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ORIGINAL PAPER

Schimke immunoosseous dysplasia: defining skeletal features

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Abstract Schimke immunoosseous dysplasia (SIOD) is an autosomal recessive multisystem disorder characterized by prominent spondyloepiphyseal dysplasia, T cell deficiency, and focal segmental glomerulosclerosis. Biallelic mutations in swi/snf-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1 (*SMARCAL1*) are the only identified cause of SIOD, but approximately half of patients referred for molecular studies do not have

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detectable mutations in *SMARCAL1*. We hypothesized that skeletal features distinguish between those with or without *SMARCAL1* mutations. Therefore, we analyzed the skeletal radiographs of 22 patients with and 11 without detectable *SMARCAL1* mutations. We found that patients with *SMARCAL1* mutations have a spondyloepiphyseal dysplasia (SED) essentially limited to the spine, pelvis, capital femoral epiphyses, and possibly the sella turcica, whereas the hands and other long bones are basically normal. Additionally, we found that several of the adolescent and young adult patients developed osteoporosis and coxarthrosis. Of the 11 patients without detectable *SMARCAL1* mutations, seven had a SED indistinguishable from patients with *SMARCAL1* mutations. We conclude therefore that SED is a feature of patients with *SMARCAL1* mutations and that skeletal features do not distinguish who of those with SED have *SMARCAL1* mutations.

Keywords Genocopy · Immunodeficiency · Proteinuria · Skeletal dysplasia · Locus heterogeneity · Schimke immunoosseous dysplasia

Abbreviations

DNA	Deoxyribonucleic acid
mRNA	Messenger ribonucleic acid
SD	Schimke immunoosseous dysplasia database
SED	Spondyloepiphyseal dysplasia
SIOD	Schimke immunoosseous dysplasia
SMARCAL1	swi/snf-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1
SNF2	Sucrose nonfermenting type 2
TIA	Transient ischemic attack

Introduction

The osteochondrodysplasias are a heterogeneous group of inherited disorders of skeletal growth and development [28]. Among these, the spondyloepiphyseal dysplasias (SEDs) are characterized by primary involvement of the vertebrae and proximal epiphyseal centers resulting in a short-trunk disproportionate dwarfism [16, 26]. The radiographic findings, which are frequently age dependent, commonly include flattened vertebrae (platyspondyly) and dysplastic femoral epiphyses.

Schimke immunoosseous dysplasia (SIOD; OMIM #242900) is an autosomal recessive, pleiotropic disorder

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with distinct spondyloepiphyseal abnormalities [27]. Non-skeletal manifestations include mild facial anomalies [3, 23], T cell immunodeficiency [3, 27], nephrotic syndrome [3, 10, 11, 24, 27], hypothyroidism [3], migraine-like headaches [15], cerebral ischemia [10, 25], and enteropathy [13, 14, 17, 18].

SIOD is caused by biallelic loss-of-function mutations in *SMARCAL1* (OMIM #606622) [4]. *SMARCAL1* encodes a protein homologous to the sucrose nonfermenting type 2 family of chromatin-remodeling proteins [8, 19]; it functions as a DNA annealing helicase [30]. However, in our experience, nearly half of patients with manifestations of SIOD do not have identifiable mutations in the coding exons of *SMARCAL1* or detectable alterations of SMARCAL1 mRNA or protein [7] suggesting a close phenotypic overlap with other conditions or genetic heterogeneity.

Despite the clinical similarity of these patients, we hypothesized that individuals with and without *SMARCAL1* mutations are distinguishable by the type of bone dysplasia. Therefore, we analyzed detailed clinical and radiographic information from a series of 33 SIOD patients with or without detectable *SMARCAL1* mutations.

Materials and methods

Human subjects

Patients referred to this study gave informed consent approved by the Institutional Review Board of the Hospital for Sick Children (Toronto, ON, Canada), Baylor College of Medicine (Houston, TX, USA), or the University of British Columbia (Vancouver, BC, Canada).

Table 1 Features of SIOD patients with and without *SMARCAL1* mutations

Features	SIOD patients with *SMARCAL1* mutations affected/total	SIOD patients without *SMARCAL1* mutations affected/total	Fisher's exact test (p)
Dysmorphism			
Hair hypoplasia	11/20	5/11	0.45
Broad low nasal bridge	12/21	7/11	0.51
Bulbous nasal tip	14/21	6/10	0.29
Hyperpigmented macules	14/20	6/11	0.89
Protuberant abdomen	15/21	9/10	0.25
Elongated upper lip	8/19	3/8	0.59
Development			
Delayed development	6/22	5/10	0.15
Schooling delay	4/11	3/7	0.78
Endocrine			
Serologic hypothyroidism	9/19	4/9	0.60
Hematology and immunology			
Lymphopenia	15/21	8/10	0.48
Recurrent infections	9/22	6/11	0.35
Neutropenia	4/18	5/11	0.18
Anemia	10/21	6/11	0.50
Thrombocytopenia	3/20	3/11	0.26
Nephrology			
Hypertension	18/21	9/10	0.61
Nephrotic syndrome	22/22	9/11	0.10
Progressive renal failure	13/20	8/11	0.49
Proteinuria	22/22	10/10	1.0
Dialysis or graft	13/22	6/10	0.64
Neurology			
TIAs	9/22	3/10	0.43
Strokes	7/22	3/11	0.56
Migraine-like headaches	8/17	1/6	0.21
Skeletal radiographic findings			
SED	22/22	7/11	0.01

SED spondyloepiphyseal dysplasia, *TIA* transient ischemic attack

Analysis of clinical features

The clinical data for patients were obtained from questionnaires completed by the referring physician as well as medical records and summaries provided by that physician. The data obtained for patients with and without *SMARCAL1* mutations were tabulated and then summed to allow comparison of the features of patients in each group. If a feature was not reported for a patient, then that patient was excluded from the denominator. Statistically significant differences between the groups were determined by the Fisher's exact test. Also, to subgroup patients according to disease severity, each patient's signs and symptoms were scored as previously described [12].

Analysis of skeletal radiographs

All radiographs were reviewed independently by Jürgen Spranger and Cornelius F. Boerkoel.

Results

Since we had previously found that only about half of patients clinically diagnosed with SIOD have detectable *SMARCAL1* mutations, we sought to identify skeletal radiographic features distinguishing these two groups of patients [7]. Identification of such features would be useful for guiding molecular diagnosis as well as for characterization of other genetic causes of SIOD. To this end, we assembled detailed clinical and skeletal radiographic data on 33 patients, 11 without *SMARCAL1* mutations and 22 with biallelic *SMARCAL1* mutations.

Phenotypic comparisons

The 22 patients with and 11 without detectable *SMARCAL1* mutations have very similar clinical features (Table 1; Supplementary Tables 1 and 2) and similar disease severity scores, which we calculated as previously described [7]. Those with *SMARCAL1* mutations have slightly more neurological complications, but these are insufficient to distinguish between the two groups of patients. Given the inadequacy of clinical features for distinguishing those with and without *SMARCAL1* mutations, we looked for distinguishing radiographic features.

Radiographic findings

As previously described [26], the spondyloepiphyseal dysplasia of SIOD is most prominent in the spine, pelvis,

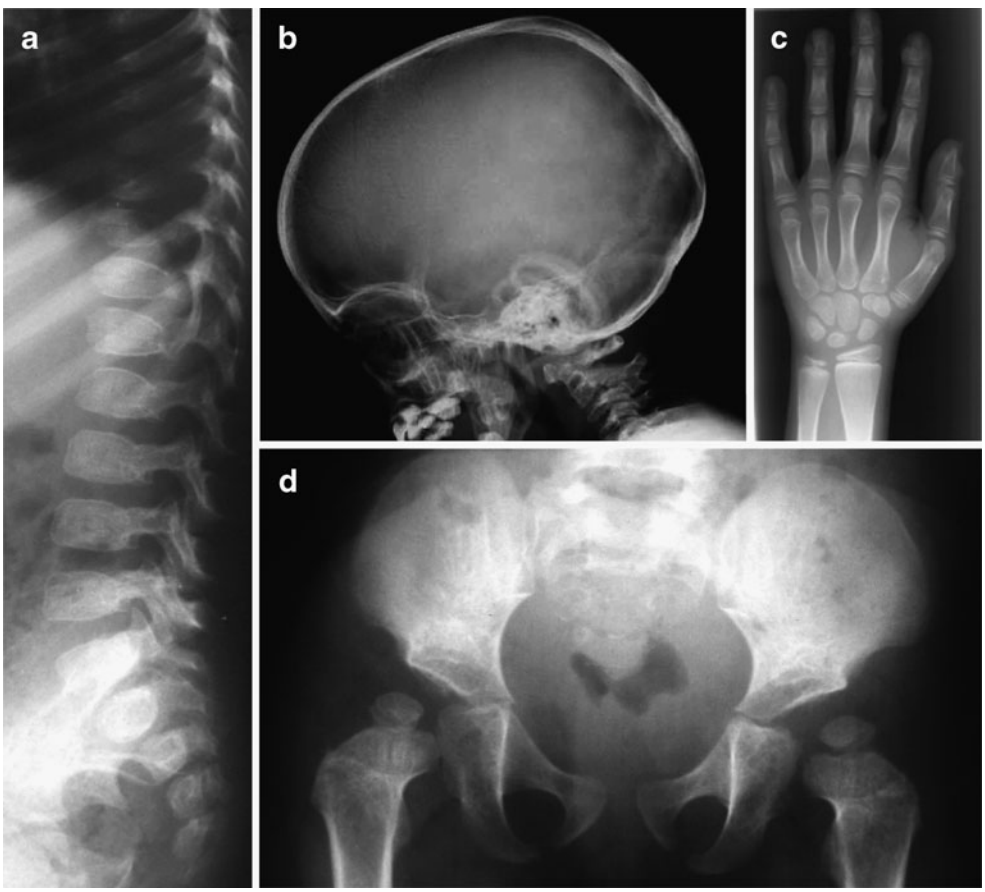


Fig. 1 Typical bony features of SIOD. **a** Lateral spine radiograph of a 5-year-old child showing dorsally flattened, pear-shaped vertebral bodies. **b** Lateral skull radiograph of a 5-year-old child showing the typical widening of the sella. **c** Posteroanterior hand radiograph of a 13-year-old adolescent showing the absence of bony abnormalities. **d** Anteroposterior hip radiograph of a 4-year-old child showing the small, laterally displaced capital femoral epiphyses, hypoplastic basilar ilia, and upslanting and poorly formed acetabula

and capital femoral epiphyses (Fig. 1). The hands and other long bones are essentially normal.

Spine findings among patients with SMARCAL1 mutations

The vertebral bodies are ovoid, dorsally flattened and without segmentation defects at all ages (Figs. 2 and 3). The spinal changes between 4 and 6 years of age show dorsally flattened, pear-shaped vertebral bodies. By 7–11 years of age, there is more generalized vertebral flattening with slightly irregular upper and lower plates (see SD114, Fig. 2). There is variable expressivity as only mild abnormalities are observed in some patients (see SD112, Fig. 2). By adulthood, all have clear signs of progressive osteopenia with compressed vertebral bodies and vertebral bone density similar to that of the soft tissue (Figs. 1 and 2). Peculiarly, SD27 also has diffuse calcification of her discs (Figs. 2 and 3).

Pelvis and capital femoral epiphyseal findings among patients with SMARCAL1 mutations

Nearly consistently at all ages, the pelvis and femora are notable for small, laterally displaced capital femoral

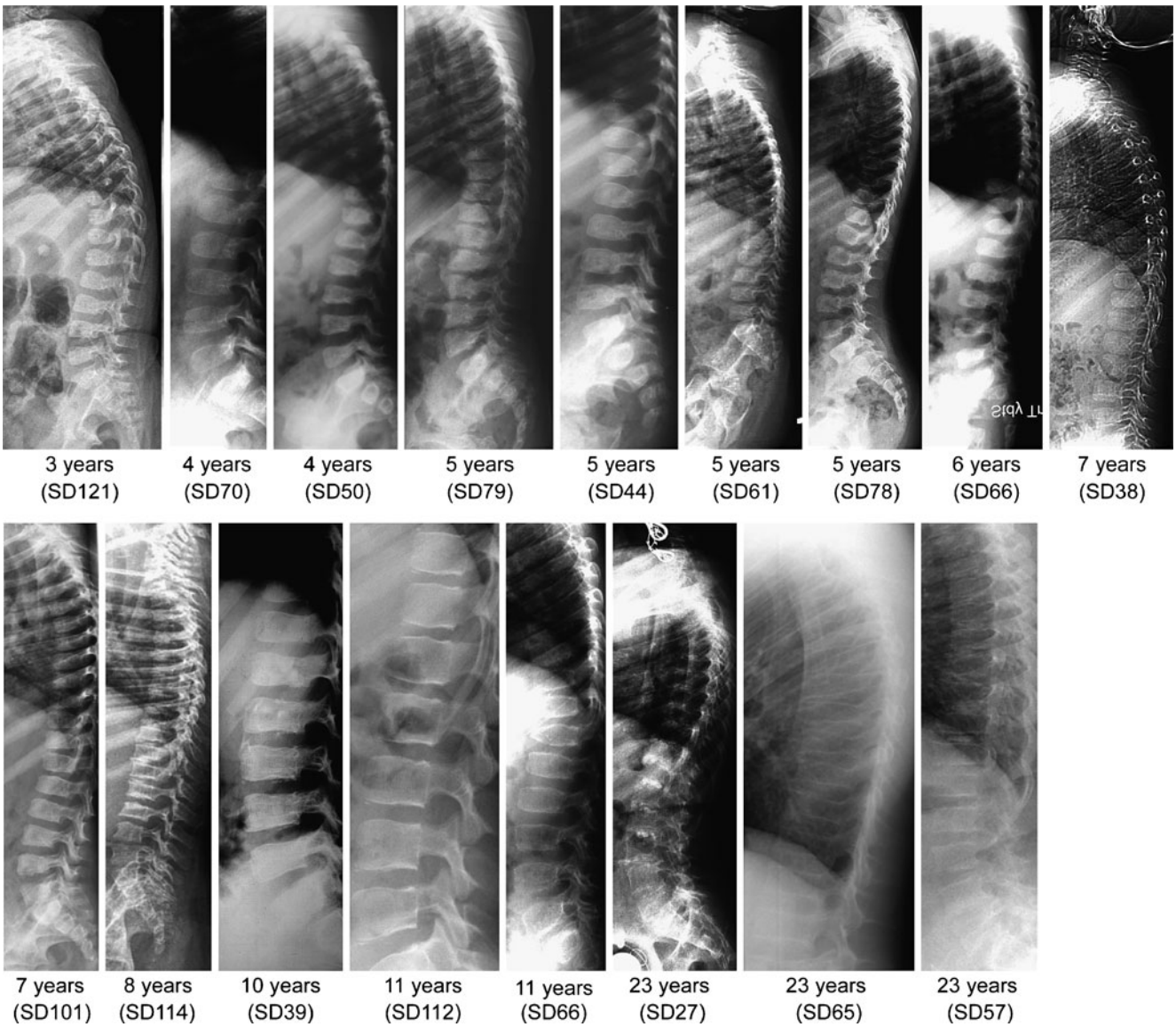


Fig. 2 Lateral spine radiographs of patients with identified *SMARCAL1* mutations at different ages. The vertebral bodies are flattened at all ages and pear-shaped between 4 and 6 years. There is generalized vertebral flattening with slightly irregular upper and lower plates in some patients. The severity of the vertebral changes is variable as illustrated by comparison of SD112 with SD66. Note the radiolucency of adult vertebrae consistent with the progressive osteopenia of SIOD patients. SD27 had diffuse disc calcification; the significance of this is uncertain

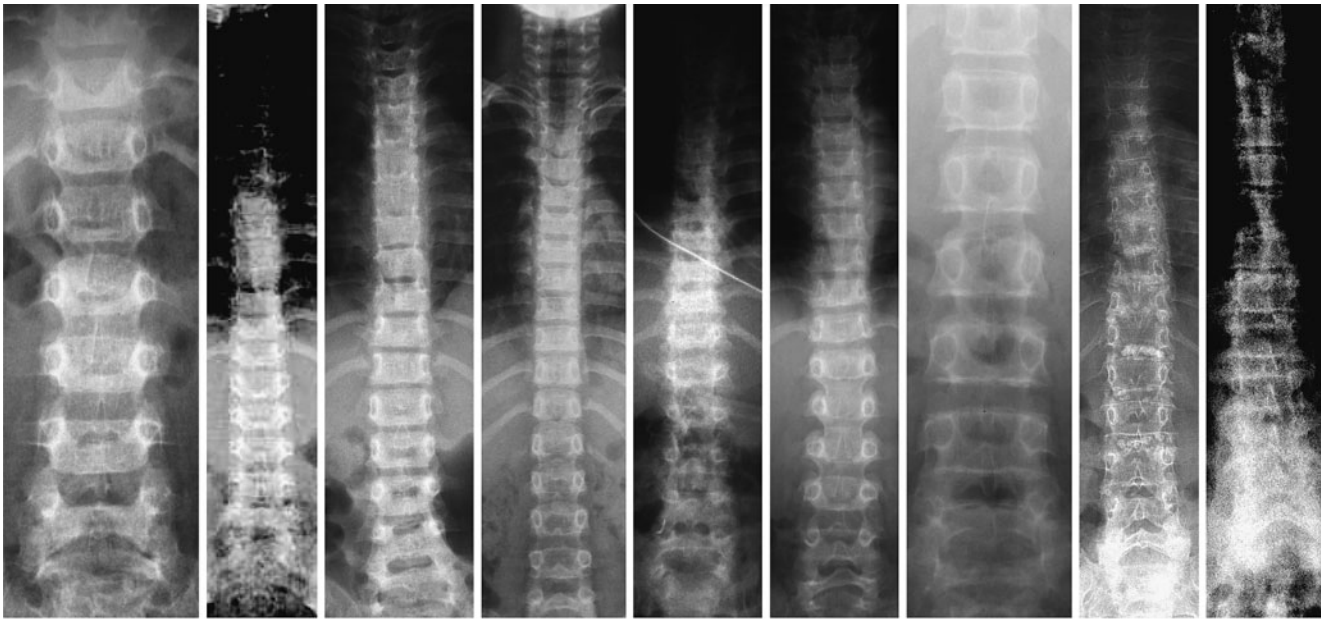


Fig. 3 Anterior–posterior spine radiographs of patients with identified *SMARCAL1* mutations at different ages show various degrees of platyspondyly. SD27 had diffuse disc calcification; the significance of this is uncertain

epiphyses, hypoplastic basilar ilia with upslanting and poorly formed acetabula (Fig. 4). The femoral dysplasia progresses to premature coxarthrosis requiring prosthetic therapy (SD27, Fig. 4).

The severity of these skeletal changes varies among the patients. For example, the proximal femoral pathology ranges from coxa valga with well-preserved capital femoral epiphyses and a normal pelvis (SD78, Fig. 4) to short femoral necks with a peculiar lip-like medial protrusion and markedly hypoplastic lower ilia (SD121, Fig. 4).

Skull findings among patients with SMARCAL1 mutations

No bony abnormalities have been reported in the skull of SIOD patients before. However, of five skull radiographs, three (SD44, SD61, SD114) show a markedly wide sella turcica, one (SD120) a depression of the anterior portion of the sella, and one (SD79) a normal sella turcica (Fig. 5).

Hand and feet findings among patients with SMARCAL1 mutations

Although one SIOD individual has been referred to us with preaxial hexadactyly (C. F. Boerkoel, unpublished data), no others have been reported with bony abnormalities of the hands or feet [26]. Consistent with this, the hand and feet radiographs from the patients in this study do not show bony abnormalities (Fig. 5).

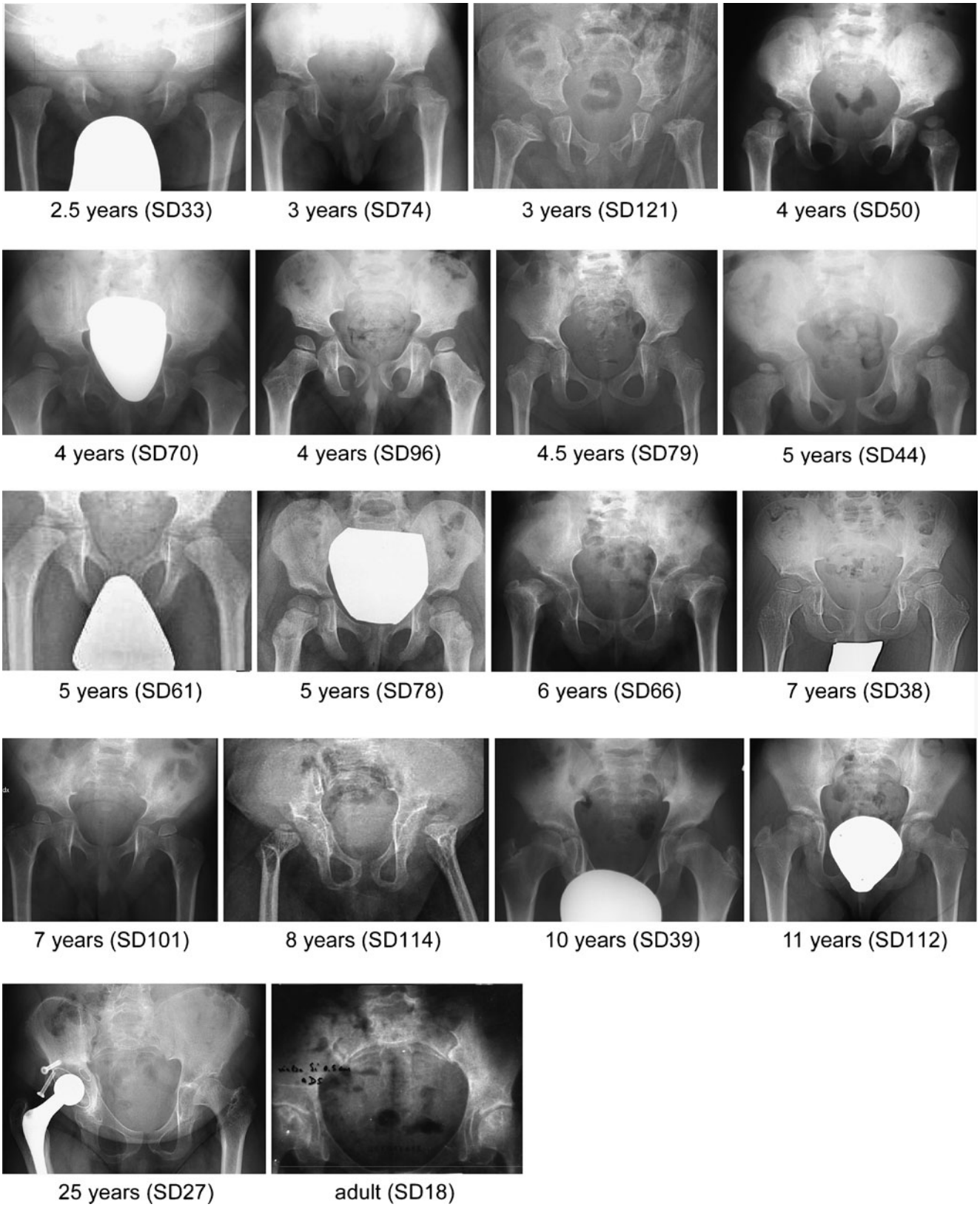
Skeletal findings among patients without detectable SMARCAL1 mutations

Among the patients without detectable *SMARCAL1* mutations, three (SD87, SD95, SD55) have skeletal abnormalities typical of SIOD (Fig. 6). Two (SD80, SD85) have a mild spondyloepiphyseal dysplasia consistent with SIOD (Fig. 6), similar to that of patient SD112 (Figs. 2, 3, and 4). One (SD54) has a typical SIOD-type spondyloepiphyseal dysplasia and severe scoliosis and anterior hypoplasia of L2; these latter changes, which have not been observed among SIOD patients with a *SMARCAL1* mutation, may be secondary to an unrelated muscular hypotonia.

Patients distinct from SIOD

Radiographs from four patients diagnosed with SIOD but without a detectable *SMARCAL1* mutation do not show the

Fig. 4 Hip radiographs of patients with identified *SMARCAL1* ▶ mutations at different ages. The femora generally have small, laterally displaced capital epiphyses, but normal epiphyseal ossification may occur (e.g., SD78, SD 112). By adulthood, the femoral dysplasia usually progresses to premature coxarthrosis (SD18 and SD27) requiring prosthetic therapy (SD27). The ilia are usually small because of hypoplastic basilar portions and have upslanting and poorly formed acetabula. The severity of the ilia and femoral changes is variable as illustrated by comparison of SD78, who had preserved capital femoral epiphyses and a normal pelvis, with SD121, who had short femoral necks with a peculiar lip-like medial protrusion and markedly hypoplastic basilar ilia


2.5 years (SD33)
3 years (SD74)
3 years (SD121)
4 years (SD50)
4 years (SD70)
4 years (SD96)
4.5 years (SD79)
5 years (SD44)
5 years (SD61)
5 years (SD78)
6 years (SD66)
7 years (SD38)
7 years (SD101)
8 years (SD114)
10 years (SD39)
11 years (SD112)
25 years (SD27)
adult (SD18)

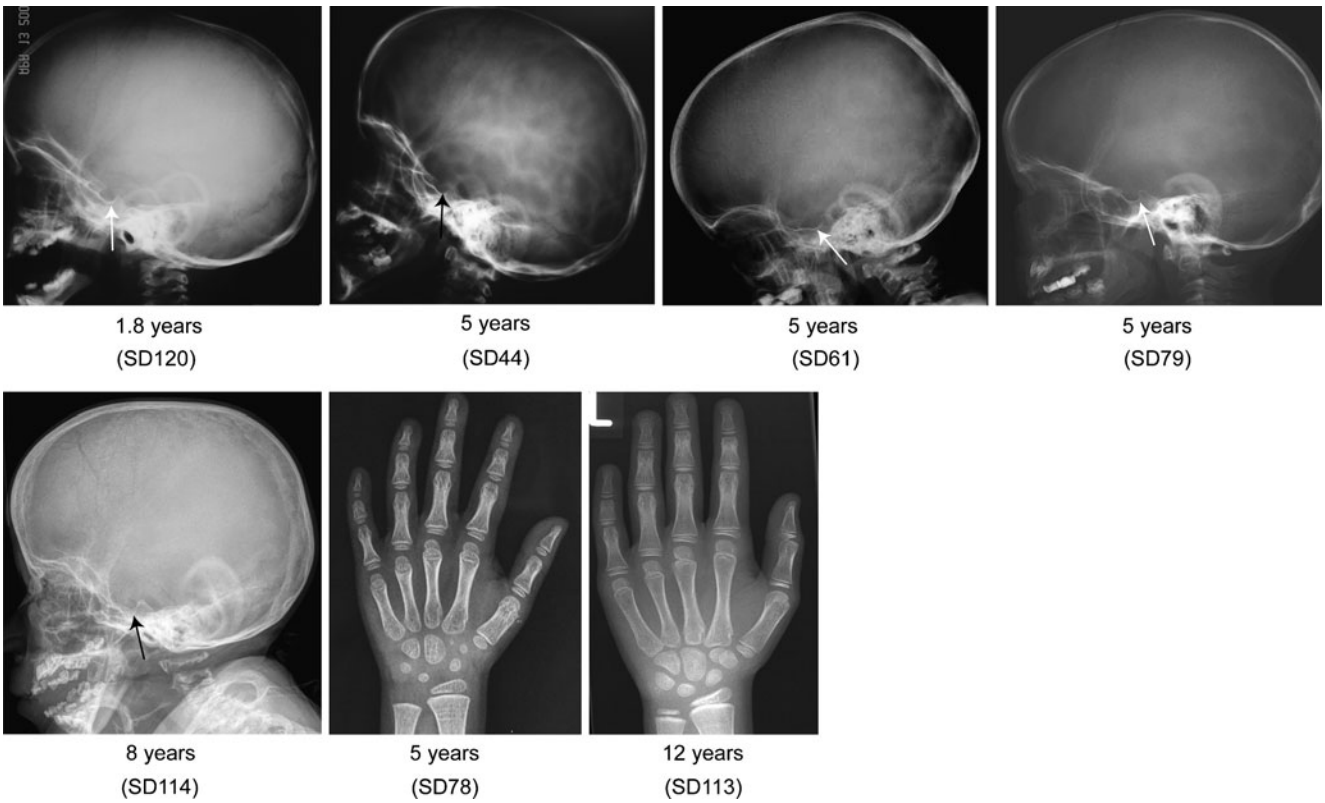


Fig. 5 Skull and hand radiographs of patients with identified *SMARCAL1* mutations at different ages. Note the marked widening of the sella in SD44, SD61, and SD79 and mild widening of the sella in SD120. No bony abnormalities are observed in the hands

skeletal features consistent with SIOD. The radiographs of one (SD89) show enchondromata in the tubular and flat bones and flattened vertebral bodies with irregular areas of increased and decreased mineralization (data not shown); these findings are most consistent with a form of spondyloenchondrodysplasia [21]. The radiographs from three (SD81, SD52a, SD52b) have no signs of SED.

Discussion

The characteristic skeletal features of SIOD patients with *SMARCAL1* mutations are (1) ovoid and flattened vertebral bodies without segmentation defects, (2) small, laterally displaced capital femoral epiphyses, hypoplastic basilar ilia, and upslanting and poorly formed acetabula, and (3) possibly a wide sella. The flattening of the vertebrae and the abnormalities of the hips usually worsen with age and do so to a degree independent of the severity of other features of SIOD. Also, during later childhood, adolescence, and early adulthood, many individuals with SIOD develop coxarthrosis and vertebral osteopenia.

A wide sella turcica has not been reported among SIOD patients previously. If additional studies confirm the findings in this small number of patients, then this will be an additional marker for the clinical diagnosis of SIOD. The wide sella turcica does not reflect anterior pituitary or adenohypophysis dysfunction since in the three patients tested, all had normal growth hormone and thyroid stimulating hormone levels. Also, prior reviews of anterior pituitary function in SIOD patients have not identified a functional pituitary defect [3].

One reason the wide sella turcica may not have been noted previously is the high degree of intra- and interfamilial variability of SIOD [2, 7]. This is reinforced by our findings that not all SIOD patients with *SMARCAL1* mutations had each of the typical skeletal findings. Additionally, we found that there was even variability among tissues within the same person since the severity of vertebral flattening did not predict the severity of hip dysplasia or vice versa.

Relevant to our question of whether the clinical skeletal radiographs can guide molecular testing, our results show that none of the patients without SED had detectable *SMARCAL1* mutations. Therefore, testing for *SMARCAL1* mutations in this group may not be indicated although studies with more patients are needed to confirm this. On the other hand, for individuals with radiographic findings of SED, there were no distinguishing radiographic or clinical features to suggest who would or would not have detectable

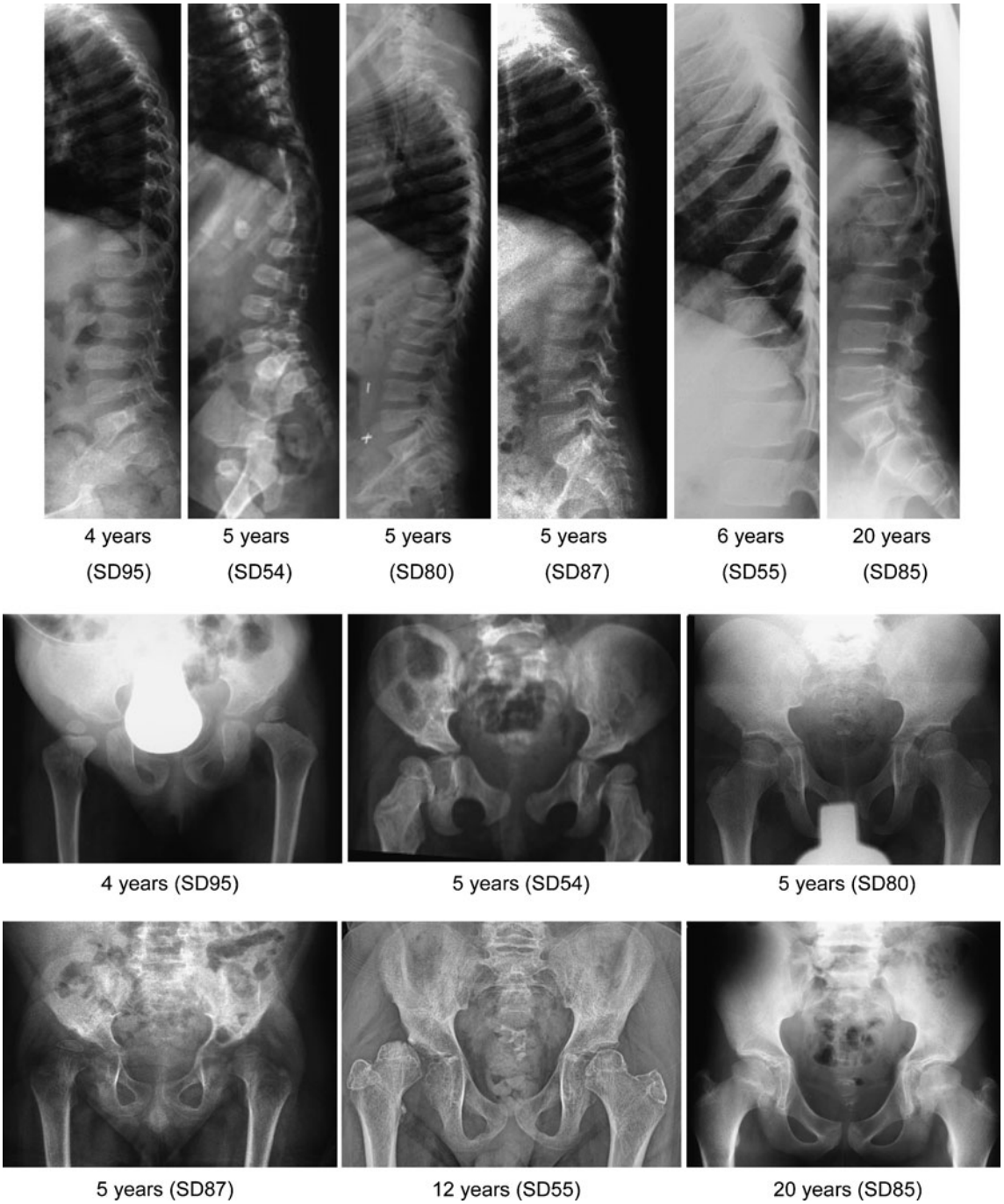


Fig. 6 Lateral spine and hip radiographs of SIOD patients without detectable *SMARCAL1* mutations at different ages. Note the similarity of bony features to those with *SMARCAL1* mutations. SD54 had kyphoscoliosis and anterior hypoplasia of L2, which may have been secondary to an unrelated muscular hypotonia

SMARCAL1 mutations. Therefore, all patients with SED and the other clinical signs of SIOD should be tested for *SMARCAL1* mutations.

The known molecular mechanism underlying SIOD is a generalized disturbance of genomic structure arising secondary to loss of SMARCAL1 DNA strand annealing [31]. This disturbance disrupts both DNA replication [1, 6, 9, 20, 29, 31] and RNA transcription (Baradaran-Heravi et al., submitted for publication; Morimoto et al., submitted for publication). Since cell proliferation and RNA transcription are quantitative traits affected by environment, stochastics, and genetic background [5, 22], the variability among patients and tissues can be accounted for by the combined impact of environment, stochastics, and genetic variation.

The similar clinical and radiographic features of individuals with and without *SMARCAL1* mutations also

suggest that SIOD could be induced by some environmental conditions or by mutations in genes other than *SMARCAL1*. Evidence supporting genetic heterogeneity as opposed to environmental factors includes the recurrence of disease in siblings, the absence of disease in parents, and the geographic dispersal of patients. Of interest for human biology, this suggests that although SMARCAL1 is the only identified annealing helicase in humans [30], other enzymes with redundant or similar function may exist or that SMARCAL1 deficiency mimics that of another global modulator of chromatin structure. Assessments of these possibilities as well as delineation of the physiologic mechanism leading to the skeletal abnormalities will require studies in model organisms.

Besides being unable to distinguish SIOD patients with and without *SMARCAL1* mutations, skeletal radiographs also do not differentiate SIOD from many other spondyloepiphyseal dysplasias. The differential diagnosis of SIOD includes other forms of spondyloepiphyseal and spondyloepimetaphyseal dysplasia listed in group 11 of the International Nosology [28]. These are distinguished from SIOD by their different clinical presentation and by the absence of the characteristic extraskeletal features such as facial dysmorphism, skin changes, T cell deficiency, and renal failure. Thus, the skeletal features are not pathognomonic of SIOD.

In summary, we further define the radiographic features of SIOD and show that SED is a feature common to all individuals with SIOD and *SMARCAL1* mutations. However, among SIOD patients with SED, no radiographic features distinguish those with *SMARCAL1* mutations from those without *SMARCAL1* mutations. Understanding of the clinical variability of this disorder as well as other possible genetic causes requires further elucidation of the molecular mechanisms underlying SIOD.

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Conflict of interest The authors declare no conflicts of interest.

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