U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Lippner E, Lücke T, Salgado C, et al. Schimke Immunoosseous Dysplasia. 2002 Oct 1 [Updated 2023 Mar 30]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Schimke Immunoosseous Dysplasia

Synonyms: *SMARCAL1*-Related Immuno-osseous Dysplasia (Schimke Type)

Elizabeth Lippner, MD,[1] Thomas Lücke, MD, PhD,[2] Carlos Salgado, MD,[3] Cornelius Boerkoel, MD, PhD,[4] and David B Lewis, MD[3]

Created: October 1, 2002; Revised: March 30, 2023.

Summary

Clinical characteristics

Schimke immunoosseous dysplasia (SIOD) is characterized by spondyloepiphyseal dysplasia (SED) resulting in short stature, nephropathy, and T cell deficiency. Radiographic manifestations of SED include ovoid and mildly flattened vertebral bodies, small ilia with shallow dysplastic acetabular fossae, and small deformed capital femoral epiphyses. Nearly all affected individuals have progressive steroid-resistant nephropathy, usually developing within five years of the diagnosis of growth failure and terminating with end-stage renal disease. The majority of tested individuals have T cell deficiency and an associated risk for opportunistic infection, a common cause of death. SIOD involves a spectrum that ranges from an infantile or severe early-onset form with a greater risk of death during childhood to a juvenile or milder later-onset form with likely survival into adulthood if renal disease is appropriately treated.

Diagnosis/testing

The diagnosis of SIOD is established in a proband with the characteristic clinical, laboratory, and radiographic features and/or biallelic pathogenic variants in *SMARCAL1* identified on molecular genetic testing.

Management

Treatment of manifestations: Treatment of scoliosis and kyphosis per orthopedist; pain management and hip replacement as needed in older individuals for degenerative hip disease; standard treatments for osteopenia; consider cyclosporin A, tacrolimus, or corticosteroids for renal disease; renal transplantation as indicated using mild immunosuppressive therapy; acyclovir for recurrent herpetic infections and/or shingles; imiquimod and cidofovir for severe disseminated cutaneous papilloma virus infections; vaccine protocol (avoidance of live

Author Affiliations: 1 Ann & Robert H Lurie Children's Hospital of Chicago;, Northwestern University Feinberg School of Medicine, Chicago, Illinois; Email: elippner@luriechildrens.org. 2 Department of Neuropediatrics, Children's Hospital, University of Bochum, Bochum, Germany; Email: luecke.thomas@ruhr-uni-bochum.de. 3 Division of Allergy, Immunology, and Rheumatology, Department of Pediatrics, Stanford University School of Medicine, Stanford, California; Email: salgado1@stanford.edu; Email: dblewis@stanford.edu. 4 Sanford University of South Dakota Medical Center and Hospital, Sioux Falls, South Dakota; Email: cornelius.boerkoel@ubc.ca.

vaccines as for T cell immunodeficiency); consider antibiotic prophylaxis for *Pneumocystis jirovecii* pneumonia; granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor for neutropenia; hematopoietic stem cell transplantation as indicated; immunosuppressive therapy for those with autoimmune manifestations; thrombopoietin receptor agonists; transfusions when indicated for thrombocytopenia and/or anemia; standard treatment of dental manifestations; developmental support as needed; medical therapy for migraine headaches as needed; agents that improve blood flow or decrease coagulability to treat transient ischemic attacks or strokes; blood pressure control; levothyroxine for hypothyroidism; treatment of malignancy per oncologist.

Surveillance: Annually: monitor growth; monitor for scoliosis/kyphosis and hip degeneration; monitor renal, immune, and hematologic status; assess for enteropathy, dental issues, and developmental concerns; assess for headaches or neurologic abnormalities; thyroid function studies; complete blood count with differential, complete metabolic panel, T and B cell flow cytometry, abdominal ultrasound, and clinical evaluation for lymphadenopathy to monitor for malignancy. At each visit: monitor blood pressure.

Agents/circumstances to avoid: Avoid hypertension; heat, stress, and lack of sleep; and live attenuated immunizations in those who are T cell deficient. Use DNA-damaging anti-cancer therapies with caution due to evidence of susceptibility to genotoxic agents.

Genetic counseling

SIOD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *SMARCAL1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *SMARCAL1* pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *SMARCAL1* pathogenic variants. Carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

Diagnosis

No consensus clinical diagnostic criteria for Schimke immunoosseous dysplasia (SIOD) have been published.

Suggestive Findings

SIOD **should be suspected** in individuals with the following clinical, laboratory, and radiographic features.

Clinical features

- **Disproportionate short stature** (99%) often of prenatal onset (70%) with short neck and trunk, lumbar lordosis, and protruding abdomen
- **Characteristic facial features.** Wide, depressed nasal bridge and a broad nasal tip
- **Hyperpigmented macules** (70%) on the trunk and occasionally extending onto the extremities, neck, and face
- **Recurrent infections** (60%-80%). Bacterial, viral, and fungal
- **Dental anomalies** (66%). Microdontia, hypodontia, and/or malformed molars
- **Neurologic manifestations.** Migraines, transient ischemic attacks, and/or strokes
- **Development** often normal but can be delayed due to recurrent cerebral ischemic events and/or chronic illness
- **Corneal opacities**

Laboratory features

- **Progressive steroid-resistant nephropathy.** Proteinuria (99%) that generally evolves into end-stage renal disease
- **T cell deficiency** (80%). Decreased CD4 and CD8 cells with normal CD4-to-CD8 ratio. The T cells are predominantly of a memory (CD45R0+CD45RA-) surface phenotype.

Radiographic features of spondyloepiphyseal dysplasia. Features are progressive:

- Ovoid and mildly flattened vertebral bodies; endplate irregularities, wedged vertebrae, and narrowed vertebral spaces have been reported.
- Small ilia with hypoplastic basilar portions and shallow dysplastic acetabular fossae
- Capital femoral epiphyses are small, deformed, and laterally displaced; flattened epiphyses at the knees and shoulders.

Establishing the Diagnosis

The diagnosis of SIOD **can be established** in a proband with characteristic clinical, laboratory, and radiographic features and/or biallelic pathogenic (or likely pathogenic) variants in *SMARCAL1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SMARCAL1* variants of uncertain significance (or of one known *SMARCAL1* pathogenic variant and one *SMARCAL1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel, single-gene testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of SIOD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A multigene panel that includes *SMARCAL1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Single-gene testing. Sequence analysis of *SMARCAL1* may be considered to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is

detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** may be possible, although availability is limited due to cost.

Note: Several reported splice site variants may not be identified on sequence analysis [Wang et al 2015, Carroll et al 2015].

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Schimke Immunoosseous Dysplasia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SMARCAL1	Sequence analysis [3]	~90% [4]
	Gene-targeted deletion/duplication analysis [5]	1 reported [6]
Unknown	NA	<10% [7]

NA = not applicable

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. Several reported splice site variants may not be identified on sequence analysis [Wang et al 2015, Carroll et al 2015].

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. A multiexon deletion that included the promoter and exons 1-4 was reported in one individual [Boerkoel et al 2002].

7. The presence of individuals with clinical features of SIOD who do not have identifiable pathogenic variants in *SMARCAL1* [Clewing et al 2007b] suggests that pathogenic variants in other, as yet unidentified genes can also cause SIOD.

Clinical Characteristics

Clinical Description

Schimke immunoosseous dysplasia (SIOD) is characterized by a constellation of clinical findings that affect a variety of organ systems. Nearly all affected individuals have disproportionate short stature, spondyloepiphyseal dysplasia causing hip disease, nephrotic syndrome that progresses to end-stage renal disease (ESRD), hyperpigmented macules, and immunodeficiency (primarily cellular immunodeficiency). Central nervous system vasculopathy (migraines, transient ischemic attacks, strokes), thyroid dysfunction, and cytopenias are also common. Secondary complications include hypertension, anemia, elevated lipids, recurrent infections, and osteopenia. Although not defining features of SIOD, bone marrow failure and lymphoproliferative disease have been reported [Boerkoel et al 2000, Baradaran-Heravi et al 2012b, Ramdeny et al 2021]. Based on review of the medical literature to date, more than 100 individuals have been identified with biallelic pathogenic variants in *SMARCAL1*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Frequency of Physical, Radiographic, and Laboratory Features in Individuals with Schimke Immunoosseous Dysplasia Confirmed on Molecular Testing

Feature		% of Persons w/Feature	Comment
Skeletal features	Disproportionate short stature	~99%	Prenatal onset (IUGR) in 70%
	Vertebral anomalies	>75%	Ovoid shaped; dorsal flattening
	Hypoplastic pelvis	65%	
	Epiphyseal dysplasia	~90%	
Renal disease	Proteinuria or nephropathy	99%	Steroid resistant
	FSGS	83%	
Immune deficiency	T cell deficiency	80%	
	Neutropenia	~40%	Bone marrow hypoplasia of neutrophil lineage may occur w/ normal peripheral blood neutrophil counts.
	Recurrent infections	60%-80%	
Autoimmune disease	Anemia	~60%	May also be secondary to bone marrow failure
	Thrombocytopenia	25%	
	Other	Rare	Enteropathy, pericarditis
Physical features	Characteristic facial features	~90%	Triangular facies; wide, depressed nasal bridge, broad nasal tip
	Hyperpigmented macules	70%	
	Fine &/or sparse hair	63%	
	Dental anomalies	>60%	Microdontia, hypodontia
	Corneal opacities	~25%	
Development	Developmental delay	34%	
	Academic delay	28%	
Vasculature	Headaches	47%	
	TIAs	41%	
	Strokes	43%	
Endocrine	Hypothyroidism	~50%	
Hematologic	Bone marrow failure	5%-10%	Contributes to neutropenia, anemia, & thrombocytopenia
Lymphoproliferative disease / Malignancy	Lymphoma/leukemia (ALL)	<10%	
	Osseous solid tumors	Rare	

ALL = acute lymphoblastic leukemia; FSGS = focal segmental glomerulosclerosis; IUGR = intrauterine growth restriction; TIAs = transient ischemic attacks

Disproportionate short stature. The mean age of diagnosis of disproportionate growth deficiency is two years (range: age 0-13 years) [Clewing et al 2007b]. Generally, affected individuals have a normal growth hormone axis and no response to growth hormone supplementation. Height in those who have survived to adulthood is 136 cm to 157 cm for men and 98.5 cm to 143 cm for women.

Short stature is not a result of renal failure. Comparison of the anthropometric measurements of persons with SIOD to persons with non-SIOD chronic kidney disease found that in nearly all parameters, persons with SIOD differed significantly from those with non-SIOD chronic renal disease. The most marked difference is that in non-SIOD chronic kidney disease, the median leg length is significantly more reduced than trunk length, while

in persons with SIOD, the reduction in trunk length was significantly more than that of leg length. Therefore, a sitting height / leg length ratio of lower than 0.83 is suggestive of SIOD in persons with chronic kidney disease [Lücke et al 2006a].

Skeletal features. Vertebrae are ovoid in more than 75% of individuals with dorsal flattening. Endplate irregularities and narrowed vertebral spaces can be seen. Short neck and trunk with lumbar lordosis are common and become more evident with age. Thoracic kyphosis and scoliosis have also been reported.

Hypoplastic pelvis and epiphyseal dysplasia leads to degenerative hip disease and chronic joint pain. Surgical intervention may be necessary, and treatment of hematopoietic and renal anomalies has not been shown to alter bony disease. The shoulder and other large joints are relatively spared.

Less frequent skeletal findings include a widened sella turcica and osteopenia. Individuals with SIOD and osteopenia are at risk for fractures. Systemic corticosteroids should be used with caution.

Renal disease. Nephropathy usually develops before age 12 years and progresses to ESRD within the subsequent one to 11 years. Both early onset (by age 5 years) and juvenile onset (typically after age 10 years) have been reported [Lipska-Ziętkiewicz et al 2017]. Usually, the diagnosis of nephropathy is made concurrent with or within five years following the diagnosis of growth deficiency. Focal segmental glomerulosclerosis (FSGS) is the predominant renal pathology in individuals with SIOD.

Immune deficiency. T cell deficiency is reported in approximately 80% of affected individuals. Those T cells that are present are predominantly of a memory (CD45R0+) rather than a naïve (CD45RA+) surface phenotype, consistent with reduced production of T cells by the thymus [Sanyal et al 2015]. The T cell deficiency is associated with a lack of interleukin-7 (IL-7) receptor alpha expression on the T cells of individuals with SIOD and their poor response to recombinant IL-7 [Sanyal et al 2015]. The IL-7 receptor is critical for T cell development and has been previously implicated in severe combined immunodeficiency [Puel et al 1998, Roifman et al 2000]. The B cell count is usually normal to slightly elevated. Hypogammaglobulinemia and poor antibody responses to immunization have been reported, and affected individuals may require replacement immunoglobulin therapy. Immunization with live vaccines is contraindicated in individuals with T cell immunodeficiency.

Neutropenia is also reported in 38% of individuals with SIOD and is likely a reflection of relative hypoplasia of the neutrophil lineage in the bone marrow [Bertaina et al 2022]. Most individuals with neutropenia have concurrent autoimmune thrombocytopenia, autoimmune hemolytic anemia, or pancytopenia from bone marrow failure [Boerkoel et al 2000, Clewing et al 2007a].

Immunodeficiency increases the risk of opportunistic infections such as *Pneumocystis jirovecii* pneumonia. More than half of individuals with SIOD have recurrent infections with various bacteria, viruses (e.g., herpes simplex virus, varicella-zoster virus, cytomegalovirus), and fungi (e.g., oral and/or cutaneous candida) [Lipska-Ziętkiewicz et al 2017]. Several individuals have developed viral cutaneous papillomas refractory to multiple antivirals that have negatively affected quality of life. Severe bacterial, viral, and/or fungal infection is a common cause of death.

Autoimmune disease. About 20% of individuals with SIOD have features of autoimmune disease. These manifestations include immune thrombocytopenia, hemolytic anemia, Evans syndrome (a combination of hemolytic anemia and immune thrombocytopenia), enteropathy, and pericarditis with anti-cardiolipin antibodies [Lipska-Ziętkiewicz et al 2017].

In one affected individual with thrombocytopenia, the autoimmune features resolved spontaneously; in one they resolved after steroid and intravenous immunoglobulin treatments, and in one they cleared after splenectomy. One individual who developed immune thrombocytopenia two years after renal transplantation was not responsive to intravenous immunoglobulin or systemic corticosteroids and required plasmapheresis and

thrombopoietin-receptor agonist therapy [Grenda et al 2016]. All other affected individuals, excepting one with Evans syndrome, were successfully treated with immunosuppressive therapy such as steroids, cyclophosphamide, or intravenous immunoglobulin.

Anemia does not often respond to supplementation with erythropoietin or renal transplantation. However, it is possible that erythropoietin has a protective effect on the endothelia. A few individuals have been transfusion dependent due to anemia or thrombocytopenia. The individual with Evans syndrome was resistant to treatment with steroids, cyclosporin A, and rituximab [Zieg et al 2011].

A few individuals with SIOD have enteropathy. In most of these individuals, the enteropathy results from infection (e.g., *Helicobacter pylori*); however, one individual without evidence of infection had gastrointestinal villous atrophy that improved with corticosteroid therapy [Kaitila et al 1998].

Physical features. Characteristic features include triangular facies, wide, depressed nasal bridge with a broad nasal tip, short neck, short trunk, and protruding abdomen. Most affected individuals have hyperpigmented macules on the trunk and occasionally on the extremities, neck, and face. Fine and/or sparse hair is present following the transition from soft newborn hair; 66% of individuals have had microdontia, hypodontia, and/or malformed deciduous and permanent molars [Morimoto et al 2012a]; corneal opacities are also reported.

Development. Most individuals with SIOD have normal intellectual and neurologic development until the onset of cerebral ischemic events. A few have developmental delay – in most cases likely a consequence of chronic illness and/or early recurrent cerebral ischemic events.

Central nervous system (CNS) symptoms, atherosclerosis, and hypertension. Nearly half of affected individuals have severe migraine-like headaches, transient ischemic attacks (TIAs), or strokes [Kilic et al 2005]. Reported migraine-like headaches had no aura and included throbbing, photophobia, nausea, and vomiting. The TIAs are usually focal and can present as hemiplegia, dysarthria, and aphasia. Some affected individuals also have heat intolerance and develop CNS symptoms (e.g., headache, aphasia) during hot weather [Baradaran-Heravi et al 2012a]. Generally, those with TIAs or strokes have diffuse, progressive cerebral arteriosclerosis, whereas those with only migraine-like headaches do not. Frequently the cerebral ischemic events are precipitated by hypertension. The onset of chronic hypertension, though variable, is often within two years of diagnosis in early-onset disease.

The cause of the severe migraine-like headaches is unknown. Two case reports describe individuals presenting with severe headaches progressing to hemiplegia, aphasia, and seizures in whom brain imaging demonstrated reversible vasoconstriction and diminished cerebral perfusion [Severino et al 2018, Haffner et al 2019]. Their presentation, consistent with reversible cerebral vasoconstriction syndrome, describes a new mechanism for headaches, TIAs, and strokes in individuals with SIOD.

Half of individuals with SIOD have symptoms suggestive of atherosclerosis (e.g., hypertension, cerebral ischemia, renal occlusive disease). Vascular changes observed on postmortem tissue from three individuals included focal intimal lipid deposition, focal myointimal proliferation, macrophage invasion, foam cells, fibrous transformation, and calcium deposits [Spranger et al 1991, Lücke et al 2004, Clewing et al 2007a]. Moyamoya disease has also been described in SIOD-associated CNS disease. The pulmonary and systemic hypertension that persisted despite renal transplantation described by Lücke et al [2004] could be explained by myointimal hyperplasia [Clewing et al 2007a].

Hypothyroidism. One third of affected individuals have subclinical hypothyroidism that persists after renal transplantation. The concentration of thyroid-stimulating hormone is increased and free, and total T3 and T4 concentrations are reduced.

Malignancy. Individuals with SIOD are at increased risk for hematologic malignancies including both non-Hodgkin lymphoma and leukemia. There is one reported [Baradaran-Heravi et al 2012b] and one unpublished

instance of osteosarcoma as well as several unpublished instances of solid organ malignancies. A diagnosis of undifferentiated sinus carcinoma has also been reported in one individual with SIOD [Collins et al 2018]. Individuals who have received renal transplants are also at risk for post-transplant lymphoproliferative disease (PTLD), although the risk of PTLD is not definitively higher when compared to all individuals following renal transplant. No definitive mechanism has been reported, but the *SMARCAL1* protein product has been shown to have a role in hypersensitivity to genotoxic agents in vivo [Baradaran-Heravi et al 2012b].

Prognosis. SIOD varies in severity, ranging from prenatal growth deficiency with death in the first few years of life to a slowly progressive course with survival into adulthood if ESRD is treated with renal dialysis and/or renal transplantation. Severity and age of onset of symptoms do not, however, invariably predict survival; a few individuals have survived beyond age 20 years despite having relatively severe early-onset disease [Lou et al 2002, Lücke et al 2004].

Most affected individuals develop other symptoms within one to five years of the diagnosis of growth deficiency. Those with severe symptoms usually die within four to eight years. The mean age of death is 11 years. Causes of death include infection (23%), stroke (13%), pulmonary hypertension and congestive heart failure (13%), renal failure (11%), complications of organ transplantation (9%), lymphoproliferative disease (4%), gastrointestinal complications (4%), respiratory failure (4%), bone marrow failure (2%), non-Hodgkin lymphoma (2%), pancreatitis (2%), and other causes not reported (13%).

Among those who have survived beyond puberty, it is unknown if any individuals with SIOD have reproduced. Women develop menses, although the menstrual cycle is usually irregular. Men develop secondary sexual characteristics, but histopathologic examination of the testes has identified azoospermia [Clewing et al 2007a].

Genotype-Phenotype Correlations

The early-onset, more severe phenotype has been associated with truncating *SMARCAL1* variants that lead to absence of protein product. It has been suggested that compound heterozygous missense variants that result in present but unstable protein may cause a milder nonrenal phenotype. However, no genotype-phenotype correlations have been confirmed; there was no association between type/severity of disease-causing variant and severity of renal disease [Lipska-Ziętkiewicz et al 2017].

Nomenclature

Ehrich et al [1990] contributed to the clinical description of the disease; thus, in parts of Germany the term "morbus Ehrich" has also been used.

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], Schimke immunoosseous dysplasia is referred to as *SMARCAL1*-related immuno-osseous dysplasia (Schimke type) and included in the spondyloepi(meta)physeal dysplasias group.

Prevalence

The prevalence is unknown. The incidence is estimated at 1:1,000,000 to 1:3,000,000 live births.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SMARCAL1*.

Differential Diagnosis

The differential diagnosis of Schimke immunoosseous dysplasia (SIOD) depends on the presenting features in the individual. Table 3a lists hereditary osteochondrodysplasias associated with nephrotic syndrome; Table 3b lists hereditary osteochondrodysplasias associated with immune defects.

The co-occurrence of disproportionate short stature with spondyloepiphyseal dysplasia, progressive nephropathy, and T cell deficiency is unique to SIOD.

Table 3a. Differential Diagnosis of Schimke Immunoosseous Dysplasia: Hereditary Osteochondrodysplasias Associated with Nephrotic Syndrome

Gene	Syndrome	MOI	Comment
IFT140	Conorenal syndrome (OMIM 266920)	AR	Cone shaped epiphyses w/constricted & short ribs; retinal disease; renal pathology of variable causes (vs in SIOD, in which the cause is nephrotic syndrome); lack of neurologic sequelae in conorenal syndrome
LMX1B	Nail-patella syndrome (NPS)	AD	NPS is assoc w/classic clinical tetrad of changes in nails, knees, & elbows, & presence of iliac horns. In NPS renal disease is due to glomerulonephritis (in SIOD: FSGS/nephrotic syndrome).

AD = autosomal dominant; AR = autosomal recessive; FSGS = focal segmental glomerulosclerosis; MOI = mode of inheritance; SIOD = Schimke immunoosseous dysplasia

Table 3b. Differential Diagnosis of Schimke Immunoosseous Dysplasia: Hereditary Osteochondrodysplasias Associated with Immune Defects

Gene	Syndrome	MOI	Immune Cell Defect	Comment
DNMT3B	Immunodeficiency-centromeric instability-facial anomalies syndrome (OMIM 242860)	AR	B cell	Assoc w/dysmorphic facial features & DD. While there is growth delay, these persons lack SED & renal disease.
RMRP	Cartilage-hair hypoplasia – anauxetic dysplasia spectrum disorders (CHH-AD)	AR	T & B cells	CHH-AD is assoc w/fine, sparse hair & short-limbed short stature (vs short stature caused by short trunk in SIOD). CHH-AD is not assoc w/ renal disease.
RNU4ATAC	Roifman syndrome (See RNU4atac-opathy.)	AR	B cell	Assoc w/hypotonia, retinal dystrophy, ID, prominent otitis, & sinopulmonary infections
TBCE	Kenny-Caffey syndrome type 1 (OMIM 244460)	AR	T cell	Short stature assoc w/long bone medullary stenosis & recurrent transient hypocalcemia
	Hypoparathyroidism-intellectual disability-dysmorphism syndrome (OMIM 241410)	AR	T cell	Characterized by hypoparathyroidism w/ hypocalcemia, seizures, & facial dysmorphism (deep-set eyes, hypertelorism, large ear lobes, long philtrum)

AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; SED = spondyloepiphyseal dysplasia; SIOD = Schimke immunoosseous dysplasia

Short stature resulting from renal failure can be distinguished from that of SIOD by the disproportion in body measures [Lücke et al 2006a]. Among individuals with chronic renal failure, median leg length was significantly more reduced than sitting height, whereas in individuals with SIOD, the reduction of sitting height was significantly more pronounced than that of leg length. SIOD is very likely if the sitting height / leg length ratio is lower than 0.83. However, other forms of chronic kidney disease have to be considered if the ratio is greater than 1.01.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Schimke immunoosseous dysplasia (SIOD), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Schimke Immunoosseous Dysplasia

System/Concern	Evaluation	Comment
Growth	Measurement of growth & assessment of body proportions using age-appropriate growth charts [1]	
Skeletal	• Orthopedic eval for symptoms of joint pain or evidence of scoliosis or kyphosis • Assessment for osteopenia at diagnosis or w/in 1 yr of diagnosis	
Renal	• Eval of renal function by measurement of serum concentrations of creatinine & urea, protein excretion in urine, & creatinine clearance • Referral to nephrologist for eval	
Immunology	Immunology eval to evaluate numbers of memory & naïve CD4 & CD8 T cells, B cells, & immunoglobulin levels	
Hematology	Assess for neutropenia, anemia, & thrombocytopenia.	
Gastrointestinal	Assess for signs/symptoms of enteropathy.	
Dental	Dental eval after teeth erupt	
Eyes	Ophthalmologic eval for corneal opacities	
Development	Assessment of developmental status	
Neurologic	• Detailed history for headaches &/or neurologic abnormalities • Blood pressure • Consider brain MRI w/vessel imaging & perfusion studies (arterial spin labeling).	Baseline imaging of brain is recommended to allow comparison w/future imaging during acute neurologic changes.
Endocrine	Thyroid function studies	
Malignancy	Eval should be considered based on clinical signs/symptoms.	
Genetic counseling	By genetics professionals [3]	To inform affected persons & families re nature, MOI, & implications of SIOD to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; SIOD = Schimke immunoosseous dysplasia
1. Lücke et al [2006a]
2. Severino et al [2018], Haffner et al [2019]
3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Schimke Immunoosseous Dysplasia

Manifestation/Concern	Treatment	Considerations/Other
Scoliosis/Kyphosis	Standard treatments per orthopedist	
Degenerative hip disease	• Pain mgmt as needed • Hip replacement as indicated	Some affected persons who have survived beyond childhood have undergone hip replacement.
Osteopenia	Standard treatments for osteopenia	• Persons w/SIOD & osteopenia are at risk for fractures. • Use systemic corticosteroids w/caution.
Renal disease	Cyclosporin A, tacrolimus, or corticosteroids	Resulted in transient reduction in renal disease progression in a few persons
	• Renal transplantation • Consider combined renal & HSCT in persons w/declining renal & immune function prior to onset of end-stage disease.	• Neither nephropathy nor arteriosclerosis recurs in the graft. [1] • Mild immunosuppressive therapy (immunosuppressive monotherapy), appears to improve outcome after renal transplant. [2] • Performing HSCT prior to renal transplantation from same donor may allow for rapid weaning of immunosuppressive therapy. [3]
Immune deficiency / Recurrent infections	Treatment per immunologist incl: • Acyclovir for recurrent herpetic infections &/or shingles; consider prophylactic acyclovir. • Imiquimod & cidofovir for severe disseminated cutaneous papilloma virus infections • Vaccine protocol for other T cell immunodeficiencies (i.e., only inactivated vaccines w/avoidance of all live-attenuated vaccines) in those w/T cell immunodeficiency • Consider prophylaxis (trimethoprim/sulfamethoxazole or atovaquone) against *Pneumocystis jirovecii* pneumonia due to ↑ risk of opportunistic infection. Neutropenia usually responds well to granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor.	• Using myeloablative conditioning, 1 person was successfully treated by HSCT, [4] but 4 others so treated died from transplant-related complications. [5] • 3 children who underwent HSCT after ↓-intensity conditioning did well w/minimal post-transplant toxicity or graft-versus-host disease. [3]
Thrombocytopenia	• Immunosuppressive therapy (steroids, cyclophosphamide, or IVIG) • Thrombopoietin-receptor agonists • Platelet transfusions as needed • Splenectomy may be considered if recommended by hematologist.	
Anemia	• Transfusions as needed • Anemia is often refractory to erythropoietin, but it can still be used. • Consider eval for bone marrow failure.	
Dental anomalies	Treatment per dentist &/or orthodontist	
Development delay	Referral for formal developmental eval & supportive treatment	If significant developmental delays or schooling delays are identified

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Migraine headaches	Ergotamine, sumatriptan, verapamil, & propranolol have helped some persons.	Note: Ergotamine & sumatriptan are contraindicated in persons w/SIOD w/severe vaso-occlusive disease or cerebral ischemic events.
Transient ischemic attacks &/or strokes	• Agents that improve blood flow or ↓ coagulability (pentoxifylline, acetylsalicylic acid, dipyridamole, warfarin, heparin) may provide temporary improvement. • Blood pressure control • ACE inhibitors have also been used w/variable results.	• To date, no curative or effective long-term therapies have been identified. • If RVCS is identified, consider use of calcium channel blockers w/neurologist consultation.
Hypothyroidism	Levothyroxine if needed	
Malignancy	• Treatments per oncologist • Blinatumomab was used in 1 person w/ALL. [6]	• Risk from genotoxic agents is present but no cancer therapeutics need to be avoided. • For HSCT, the authors have used ↓-intensity conditioning considering ↑ risk of sensitivity to genotoxic agents & telomere shortening that has been identified in several persons. [7]

ALL = acute lymphoblastic leukemia; HSCT = hematopoietic stem cell transplantation; RVCS = reversible cerebral vasoconstriction syndrome; SIOD = Schimke immunoosseous dysplasia

1. Lücke et al [2004], Elizondo et al [2006], Clewing et al [2007a]
2. Lücke et al [2009]
3. Bertaina et al [2022]
4. Petty et al [2000], Thomas et al [2004]
5. Baradaran-Heravi et al [2013]
6. Ramdeny et al [2021]
7. Authors, unpublished data

Surveillance

Table 6. Recommended Surveillance for Individuals with Schimke Immunoosseous Dysplasia

System/Concern	Evaluation	Frequency/Comment
Growth	Growth assessment	• Persons w/SIOD usually have normal growth hormone studies. • No affected person treated w/growth hormone supplementation has responded w/improved growth.
Skeletal	• Assessment of scoliosis &/or kyphosis & joint pain (degenerative hip disease) • Assessment for osteopenia w/DXA scan	Annually or more frequently depending on signs/symptoms
Renal	• Eval of renal function by measurement of serum concentrations of creatinine & urea, protein excretion in urine, & creatinine clearance • Serum calcium, phosphorus, alkaline phosphatase, vitamin D, parathyroid hormone	
Immunology	Immunology eval incl total T & B cells, numbers of memory & naïve CD4 & CD8 T cells, & immunoglobulin levels	
Hematology	Hematology eval to assess for thrombocytopenia &/or anemia	

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency/Comment
Enteropathy	Assess for signs/symptoms of bowel disease.	Annually
Dental	Dental eval after teeth erupt	
Development	Assessment of developmental status	
Neurologic	Monitor blood pressure.	At each visit
	Detailed history for headaches or neurologic abnormalities	Annually
Endocrine	Thyroid function studies	
Malignancy	• Complete blood count w/differential • Complete metabolic panel • T & B cell flow cytometry • Abdominal ultrasound • Clinical eval for lymphadenopathy	

DXA = dual-energy x-ray absorptiometry

Agents/Circumstances to Avoid

Avoid the following:

- **Hypertension.** Poor blood pressure control can exacerbate or evoke cerebral ischemia. In particular, the hypertension arising from using high-dose steroids for empiric treatment of the nephrotic syndrome can evoke cerebral ischemia.
- **Heat, stress, and lack of sleep.** Individuals with transient neurologic attacks that are not of an ischemic origin have found that heat, stress, and lack of sleep can precipitate the attacks.
- **Vaccinations with live vaccines.** The T cell deficiency is substantial and there have been serious infections in some individuals. Therefore, in those with T cell immunodeficiency, vaccination with all live vaccines should be avoided, including rotavirus, measles-mumps-rubella (MMR), varicella, bacillus Calmette-Guérin (BCG), oral *Salmonella typhi*, and yellow fever virus vaccines.

Note: Cells from individuals with SIOD and model organisms are hypersensitive to DNA-damaging agents [Bansbach et al 2009, Ciccia et al 2009, Postow et al 2009, Yuan et al 2009, Yusufzai et al 2009, Bansbach et al 2010, Baradaran-Heravi et al 2012b].

Evaluation of Relatives at Risk

It is appropriate to evaluate (see Diagnosis) older and younger sibs of a proband in order to identify as early as possible those who would benefit from surveillance and prompt management of renal disease, immunodeficiency, and other complications.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Studies of mitochondrial function and nitrous oxide production have not detected any impairment; therefore, empiric treatments addressing such etiologies would be expected to have little effect [Lücke et al 2005, Lücke et al 2006b].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Schimke immunoosseous dysplasia (SIOD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *SMARCAL1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *SMARCAL1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *SMARCAL1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *SMARCAL1* pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *SMARCAL1* pathogenic variants.
- Sibs with biallelic *SMARCAL1* pathogenic variants can have variable phenotypes (see Genotype-Phenotype Correlations).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with SIOD are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SMARCAL1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SMARCAL1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *SMARCAL1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for SIOD are possible.

Ultrasound examination. The diagnosis may be suspected in a fetus with intrauterine growth restriction (IUGR) and an affected sib; however, approximately 30% of affected fetuses will not have IUGR (IUGR is reported in 70% of individuals with a confirmed molecular diagnosis of SIOD).

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Human Growth Foundation**
  www.hgfound.org
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry

- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Schimke Immunoosseous Dysplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SMARCAL1	2q35	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1	SMARCAL1 database SMARCAL1base: Mutation registry for Schimke immuno-osseous dysplasia	SMARCAL1	SMARCAL1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Schimke Immunoosseous Dysplasia (View All in OMIM)

242900	SCHIMKE IMMUNOOSSEOUS DYSPLASIA; SIOD
606622	SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY A-LIKE PROTEIN 1; SMARCAL1

Molecular Pathogenesis

SMARCAL1 encodes SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1 (also referred to as HARP or SMARCAL1), the SNF2-related protein most similar to the prokaryotic HepA proteins [Coleman et al 2000]. SNF2-related proteins participate in the DNA-nucleosome restructuring that commonly occurs during gene regulation and DNA replication, recombination, methylation, repair, and transcription [Pazin & Kadonaga 1997, Havas et al 2001]. HARP binds DNA at single-to-double strand transitions and hydrolyzes ATP [Muthuswami et al 2000] to produce energy to reanneal open strands of DNA [Yusufzai & Kadonaga 2008]. Such DNA structures are commonly seen during DNA replication, repair, and transcription. At these sites, HARP reanneals the single-stranded DNA, thereby preventing DNA damage. Consequently, HARP deficiency leads to increased DNA damage and hypersensitivity to DNA-damaging agents [Bansbach et al 2009, Ciccia et al 2009, Postow et al 2009, Yuan et al 2009, Yusufzai et al 2009, Baradaran-Heravi et al 2012b] and to shortened telomeres as a result of impaired telomere maintenance [Poole & Cortez 2017, Bertaina et al 2022]. Also, as a modulator of DNA structure, HARP regulates gene expression [Baradaran-Heravi et al 2012a, Morimoto et al 2012b]. In summary, HARP-mediated maintenance of genomic integrity is required for the basic cellular processes of modulating DNA replication, DNA repair and transcription, and possibly DNA recombination.

Mechanism of disease causation. Pathogenic variants in *SMARCAL1* are predicted to cause loss of function in HARP. Pathogenic variants are distributed throughout *SMARCAL1*. The abnormalities reported for *SMARCAL1* are gene deletions eliminating expression, pathogenic truncating variants, or single-nucleotide variants. Pathogenic missense variants occur at amino acids conserved across species.

Chapter Notes

Author Notes

The David B Lewis laboratory at the Stanford University School of Medicine is pursuing studies with primary cells and induced pluripotent stem cells from individuals with Schimke immunoosseous dysplasia (SIOD) and their parents in order to determine how biallelic *SMARCAL1* pathogenic variants result in the unique phenotype of SIOD and to compile a clinical registry of individuals with SIOD to further advance our knowledge of this disease. Dr Lewis can be contacted by email at dblewis@stanford.edu.

Acknowledgments

The authors gratefully acknowledge the Kruzn' for a Kure Foundation, Muscle Shoals, Alabama, and the Little Giants Foundation, Omaha, Nebraska, for their support of research on the mechanisms of disease and treatment of SIOD.

Author History

Alireza Baradaran-Heravi, MD; University of British Columbia (2011-2016)
Cornelius F Boerkoel, MD, PhD (2002-present)
Leah I Elizondo, BSc; Baylor College of Medicine (2006-2011)
David B Lewis, MD (2016-present)
Elizabeth Lippner, MD (2022-present)
Shu Lou, MD; Baylor College of Medicine (2002-2006)
Thomas Lücke, MD, PhD (2006-present)
Marie Morimoto, BSc; University of British Columbia (2011-2022)
Carlos Salgado, MD (2022-present)

Revision History

- 30 March 2023 (sw) Revision: "*SMARCAL1*-Related Immuno-osseous Dysplasia (Schimke Type)" added as synonym; Nosology of Genetic Skeletal Disorders: 2023 Revision [Unger et al 2023] added to Nomenclature
- 14 April 2022 (sw) Comprehensive update posted live
- 11 February 2016 (sw) Comprehensive update posted live
- 22 August 2013 (me) Comprehensive update posted live
- 29 December 2011 (cd) Revision: prenatal testing available clinically
- 22 March 2011 (me) Comprehensive update posted live
- 7 December 2006 (me) Comprehensive update posted live
- 30 August 2004 (me) Comprehensive update posted live
- 1 October 2002 (me) Review posted live
- 18 June 2002 (cfb) Original submission

References

Literature Cited

Bansbach CE, Bétous R, Lovejoy CA, Glick GG, Cortez D. The annealing helicase SMARCAL1 maintains genome integrity at stalled replication forks. Genes Dev. 2009;23:2405–14. PubMed PMID: 19793861.

Bansbach CE, Boerkoel CF, Cortez D. SMARCAL1 and replication stress: An explanation for SIOD? Nucleus. 2010;1:245–8. PubMed PMID: 21327070.

Baradaran-Heravi A, Cho KS, Tolhuis B, Sanyal M, Morozova O, Morimoto M, Elizondo LI, Bridgewater D, Lubieniecka J, Beirnes K, Myung C, Leung D, Fam HK, Choi K, Huang Y, Dionis KY, Zonana J, Keller K, Stenzel P, Mayfield C, Lücke T, Bokenkamp A, Marra MA, van Lohuizen M, Lewis DB, Shaw C, Boerkoel CF. Penetrance of biallelic SMARCAL1 mutations is associated with environmental and genetic disturbances of gene expression. Hum Mol Genet. 2012a;21:2572–87. PubMed PMID: 22378147.

Baradaran-Heravi A, Lange J, Asakura Y, Cochat P, Massella L, Boerkoel CF. Bone marrow transplantation in Schimke immuno-osseous dysplasia. Am J Med Genet A. 2013;161A:2609–13. PubMed PMID: 23950031.

Baradaran-Heravi A, Raams A, Lubieniecka J, Cho KS, DeHaai KA, Basiratnia M, Mari PO, Xue Y, Rauth M, Olney AH, Shago M, Choi K, Weksberg RA, Nowaczyk MJ, Wang W, Jaspers NG, Boerkoel CF. SMARCAL1 deficiency predisposes to non-Hodgkin lymphoma and hypersensitivity to genotoxic agents in vivo. Am J Med Genet A. 2012b;158A:2204–13. PubMed PMID: 22888040.

Bertaina A, Grimm PC, Weinberg K, Parkman R, Kristovich KM, Barbarito G, Lippner E, Dhamdhere G, Ramachandran V, Spatz JM, Fathallah-Shaykh S, Atkinson TP, Al-Uzri A, Aubert G, van der Elst K, Green SG, Agarwal R, Slepicka PF, Shah AJ, Roncarolo MG, Gallo A, Concepcion W, Lewis DB. Sequential stem cell-kidney transplantation in Schimke immuno-osseous dysplasia. N Engl J Med. 2022;386:2295–302. PubMed PMID: 35704481.

Boerkoel CF, O'Neill S, André JL, Benke PJ, Bogdanović R, Bulla M, Burguet A, Cockfield S, Cordeiro I, Ehrich JH, Fründ S, Geary DF, Ieshima A, Illies F, Joseph MW, Kaitila I, Lama G, Leheup B, Ludman MD, McLeod DR, Medeira A, Milford DV, Ormälä T, Rener-Primec Z, Santava A, Santos HG, Schmidt B, Smith GC, Spranger J, Zupancic N, Weksberg R. Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and a review of the literature. Eur J Pediatr. 2000;159:1–7. PubMed PMID: 10653321.

Boerkoel CF, Takashima H, John J, Yan J, Stankiewicz P, Rosenbarker L, André JL, Bogdanovic R, Burguet A, Cockfield S, Cordeiro I, Fründ S, Illies F, Joseph M, Kaitila I, Lama G, Loirat C, McLeod DR, Milford DV, Petty EM, Rodrigo F, Saraiva JM, Schmidt B, Smith GC, Spranger J, Stein A, Thiele H, Tizard J, Weksberg R, Lupski JR, Stockton DW. Mutant chromatin remodeling protein SMARCAL1 causes Schimke immuno-osseous dysplasia. Nat Genet. 2002;30:215–20. PubMed PMID: 11799392.

Carroll C, Hunley TE, Guo Y, Cortez D. A novel splice site mutation in SMARCAL1 results in aberrant exon definition in a child with Schimke immunoosseous dysplasia. Am J Med Genet A. 2015;167A:2260–4. PubMed PMID: 25943327.

Ciccia A, Bredemeyer AL, Sowa ME, Terret ME, Jallepalli PV, Harper JW, Elledge SJ. The SIOD disorder protein SMARCAL1 is an RPA-interacting protein involved in replication fork restart. Genes Dev. 2009;23:2415–25. PubMed PMID: 19793862.

Clewing JM, Antalfy BC, Lücke T, Najafian B, Marwedel KM, Hori A, Powel RM, Do AF, Najera L, SantaCruz K, Hicks MJ, Armstrong DL, Boerkoel CF. Schimke immuno-osseous dysplasia: a clinicopathological correlation. J Med Genet. 2007a;44:122–30. PubMed PMID: 16840568.

Clewing JM, Fryssira H, Goodman D, Smithson SF, Sloan EA, Lou S, Huang Y, Choi K, Lücke T, Alpay H, André JL, Asakura Y, Biebuyck-Gouge N, Bogdanovic R, Bonneau D, Cancrini C, Cochat P, Cockfield S, Collard L, Cordeiro I, Cormier-Daire V, Cransberg K, Cutka K, Deschenes G, Ehrich JH, Fründ S, Georgaki H, Guillen-Navarro E, Hinkelmann B, Kanariou M, Kasap B, Kilic SS, Lama G, Lamfers P, Loirat C, Majore S, Milford D, Morin D, Ozdemir N, Pontz BF, Proesmans W, Psoni S, Reichenbach H, Reif S, Rusu C, Saraiva JM, Sakallioglu O, Schmidt B, Shoemaker L, Sigaudy S, Smith G, Sotsiou F, Stajic N, Stein A, Stray-Pedersen A, Taha D, Taque S, Tizard J, Tsimaratos M, Wong NA, Boerkoel CF. Schimke immunoosseous dysplasia: suggestions of genetic diversity. Hum Mutat. 2007b;28:273–83. PubMed PMID: 17089404.

Coleman MA, Eisen JA, Mohrenweiser HW. Cloning and characterization of HARP/SMARCAL1: a prokaryotic HepA-related SNF2 helicase protein from human and mouse. Genomics. 2000;65:274–82. PubMed PMID: 10857751.

Collins MK, Peters K, English JC 3rd, Rady P, Tyring S, Jedrych J. Cutaneous squamous cell carcinoma with epidermodysplasia verruciformis-like features in a patient with Schimke immune-osseous dysplasia. J Cutan Pathol. 2018;45:465–7. PubMed PMID: 29498428.

Ehrich JH, Offner G, Schirg E, Hoyer PF, Helmchen U, Brodehl J. Association of spondylo-epiphyseal dysplasia with nephrotic syndrome. Pediatr Nephrol. 1990;4:117–21. PubMed PMID: 2397176.

Elizondo LI, Huang C, Northrop JL, Deguchi K, Clewing JM, Armstrong DL, Boerkoel CF. Schimke immuno-osseous dysplasia: a cell autonomous disorder? Am J Med Genet A. 2006;140:340–8. PubMed PMID: 16419127.

Grenda R, Jarmużek W, Latoszyńska J, Prokurat S, Rubik J. Eltrombopag (thrombopoietin-receptor agonist) and plasmapheresis as rescue therapy of acute post-renal transplant immune thrombocytopenia in a child with Schimke immuno-osseous dysplasia-case report. Pediatr Transplant. 2016;20:1148–51. PubMed PMID: 27671102.

Haffner DN, Rollins NK, Dowling MM. Reversible cerebral vasoconstriction syndrome: a novel mechanism for neurological complications in Schimke immuno-osseous dysplasia. Pediatr Neurol. 2019;92:67–70. PubMed PMID: 30635151.

Havas K, Whitehouse I, Owen-Hughes T. ATP-dependent chromatin remodeling activities. Cell Mol Life Sci. 2001;58:673–82. PubMed PMID: 11437229.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Kaitila I, Savilahti E, Ormälä T. Autoimmune enteropathy in Schimke immunoosseous dysplasia. Am J Med Genet. 1998;77:427–30. PubMed PMID: 9632175.

Kilic SS, Donmez O, Sloan EA, Elizondo LI, Huang C, André JL, Bogdanovic R, Cockfield S, Cordeiro I, Deschenes G, Fründ S, Kaitila I, Lama G, Lamfers P, Lücke T, Milford DV, Najera L, Rodrigo F, Saraiva JM, Schmidt B, Smith GC, Stajic N, Stein A, Taha D, Wand D, Armstrong D, Boerkoel CF. Association of migraine-like headaches with Schimke immuno-osseous dysplasia. Am J Med Genet A. 2005;135:206–10. PubMed PMID: 15884045.

Lipska-Ziętkiewicz BS, Gellermann J, Boyer O, Gribouval O, Ziętkiewicz S, Kari JA, Shalaby MA, Ozaltin F, Dusek J, Melk A, Bayazit AK, Massella L, Hyla-Klekot L, Habbig S, Godron A, Szczepańska M, Bieniaś B, Drożdż D, Odeh R, Jarmużek W, Zachwieja K, Trautmann A, Antignac C, Schaefer F. PodoNet Consortium. Low renal but high extrarenal phenotype variability in Schimke immuno-osseous dysplasia. PLoS One. 2017;12:e0180926. PubMed PMID: 28796785.

Lou S, Lamfers P, McGuire N, Boerkoel CF. Longevity in Schimke immuno-osseous dysplasia. J Med Genet. 2002;39:922–5. PubMed PMID: 12471207.

Lücke T, Ehrich JH, Das AM. Mitochondrial function in schimke-immunoosseous dysplasia. Metab Brain Dis. 2005;20:237–42. PubMed PMID: 16167201.

Lücke T, Franke D, Clewing JM, Boerkoel CF, Ehrich JH, Das AM, Zivicnjak M. Schimke versus non-Schimke chronic kidney disease: an anthropometric approach. Pediatrics. 2006a;118:e400–7. PubMed PMID: 16816006.

Lücke T, Kanzelmeyer N, Baradaran-Heravi A, Boerkoel CF, Burg M, Ehrich JH, Pape L. Improved outcome with immunosuppressive monotherapy after renal transplantation in Schimke-immuno-osseous dysplasia. Pediatr Transplant. 2009;13:482–9. PubMed PMID: 18785907.

Lücke T, Marwedel KM, Kanzelmeyer NK, Hori A, Offner G, Kreipe HH, Ehrich JH, Das AM. Generalized atherosclerosis sparing the transplanted kidney in Schimke disease. Pediatr Nephrol. 2004;19:672–5. PubMed PMID: 15054643.

Lücke T, Tsikas D, Kanzelmeyer NK, Boerkoel CF, Clewing JM, Vaske B, Ehrich JH, Das AM. Vaso-occlusion in Schimke-immuno-osseous dysplasia: is the NO pathway involved? Horm Metab Res. 2006b;38:678–82. PubMed PMID: 17075778.

Morimoto M, Kérourédan O, Gendronneau M, Shuen C, Baradaran-Heravi A, Asakura Y, Basiratnia M, Bogdanovic R, Bonneau D, Buck A, Charrow J, Cochat P, Dehaai KA, Fenkçi MS, Frange P, Fründ S, Fryssira H, Keller K, Kirmani S, Kobelka C, Kohler K, Lewis DB, Massella L, McLeod DR, Milford DV, Nobili F, Olney AH, Semerci CN, Stajic N, Stein A, Taque S, Zonana J, Lücke T, Hendson G, Bonnaure-Mallet M, Boerkoel CF. Dental abnormalities in Schimke immuno-osseous dysplasia. J Dent Res. 2012a;91:29S–37S. PubMed PMID: 22699664.

Morimoto M, Yu Z, Stenzel P, Clewing JM, Najafian B, Mayfield C, Hendson G, Weinkauf JG, Gormley AK, Parham DM, Ponniah U, André JL, Asakura Y, Basiratnia M, Bogdanović R, Bokenkamp A, Bonneau D, Buck A, Charrow J, Cochat P, Cordeiro I, Deschenes G, Fenkçi MS, Frange P, Fründ S, Fryssira H, Guillen-Navarro E, Keller K, Kirmani S, Kobelka C, Lamfers P, Levtchenko E, Lewis DB, Massella L, McLeod DR, Milford DV, Nobili F, Saraiva JM, Semerci CN, Shoemaker L, Stajić N, Stein A, Taha D, Wand D, Zonana J, Lücke T, Boerkoel CF. Reduced elastogenesis: a clue to the arteriosclerosis and emphysematous changes in Schimke immuno-osseous dysplasia? Orphanet J Rare Dis. 2012b;7:70. PubMed PMID: 22998683.

Muthuswami R, Truman PA, Mesner LD, Hockensmith JW. A eukaryotic SWI2/SNF2 domain, an exquisite detector of double-stranded to single-stranded DNA transition elements. J Biol Chem. 2000;275:7648–55. PubMed PMID: 10713074.

Pazin MJ, Kadonaga JT. SWI2/SNF2 and related proteins: ATP-driven motors that disrupt protein-DNA interactions? Cell. 1997;88:737–40. PubMed PMID: 9118215.

Petty EM, Yanik GA, Hutchinson RJ, Alter BP, Schmalstieg FC, Levine JE, Ginsburg D, Robillard JE, Castle VP. Successful bone marrow transplantation in a patient with Schimke immuno- osseous dysplasia. J Pediatr. 2000;137:882–6. PubMed PMID: 11113849.

Poole LA, Cortez D. Functions of SMARCAL1, ZRANB3, and HLTF in maintaining genome stability. Crit Rev Biochem Mol Biol. 2017;52:696–714. PubMed PMID: 28954549.

Postow L, Woo EM, Chait BT, Funabiki H. Identification of SMARCAL1 as a component of the DNA damage response. J Biol Chem. 2009;284:35951–61. PubMed PMID: 19841479.

Puel A, Ziegler SF, Buckley RH, Leonard WJ. Defective IL7R expression in T(-)B(+)NK(+) severe combined immunodeficiency. Nat Genet. 1998;20:394–7. PubMed PMID: 9843216.

Ramdeny S, Chaudhary A, Worth A, S, Slatter M, Lum SH, Vora A. Activity of blinatumomab in lymphoblastic leukemia with impaired T-cell immunity due to congenital immunodeficiency. Blood Adv. 2021;5:2153–55. PubMed PMID: 33881461.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Roifman CM, Zhang J, Chitayat D, Sharfe N. A partial deficiency of interleukin-7R alpha is sufficient to abrogate T-cell development and cause severe combined immunodeficiency. Blood. 2000;96:2803–7. PubMed PMID: 11023514.

Sanyal M, Morimoto M, Baradaran-Heravi A, Choi K, Kambham N, Jensen K, Dutt S, Dionis-Petersen KY, Liu LX, Felix K, Mayfield C, Dekel B, Bokenkamp A, Fryssira H, Guillen-Navarro E, Lama G, Brugnara M, Lücke T, Olney AH, Hunley TE, Polat AI, Yis U, Bogdanovic R, Mitrovic K, Berry S, Najera L, Najafian B, Gentile M, Nur Semerci C, Tsimaratos M, Lewis DB, Boerkoel CF. Lack of IL7Rα expression in T cells is a hallmark of T-cell immunodeficiency in Schimke immuno-osseous dysplasia (SIOD). Clin Immunol. 2015;161:355–65. PubMed PMID: 26499378.

Severino M, Giacomini T, Verrina E, Prato G, Rossi A. Reversible cerebral vasoconstriction complicating cerebral atherosclerotic vascular disease in Schimke immuno-osseous dysplasia. Neuroradiology. 2018;60:885–8. PubMed PMID: 29978300.

Spranger J, Hinkel GK, Stoss H, Thoenes W, Wargowski D, Zepp F. Schimke immuno-osseous dysplasia: a newly recognized multisystem disease. J Pediatr. 1991;119:64–72. PubMed PMID: 2066860.

Thomas SE, Hutchinson RJ, Debroy M, Magee JC. Successful renal transplantation following prior bone marrow transplantation in pediatric patients. Pediatr Transplant. 2004;8:507–12. PubMed PMID: 15367289.

Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, Cohn DH, Cormier-Daire V, Girisha KM, Hall C, Krakow D, Makitie O, Mundlos S, Nishimura G, Robertson SP, Savarirayan R, Sillence D, Simon M, Sutton VR, Warman ML, Superti-Furga A. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A. 2023. Epub ahead of print.

Wang W, Song H, Wei M, Qiu Z, Wang C, Zhang Y, Li M, Yuan Y, Tang X. Zhonghua Er Ke Za Zhi. 2015;53:45–50. [SMARCAL1 gene analysis of 2 Chinese Schimke immuno-osseous dysplasia children]. PubMed PMID: 25748404.

Yuan J, Ghosal G, Chen J. The annealing helicase HARP protects stalled replication forks. Genes Dev. 2009;23:2394–9. PubMed PMID: 19793864.

Yusufzai T, Kadonaga JT. HARP is an ATP-driven annealing helicase. Science. 2008;322:748–50. PubMed PMID: 18974355.

Yusufzai T, Kong X, Yokomori K, Kadonaga JT. The annealing helicase HARP is recruited to DNA repair sites via an interaction with RPA. Genes Dev. 2009;23:2400–4. PubMed PMID: 19793863.

Zieg J, Krepelova A, Baradaran-Heravi A, Levtchenko E, Guillén-Navarro E, Balascakova M, Sukova M, Seeman T, Dusek J, Simankova N, Rosik T, Skalova S, Lebl J, Boerkoel CF. Rituximab resistant Evans syndrome and autoimmunity in Schimke immuno-osseous dysplasia. Pediatr Rheumatol Online J. 2011;9:27. PubMed PMID: 21914180.

License