee complaints. Both her father and her mother were unavailable for examination and further clinical or radiological information could not be obtained.

Informed consent for molecular genetic investigation was obtained from two affected and three unaffected members of family A, and two affected and five unaffected members of family B. Genomic DNA was extracted from peripheral blood lymphocytes by a salt extraction procedure.[17] The DNA concentration was measured by optical density (OD_{260}) and purity checked by determining the OD_{260}/OD_{280} ratio. Manual genotyping of microsatellite markers on chromosome 9q34 and 17q21-22 was carried out as described elsewhere.[18] Microsatellite markers were chosen from the final Généthon linkage map.[19] Four patients with SPS from two families were investigated (figs 1-3). Given the overlap of the clinical features of these families with PTLAH[10] and NPS,[11] microsatellite markers from the relevant chromosomal regions were tested for possible linkage in family A and family B. The results of haplotype analysis in these two families are shown in fig 4. Linkage to chromosome region 9q34 was excluded in families A and B. Both families A and B are compatible with linkage to the PTLAH critical region on chromosome 17q21-22,[10] assuming a de novo mutation in case 4 (family B, case II.2, fig 4).

Since the first description of a family with 12 affected cases of SPS by Scott and Taor[1] in 1979, 30 patients have been described with this condition.[2–9] Additionally, several possible cases of SPS have been reported. In 1970, Goeminne and Dujardin[12] described a family with three affected members with bilateral patellar aplasia, bilateral congenital hip dysplasia, hypoplasia of the descending part of the pubic arches, and absent ischiopubic synostosis, accompanied by pes planus, tarsal synostosis, short stature, and oligodactyly of the feet in one subject. Habboub and Thneibat[13] reported a sporadic case with aplastic patellae and bilateral absence of the ischiopubic rami, and suggested the name ischio-pubic-patellar hypoplasia for a possible new syndrome. The clinical and radiological features of the patients described in both reports[12 13] are strikingly similar to those of SPS. Therefore, we believe that these cases do not represent new syndromes but are further examples of SPS. Thus, a total of 51 cases with SPS have currently been described, including the cases of Goeminne and Dujardin,[12] Habboub and Thneibat,[13] and the present cases.

The clinical and radiographic anomalies of the five patients presented here and previously reported cases are summarised in table 1. Patellar a/hypo/dysplasia has been found in all cases, except for one familial case with patellar dislocation in which radiological examination was not mentioned.[8] Complaints and symptoms varied from pain resulting from gonarthrosis in elderly subjects to recurrent luxations from infancy, knee pain, and inability to run and ride a bicycle. In some cases, however, there were no symptoms. In this report, all cases had absent, delayed, or irregular ossification of the ischiopubic joint accompanied by

infra-acetabular axe cut notches, but no related complaints or additional clinical features were noted. In family B, the medial femoral and tibial condyles were small compared to the lateral femoral and tibial condyles. These features have also been mentioned by Vanek[2] and can also be seen on radiographs from other reports.[3–5] Hypoplasia of the lesser trochanter, elongated femoral necks, and flattened and widened epiphyses of the proximal femora were found in most of the present patients, but have been reported in only a minority of the previously reported cases. The main clinical features of the feet, comprising an increased space between the first and second toes, short fourth and fifth rays, and pes planus, were found in all our patients, and in a majority of the previously reported cases. Furthermore, hypertrophy of the neck of the talus, short fourth metatarsals, tarsal coalition or synostosis, winging or an abnormal shape of the scapulae, short fourth and fifth metacarpals, coxa valga, coxa vara, and genu valgum have been described in a minority of the previously reported cases.

Additional anomalies have only been found in five cases. One of the present cases (case 5) showed a high nasal bridge, micrognathia, and a high arched palate. One of the two sporadic cases described by Kozlowski and Nelson[6] had synophrys, epicanthic folds, a broad nasal bridge, apparently low set, posteriorly angulated ears, anteverted nares, long philtrum, high palate, prominent lower lip, and micrognathia, and the other case had a flattened nose and a prominent forehead. Subsequently, Azouz and Kozlowski[9] described another sporadic case with macrocephaly and cleft palate. As yet, it is not possible to establish whether these anomalies are variable features of SPS. Clinical examination of additional cases and the elucidation of the causative gene defect is required to delineate the phenotypic variability of SPS.

Diagnostic radiographic characteristics of SPS have already been mentioned by Kozlowski and Nelson.[6] Here, a review of the clinical and radiological features of the cases with SPS shows that all the radiologically examined cases have patellar a/hypoplasia as well as pelvic anomalies (table 1). Based on these findings we propose a/hypoplasia of the patellae and absent/delayed/irregular ossification of the ischiopubic junctions or infra-acetabular axe cut notches as minimal criteria for the diagnosis of SPS. In only one child could pelvic anomalies not be excluded[12] because she was too young at the time of radiological pelvic examination. Additional major signs comprise an increased space between the first and second toes and short fourth and fifth rays of the feet accompanied by flat feet. Various other skeletal anomalies have been described but do not contribute to the diagnosis.

This syndrome should be differentiated from disorders with a/hypoplastic patellae, including NPS and isolated familial PTLAH. In NPS, patellar a/hypoplasia is associated with nail anomalies, deformation or luxation of the head of the radius resulting in impaired mobility of the elbow, iliac horns and, frequently, nephropathy. Nail a/hypo/dysplasia and absent or hypoplastic patellae are essential features for the diagnosis. Posterior iliac horns are pathognomonic for NPS, but reported to be present in only 70% of cases. Various other skeletal anomalies, including pes equinovarus, dislocated hips, and contractures of major joints have been described in NPS but do not contribute to the diagnosis. This skeletal dysplasia results from mutations in the *LMX1B* gene.[11] In patients with PTLAH, patellar a/hypoplasia is an isolated anomaly without additional radiological or clinical features. Pelvic anomalies, including anomalies of the ischiopubic joint or infra-acetabular notches have never been mentioned in PTLAH.[10 14–16] Radiological examination of the pelvis and feet should be performed in all patients with a/hypoplasia of the patellae in order to differentiate SPS from PTLAH, and to further evaluate the diagnostic value of pelvic and feet anomalies in SPS.

In conclusion, given the clinical overlap between SPS, PTLAH, and NPS we hypothesised that SPS might be allelic to either of these disorders, which map to the chromosomal regions 17q21-22 and 9q34, respectively. Linkage studies excluded allelism with NPS in two of the present families that were available for molecular analysis. Allelism with PTLAH cannot be excluded in our families at the moment. Further linkage studies in other families with SPS are needed to confirm linkage to chromosome 17q21-22 and to examine whether SPS is genetically homogeneous. In view of the small size of most families, only the elucidation of the genetic defect will provide the final answer for allelism of SPS and PTLAH.

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Uniparental isodisomy for paternal 2p and maternal 2q in a phenotypically normal female with two isochromosomes, i(2p) and i(2q)

EDITOR—Recently, Bernasconi *et al*[1] and Shaffer *et al*[2] described carriers of isochromosomes 2p (i(2p)) and 2q (i(2q)). In both patients maternal uniparental disomy (UPD) (2), the exceptional inheritance of both chromosomes 2 from the mother, was detected. Isochromosome formation of both the short and the long arms of a chromosome in one carrier is a rare event. In addition to isochromosomes 2, there exist single reports on only isochromosomes 4p and 4q,[3] isochromosomes 7p and 7q,[4] and isochromosomes 9p and 9q.[5] In these cases, the parental origin was determined and was mostly maternal.

The phenotypes of the carriers of i(2p) and i(2q) and maternal UPD(2) are rather inconsistent. Bernasconi *et al*[1] reported a healthy woman with a history of five spontaneous abortions. In contrast, the patient of Shaffer *et al*[2] showed features similar to those of three maternal UPD(2) patients ascertained because of confined placental mosaicism (CPM) for trisomy 2.[6–8] In all these four patients, severe intrauterine growth retardation with oligohydramnios or anhydramnios and postnatal growth retardation were observed, with additional findings including hypospadias and pulmonary dysplasia or hypoplasia. Three patients showed good motor and intellectual development[2 6 7] and the fourth patient died of severe pulmonary hypoplasia shortly after birth. The phenotypically normal girl published by Heide *et al*,[9] who shows maternal UPD(2) and a normal chromosomal complement supports the observations that maternal UPD(2) has no clinical effects.

Up to now, partial or complete paternal UPD(2) has never been reported. Here we describe a healthy carrier of i(2p) and i(2q), in whom molecular studies showed a paternal UPD(2p) and a maternal UPD(2q).

The healthy, 36 year old woman was referred for chromosomal analysis because all of her six pregnancies had resulted in spontaneous abortion during the first trimester. She had normal physical and mental development. She went through normal puberty and her final height is 176 cm (+2 SD). She is of normal intelligence and works as a nurse.

GTG banded chromosome analysis on lymphocyte cultures of the proband showed a non-mosaic, 46,XX,i(2)(p10),i(2)(q10) chromosome complement. Cytogenetic analyses of the proband's parents showed normal 46,XX and 46,XY karyotypes.

Table 1 Results of STR typing in the UPD(2) family. Data from markers other than chromosome 2 are not shown; the order and localisation of markers correspond to those published by Gyapay et al[10]

STR	*Localisation*	*Father*	*Mother*	*Proband*	*Informativity*
	2pter				
D2S319	2pter-qter	1–2	2–2	1–1	Paternal UPiD
D2S168	2p25	1–4	2–3	4–4	Paternal UPiD
D2S131	2p22-p25	2–2	1–3	2–2	Paternal UPD
D2S160	2p13-q14	1–1	1–1	1–1	—
	Cen				
D2S121	2q12-q13	1–1	2–2	2–2	Maternal UPD
D2S118	2q32	1–2	3–4	3–3	Maternal UPiD
D2S117	2qter-qter	1–1	1–1	1–1	—
D2S116	2q32	2–2	1–1	1–1	Maternal UPD
D2S325	2qter-qter	1–1	2–3	2–2	Maternal UPiD
D2S125	2qter-qter	1–1	2–2	2–2	Maternal UPD
	2qter				

For molecular studies, DNA was isolated from peripheral lymphocytes from the proband and her parents. UPD(2) was determined by short tandem repeat typing (STR). Primers and map location were obtained from the chromosome 2 linkage map published by Gyapay *et al*.[10] Typing of four markers on chromosomes other than chromosome 2 was carried out to confirm normal maternal and paternal contributions.

The results of STR typing are shown in table 1. In three out of four 2p markers, only one paternal allele could be identified; the fourth STR was not informative. On 2q, we detected only one maternal allele in five out of six markers with the sixth not being informative. Therefore, paternal uniparental isodisomy (UPiD)(2p) and a maternal UPiD(2q) is present. A similar condition has been described formerly for chromosome 7[4]; in a postnatally growth retarded girl, a paternal isochromosome 7p and a maternal isochromosome 7q were detected. The following mechanism of formation can be postulated. An incomplete mitotic recombination occurred in a zygote primarily biparental for chromosome 2, followed by the loss of paternal 2q and maternal 2p without the centromere, and centromeric misdivision of the rearranged chromosomes.

To the best of our knowledge, paternal UPD(2) has not previously been described. The finding of a paternal UPD(2p) in a phenotypically normal person indicates that this condition does not seem to have any phenotypic effect. It can be speculated that no paternally imprinted genes are located on the short arm of chromosome 2. Of course, based on only one case, the possibility of the existence of a paternally imprinted gene in 2p cannot be excluded with certainty.

Additionally, maternal UPD(2q) in our proband provides further evidence that there are no imprinted genes on the long arm of chromosome 2, corresponding to the results of Bernasconi *et al*[1] and Heide *et al*.[9] Therefore, our data support the hypothesis that maternal UPD(2) does not influence the phenotype. The clinical findings in the patients with maternal UPD(2) showing abnormalities can probably be attributed to placental dysfunction owing to CPM or to possible mosaicism for trisomy 2. In the case of the phenotypically affected carrier of i(2p) and i(2q),[2] the most probable method is formation of the zygote with biparental disomy 2, subsequent centromeric misdivision resulting in maternal i(2p) and i(2q), and loss of paternal chromosome 2. This mechanism is compatible with CPM for trisomy 2. Thus, this might be the cause of the clinical findings in this patient.

Except for the possibility of homozygosity for recessive mutations, neither paternal UPD(2p) nor maternal UPD(2q) appears to have any adverse effect on the phenotype. There is no evidence for paternally imprinted genes on 2q or maternally imprinted genes on 2p.

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1 Bernasconi F, Kargüzel A, Celep F, Keser I, Lüleci G, Dutly F, Schinzel AA. Normal phenotype with maternal isodisomy in a female with two isochromosomes i(2p) and i(2q). *Am J Hum Genet* 1996;**59**:1114-18.