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Schimke Immunoosseous Dysplasia

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Summary

Clinical characteristics. Schimke immunoosseous dysplasia (SIOD) is an autosomal recessive multisystem disorder 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 deformed capital femoral epiphyses, and shallow dysplastic acetabular fossae. Adult height is 136-157 cm for men and 98.5-143 cm for women. 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 (ESRD). 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 death early in life to a juvenile or milder later-onset form with survival into adulthood if renal disease is appropriately treated.

Diagnosis/testing. The diagnosis of SIOD is established in a proband with the characteristic clinical and radiographic features. Identification of biallelic pathogenic variants in *SMARCAL1* on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.

Management. *Treatment of manifestations*: Renal transplantation as indicated using mild immunosuppressive therapy; hip replacement as needed in older individuals; granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor for neutropenia; bone marrow transplantation as indicated; immunosuppressive therapy for those with autoimmune manifestations; acyclovir for recurrent herpetic infections; imiquimod and cidofovir for severe disseminated cutaneous papilloma virus infections; agents that improve blood flow or decrease coagulability to treat transient ischemic attacks or strokes; standard treatment for hypothyroidism.

Prevention of secondary complications: Vaccinations according to the protocol for other T-cell immunodeficiencies (i.e., an avoidance of live attenuated vaccines) in individuals with severe early-onset disease; prophylaxis against *Pneumocystis jirovecii* pneumonia; prophylactic acyclovir or valacylovir if recurrent oral herpetic infections or shingles occur.

Surveillance: Regular monitoring of the hips; annual monitoring of renal, immune, and hematologic status.

Agents/circumstances to avoid: Hypertension; heat, stress, and lack of sleep; live attenuated immunizations in those who are T-cell deficient; DNA damaging anti-cancer therapies.

Genetic counseling. SIOD is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of

being unaffected and not a carrier. Carrier testing and prenatal testing are possible if both pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Schimke immunoosseous dysplasia (SIOD) **should be suspected** in individuals with the following:

- **Short stature** (99% of individuals) that typically manifests as a short neck and trunk with lumbar lordosis and a protruding abdomen
- **Spondyloepiphyseal dysplasia** (75%). The most commonly observed radiologic abnormalities are ovoid and mildly flattened vertebral bodies, small deformed capital femoral epiphyses, and shallow dysplastic acetabular fossae. Other bony abnormalities are less common.
- **Progressive steroid-resistant nephropathy.** Almost all (99%) individuals with SIOD have proteinuria; this generally evolves into ESRD. The renal pathology has been reported as focal segmental glomerulosclerosis without pathognomonic features in 83% of individuals.
- **T-cell deficiency** (76% of tested individuals). In general, both CD4 and CD8 cells are reduced and the CD4/CD8 ratio is normal. The T cells are predominantly of a memory (CD45R0+CD45RA-) surface phenotype.
- **Characteristic facial features** that include a wide, depressed nasal bridge (65%) and a broad nasal tip (78%)
- **Hyperpigmented macules** (70%) on the trunk and occasionally extending onto the arms, neck, and legs

Establishing the Diagnosis

The diagnosis of SIOD **is established** in a proband with the above clinical features. Identification of biallelic pathogenic variants in *SMARCAL1* on molecular genetic testing (see Table 1) confirms the diagnosis if clinical features are inconclusive.

Molecular testing approaches can include **single-gene testing,** use of a **multi-gene panel,** and **more comprehensive genomic testing.**

- **Single-gene testing.** Sequence analysis of *SMARCAL1* is performed first followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multi-gene panel** that includes *SMARCAL1* and other genes of interest (see Differential Diagnosis) may also be considered. Note: The genes included and sensitivity of multi-gene panels varies by laboratory and over time.
- **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multi-gene panel) fails to confirm a diagnosis in an individual with features of SIOD. For more information on comprehensive genome sequencing click here.

Table 1.

Molecular Genetic Testing Used in Schimke Immunoosseous Dysplasia

Gene [1]	Test Method	Proportion of Probands with Pathogenic Variants [2] Detectable by This Method
SMARCAL1	Sequence analysis [3]	~90% [4]
	Gene-targeted deletion/duplication analysis [5]	1 individual [6]
Unknown [7]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Of individuals diagnosed with SIOD based on co-occurrence of spondyloepiphyseal dysplasia, renal failure, T-cell deficiency and typical facial features
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used include: 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. Boerkoel et al [2002]; Author, personal observation
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 a multisystem progressive disorder. Table 2 indicates the frequency of clinical findings in this condition based on published reports.

Table 2.

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

Feature		Number of Affected Individuals with Feature	Total Individuals with SIOD [1]
Growth	IUGR [2]	58 (70%)	83
	Short stature	82 (99%)	83
	Short neck	66 (86%)	77
	Short trunk	68 (85%)	80
Skeletal features	Lumbar lordosis	57 (74%)	77
	Ovoid flat vertebrae	54 (77%)	70
	Hypoplastic pelvis	44 (65%)	68
	Abnormal femoral heads	64 (89%)	72
Renal disease	Proteinuria or nephropathy	84 (99%)	85
	FSGS	43 (83%)	52
Hematologic abnormalities	T-cell deficiency	47 (76%)	62
	Lymphopenia	58 (74%)	78
	Neutropenia	27 (38%)	71
	Thrombocytopenia	19 (25%)	77
	Anemia	43 (57%)	75
Physical features	Broad nasal tip	61 (78%)	78
	Wide and depressed nasal bridge	53 (65%)	81
	Protruding abdomen	59 (77%)	77
	Pigmented macules	57 (70%)	81
	Unusual hair	43 (63%)	68

Feature		Number of Affected Individuals with Feature	Total Individuals with SIOD [1]
	Microdontia	31 (53%)	59
	Corneal opacities	11 (17%)	65
Development	Developmental delay	26 (34%)	77
	Academic delay	10 (28%)	36
	Headaches	28 (47%)	60
Vasculature	TIAs	31 (41%)	76
	Strokes	30 (43%)	69
Other	Hypothyroidism	24 (36%)	66
	Non-Hodgkin lymphoma [3]	3 (3%)	86

IUGR = intrauterine growth retardation

FSGS = focal segmental glomerulosclerosis

TIAs = transient ischemic attacks

1. Total individuals with SIOD for whom the feature of interest has been reported to be present or absent
2. IUGR is defined as having a birth weight and/or birth length at or below the 3rd percentile for gestational age.
3. EBV-positive and -negative non-Hodgkin lymphoma

Growth. Most affected children have prenatal and postnatal disproportionate growth failure. A few have normal intrauterine growth followed by postnatal growth failure. The observed disproportionate growth deficiency 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 for leg length. Therefore, a sitting height/leg-length ratio of less than 0.83 is suggestive of SIOD in persons with chronic kidney disease [Lücke et al 2006a].

The mean age of diagnosis with growth failure was 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 136-157 cm for men and 98.5-143 cm for women.

Skeletal features. In addition to the prominent vertebral and femoral abnormalities, less frequent skeletal problems include a widened sella turcica, thoracic kyphosis, scoliosis, and osteopenia. Affected individuals do not usually have joint pain until they develop degenerative hip disease.

Renal disease. Nephropathy usually develops before age 12 years and progresses to ESRD within the subsequent one to 11 years. Usually the diagnosis of nephropathy is made concurrent with or within the five years following the diagnosis of growth failure. Focal segmental glomerulosclerosis (FSGS) is the predominant renal pathology in individuals with SIOD. The FSGS of SIOD is associated with a significant increase in expression of the NOTCH receptors and ligands in the renal glomeruli [Morimoto et al, submitted]. Increased NOTCH signaling is a known cause of FSGS [Niranjan et al 2008, Murea et al 2010].

Hematologic abnormalities. T-cell deficiency causes lymphopenia 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 B-cell count is usually normal to slightly elevated. In addition to T-cell deficiency, several individuals with SIOD have had deficiencies of other blood cell lineages. See Table 2 for types and frequency. The T-cell deficiency is associated with a lack of interleukin 7 receptor alpha expression on the T cells of patients with SIOD [Sanyal et al 2015]. This receptor is critical for T-cell development and has been previously implicated in severe combined immunodeficiency [Puel et al 1998, Roifman et al 2000].

Immunodeficiency increases the risk of opportunistic infections such as *Pneumocystis jiroveciii* pneumonia. More than half of individuals with SIOD have recurrent infections with various bacteria, viruses (including herpes simplex virus, varicella-zoster virus, cytomegalovirus), and fungi (e.g., oral and/or cutaneous candida) [Boerkoel et al 2000, Boerkoel et al 2002]. Infection is a common cause of death.

About 20% of individuals with SIOD have features of autoimmune disease. These manifestations include immune thrombocytopenia, hemolytic anemia, enteropathy, pericarditis with anti-cardiolipin antibodies, and Evans syndrome (a combination of hemolytic anemia and immune thrombocytopenia) [Zieg et al 2011].

Physical features. Most affected individuals have hyperpigmented macules on the trunk and occasionally on the extremities, neck, and face. Less common ectodermal abnormalities include fine and/or sparse hair; 66% have had microdontia, hypodontia and/or malformed deciduous and permanent molars [Morimoto et al 2012a], and corneal opacities.

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 of these, the delay can be ascribed to the deleterious consequences 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 neurologic attacks (TNAs), or ischemic events [Kilic et al 2005]. The TNAs are usually focal and generally do not have an ischemic origin. Some affected individuals also have heat intolerance and develop CNS symptoms during hot weather [Baradaran-Heravi et al 2012a]. Generally, those with transient ischemic attacks 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 cause of the severe migraine-like headaches is unknown.

Half of individuals with SIOD have symptoms suggestive of atherosclerosis. 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]. 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].

Also, gene expression studies have identified a significant decrease in the expression of *ELN* in individuals with SIOD [Morimoto et al 2012b]. This gene encodes for the precursor to elastin protein, which is critical for maintaining the integrity of the arterial wall. Histopathologic analysis of postmortem arterial tissue from three individuals with SIOD showed splitting and fragmentation of elastin fibers [Clewing et al 2007a, Morimoto et al 2012b]. Reduction in the elastin protein results in the increased proliferation of smooth muscle cells in arterial walls and leads to intimal hyperplasia [Urbán et al 2002]. The reduction in elastin expression in the SIOD aorta appears to arise from reduced transcription of *ELN* as well as increased post-transcriptional *ELN* mRNA decay [Morimoto et al 2015].

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

Gastrointestinal findings. 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].

Clinical course and outcome. SIOD varies in severity, ranging from *in utero* onset of growth retardation with death in the first few years of life to a slowly progressive course with survival into adulthood. Classically, SIOD has been divided into an infantile- or severe early-onset form and a juvenile- or milder later-onset form. SIOD follows a continuum such that affected individuals with early-onset and severe symptoms usually die early in life, whereas those with mild symptoms survive 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 failure. 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, none has reproduced yet. Women develop menses, although the menstrual cycle is usually irregular. Men develop secondary sexual characteristics, but histopathologic examination of the testes identified azoospermia [Clewing et al 2007a].

Genotype-Phenotype Correlations

Ongoing correlations of genotype to phenotype have shown that genotype does not predict disease severity or outcome either within or among families [Bökenkamp et al 2005, Lücke et al 2005a, Clewing et al 2007b, Dekel et al 2008, Baradaran-Heravi et al 2012a]. The phenotypic heterogeneity and variable expressivity suggest that SIOD is modified by factors such as environment, epigenetics, and oligogenic inheritance.

In five multiplex families, the phenotype of sibs has been variable:

- A boy succumbed to a stroke at age 3.7 years after developing ESRD; his sister succumbed to bone marrow failure at age 2.75 years before developing renal failure and without symptoms of cerebral ischemia [Lou et al 2002].
- Of two brothers, one had severe disease and the other had relatively mild disease [Lücke et al 2005a].
- Of two brothers with homozygous *SMARCAL1* pathogenic variants, one presented with growth failure at age six years [Bökenkamp et al 2005], while the other had normal growth at age ten years [unpublished data].
- Of three sibs reported by Lama et al [1995], one died as a child with severe disease, one had normal stature and died of a pulmonary infection at 43 years, and one has survived into the fourth decade.
- Of three sibs reported by Dekel et al [2008] the elder brother demonstrated severe disease from age 3.5 years and two younger non-identical twin brothers had relatively mild disease.

As a group, those individuals with prominent features of SIOD without detectable *SMARCAL1* pathogenic variants have a lower frequency of hyperpigmented macules, lymphopenia, focal segmental glomerulosclerosis, and cerebral ischemic symptoms and a higher frequency of cognitive impairment [Clewing et al 2007b, Baradaran-Heravi et al 2008].

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.

Prevalence

The prevalence is unknown. However, based on referrals and published birth rates, the incidence in North America is estimated at 1:1,000,000 to 1:3,000,000 live births [Author, personal observation].

SIOD is pan ethnic.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

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

Table 3.

Hereditary Osteochondrodysplasias Associated with Nephrotic Syndrome or Immune Defects

Syndrome (OMIM)		Immune Cell Defect	Gene
Associated w/nephrotic syndrome	Conorenal syndrome (266920)		*IFT140*
	Nail-patella syndrome		*LMX1B*
	Schimke immunoosseous dysplasia	T cell	*SMARCAL1*
	Short-limb skeletal dysplasia with severe combined immunodeficiency (200900)	T & B cells	
	Cartilage-hair hypoplasia	T & B cells	*RMRP*
	Short-limb skeletal dysplasia with humoral immunodeficiency [1]	B cell	
Associated w/immune defects	Roifman syndrome (616651)	B cell	*RNU4ATAC*
	Kenny-Caffey syndrome, autosomal recessive (244460)	T cell	*TBCE*
	Sanjad-Sakati syndrome (241410)	T cell	*TBCE*
	Immunodeficiency-centromeric instability-facial anomalies syndrome (242860)	B cell	*DNMT3B*
	Spondylomesomelic acrodysplasia [2]	T & B cells	
	Ramanan syndrome [3]	T & B cells	

1. Ammann et al [1974]
2. Castriota-Scanderbeg et al [1997]
3. Ramanan et al [2000]

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

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 for leg length. SIOD is very likely if this ratio is less 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 following evaluations are recommended:

- Measurement of growth and assessment of body proportions, with plotting on age-appropriate growth charts [Lücke et al 2006a]
- Evaluation of renal function by measurement of serum concentrations of creatinine and urea, protein excretion in urine, and creatinine clearance
- Referral to a nephrologist for evaluation
- Hematology evaluations to assess lymphopenia, anemia, neutropenia, and thrombocytopenia
- Immunology evaluations to evaluate the numbers of memory and naïve CD4 and CD8 T cells and B cells and immunoglobulin levels
- Assessment of developmental status with referral for formal evaluation if significant developmental delays or schooling delays are identified
- Dental evaluation after teeth are present

- Ophthalmologic evaluation
- Detailed history for headaches or neurologic abnormalities
- Orthopedic evaluation for symptoms of joint pain or evidence of scoliosis or kyphosis
- Assessment for osteopenia
- Thyroid function studies
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Renal manifestations

- The renal disease progresses from proteinuria to ESRD at variable rates and is not prevented by any known drug therapies, although a few affected individuals treated with cyclosporin A, tacrolimus, or corticosteroids have had a transient reduction in the rate of renal disease progression.
- Renal transplantation effectively treats the nephropathy and neither nephropathy nor arteriosclerosis recurs in the graft [Lücke et al 2004, Elizondo et al 2006, Clewing et al 2007a]. Mild immunosuppressive therapy, such as immunosuppressive monotherapy, appears to improve outcome after renal transplantation [Lücke et al 2009].

Orthopedic manifestations

- Some affected individuals who have survived beyond childhood have required hip replacement.
- Treatment of scoliosis and/or kyphosis is standard.

Immunologic manifestations

- Neutropenia usually responds well to supplementation with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor.
- One affected individual has been successfully treated by bone marrow transplantation (BMT) [Petty et al 2000, Thomas et al 2004], and four affected individuals have died after BMT [Baradaran-Heravi et al 2013].
- Individuals with autoimmune problems have had variable responses to treatment.
    - A few individuals have been transfusion dependent because of anemia or thrombocytopenia.
    - In one affected individual with thrombocytopenia, the autoimmune features resolved spontaneously; in one they resolved after steroid and IVIG treatments, and in one they cleared after splenectomy. All other affected individuals, excepting one with Evans syndrome, were successfully treated with immunosuppressive therapy such as steroids, cyclophosphamide, or IVIG. The individual with Evans syndrome was resistant to treatment with steroids, cyclosporin A, and rituximab [Zieg et al 2011].

Infectious disease manifestations. Individuals with recurrent infections, opportunistic infections, or declining lymphocytes or T-cell counts frequently require the care of an immunologist.

- Affected individuals with recurrent herpetic infections benefit from treatment with acyclovir.
- A few affected individuals have developed severe disseminated cutaneous papilloma virus infections that have improved with imiquimod and cidofovir.

Neurologic manifestations

- Individuals with transient ischemic attacks or strokes usually show temporary improvement on treatment with agents that improve blood flow or decrease coagulability (pentoxifylline, acetylsalicylic acid, dipyridamole, warfarin, heparin). To date, no curative or effective long-term therapies have been identified.
- Migraine headaches are often difficult to treat since response to anti-migraine medication is variable. Medications that have helped some individuals include ergotamine, sumatriptan, verapamil, and propranolol.

Note: Use of ergotamine and sumatriptan is contraindicated in individuals with SIOD with severe vasoocclusive disease or cerebral ischemic events.

Hypothyroidism can be treated with levothyroxine supplementation; however, supplementation does not have an ameliorative effect on the renal disease or T-cell deficiency.

Prevention of Secondary Complications

Individuals with severe early-onset disease are best vaccinated according to the protocol for other T-cell immunodeficiencies (i.e., only inactivated vaccines should be used with avoidance of all live-attenuated vaccines).

Because of the increased risk of opportunistic infection, prophylaxis (trimethoprim/sulfamethoxazole or atovquone) against *Pneumocystis jirovecii* pneumonia is usually recommended.

If recurrent oral herpetic infections or shingles occur, prophylactic acyclovir may reduce the morbidity.

Surveillance

The following are appropriate:

- Regular monitoring of the hips
- Annual monitoring of renal, immune, and hematologic status

Agents/Circumstances to Avoid

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, vaccination with all live vaccines should be avoided, including rotavirus, MMR, varicella, BCG, oral Salmonella typhi vaccine, and yellow fever virus vaccine.

Anti-cancer therapies. SIOD cells 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 preventive measures.

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

Therapies Under Investigation

Combined renal and bone marrow transplantation may be discussed as an approach in individuals with declining renal and immune function prior to the onset of end-stage disease.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Individuals with SIOD usually have normal growth hormone studies. No affected individual treated with growth hormone supplementation has responded with improved growth.

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.

Because of the T-cell defect, individuals with SIOD usually require milder immunosuppressive therapy for bone marrow transplantation than those undergoing transplantation for other diseases.

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 2005b, Lücke et al 2006b].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face 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 obligate heterozygotes (i.e., carriers of one *SMARCAL1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of inheriting biallelic *SMARCAL1* pathogenic variants and being at risk of developing SIOD, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- 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 (Heterozygote) Detection

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

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

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

Ultrasound examination. The diagnosis may be suspected in a fetus with intrauterine growth retardation and an affected sib.

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 (HGF)**
  997 Glen Cove Avenue
  Suite 5
  Glen Head NY 11545
  Phone: 800-451-6434 (toll-free)
  Fax: 516-671-4055
  Email: hgf1@hgfound.org
  www.hgfound.org
- **Little People of America, Inc. (LPA)**
  250 El Camino Real
  Suite 201
  Tustin CA 92780
  Phone: 888-572-2001 (toll-free); 714-368-3689
  Fax: 714-368-3367
  Email: info@lpaonline.org
  www.lpaonline.org
- **MAGIC Foundation**
  6645 West North Avenue
  Oak Park IL 60302
  Phone: 800-362-4423 (Toll-free Parent Help Line); 708-383-0808
  Fax: 708-383-0899
  Email: ContactUs@magicfoundation.org
  www.magicfoundation.org
- **European Society for Immunodeficiencies (ESID) Registry**
  Dr. Gerhard Kindle
  University Medical Center Freiburg Centre of Chronic Immunodeficiency
  Engesserstr. 4
  79106 Freiburg
  Germany
  Phone: 49-761-270-34450
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **International Skeletal Dysplasia Registry**
  UCLA
  615 Charles E. Young Drive
  South Room 410
  Los Angeles CA 90095-7358
  Phone: 310-825-8998
  Email: AZargaryan@mednet.ucla.edu
  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	HGMD
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

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) 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

Gene structure. *SMARCAL1* contains 18 exons spanning approximately 70 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Normal variants of *SMARCAL1* have not been cataloed.

Pathogenic variants. 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.

Normal gene product. *SMARCAL1* encodes SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1, 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]. The *SMARCAL1* protein product is known as HARP or SMARCAL1. HARP binds DNA at single-to-double strand transitions and hydrolyzes ATP [Muthuswami et al 2000] to produce energy to re-anneal open strands of DNA [Yusufzai & Kadonaga 2008]. Such DNA structures are commonly seen during DNA replication and repair and transcription. At these sites, HARP re-anneals 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]. 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.

Abnormal gene product. Pathogenic variants in *SMARCAL1* are predicted to cause loss of function in HARP.

References

Literature Cited

1. Ammann AJ, Sutliff W, Millinchick E. Antibody-mediated immunodeficiency in short-limbed dwarfism. J Pediatr. 1974;84:200–3. [PubMed: 4810726]
2. 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. [PMC free article: PMC2764496] [PubMed: 19793861]

3. Bansbach CE, Boerkoel CF, Cortez D. SMARCAL1 and replication stress: An explanation for SIOD? Nucleus. 2010;1:245–8. [PMC free article: PMC3027029] [PubMed: 21327070]
4. 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. [PMC free article: PMC3349428] [PubMed: 22378147]
5. 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. [PMC free article: PMC3788057] [PubMed: 23950031]
6. 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. [PMC free article: PMC3429644] [PubMed: 22888040]
7. Baradaran-Heravi A, Thiel C, Rauch A, Zenker M, Boerkoel CF, Kaitila I. Clinical and genetic distinction of Schimke immuno-osseous dysplasia and cartilage-hair hypoplasia. Am J Med Genet A. 2008;146A:2013–7. [PMC free article: PMC2576743] [PubMed: 18627050]
8. 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: 10653321]
9. 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: 11799392]
10. Bökenkamp A, deJong M, van Wijk JA, Block D, van Hagen JM, Ludwig M. R561C missense mutation in the SMARCAL1 gene associated with mild Schimke immuno-osseous dysplasia. Pediatr Nephrol. 2005;20:1724–8. [PubMed: 16237566]
11. Castriota-Scanderbeg A, Mingarelli R, Caramia G, Osimani P, Lachman RS, Rimoin DL, Wilcox WR, Dallapiccola B. Spondylo-mesomelic-acrodysplasia with joint dislocations and severe combined immunodeficiency: a newly recognised immuno-osseous dysplasia. J Med Genet. 1997;34:854–6. [PMC free article: PMC1051096] [PubMed: 9350822]
12. 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. [PMC free article: PMC2764500] [PubMed: 19793862]
13. 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. [PMC free article: PMC2598061] [PubMed: 16840568]
14. 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: 17089404]
15. 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: 10857751]
16. Dekel B, Metsuyanim S, Goldstein N, Pode-Shakked N, Kovalski Y, Cohen Y, Davidovits M, Anikster Y. Schimke immuno-osseous dysplasia: expression of SMARCAL1 in blood and kidney provides novel insight into disease phenotype. Pediatr Res. 2008;63:398–403. [PubMed: 18356746]

17. 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: 2397176]
18. 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: 16419127]
19. Havas K, Whitehouse I, Owen-Hughes T. ATP-dependent chromatin remodeling activities. Cell Mol Life Sci. 2001;58:673–82. [PubMed: 11437229]
20. Kaitila I, Savilahti E, Ormälä T. Autoimmune enteropathy in Schimke immunoosseous dysplasia. Am J Med Genet. 1998;77:427–30. [PubMed: 9632175]
21. 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: 15884045]
22. Lama G, Marrone N, Majorana M, Cirillo F, Salsano ME, Rinaldi MM. Spondyloepiphyseal dysplasia tarda and nephrotic syndrome in three siblings. Pediatr Nephrol. 1995;9:19–23. [PubMed: 7742215]
23. Lou S, Lamfers P, McGuire N, Boerkoel CF. Longevity in Schimke immuno-osseous dysplasia. J Med Genet. 2002;39:922–5. [PMC free article: PMC1757210] [PubMed: 12471207]
24. Lücke T, Billing H, Sloan EA, Boerkoel CF, Franke D, Zimmering M, Ehrich JH, Das AM. Schimke-immuno-osseous dysplasia: new mutation with weak genotype-phenotype correlation in siblings. Am J Med Genet A. 2005a;135:202–5. [PubMed: 15880370]
25. Lücke T, Ehrich JH, Das AM. Mitochondrial function in schimke-immunoosseous dysplasia. Metab Brain Dis. 2005b;20:237–42. [PubMed: 16167201]
26. 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: 16816006]
27. 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: 18785907]
28. 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: 15054643]
29. 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: 17075778]
30. Morimoto M, Cho KS, Myung C, Beirnes K, Leung D, Fam HK, Choi K, Huang Y, Lou S, Wang KJ, Najafian B, Bridgewater D, Boerkoel CF. Impaired Notch signaling in Schimke immuno-osseous dyplasia. Submitted.
31. 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. [PMC free article: PMC3383106] [PubMed: 22699664]
32. Morimoto M, Wang KJ, Yu Z, Gormley AK, Parham D, Bogdanovic R, Lücke T, Mayfield C, Weksberg R, Hendson G, Boerkoel CF. Transcriptional and posttranscriptional mechanisms contribute to the dysregulation of elastogenesis in Schimke immuno-osseous dysplasia. Pediatr Res. 2015;78:609–17. [PubMed: 26309238]
33. 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. [PMC free article: PMC3568709] [PubMed: 22998683]
34. Murea M, Park JK, Sharma S, Kato H, Gruenwald A, Niranjan T, Si H, Thomas DB, Pullman JM, Melamed ML, Susztak K. Expression of Notch pathway proteins correlates with albuminuria, glomerulosclerosis, and renal function. Kidney Int. 2010;78:514–22. [PMC free article: PMC3164583] [PubMed: 20531454]

35. 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: 10713074]
36. Niranjan T, Bielesz B, Gruenwald A, Ponda MP, Kopp JB, Thomas DB, Susztak K. The Notch pathway in podocytes plays a role in the development of glomerular disease. Nat Med. 2008;14:290–8. [PubMed: 18311147]
37. Pazin MJ, Kadonaga JT. SWI2/SNF2 and related proteins: ATP-driven motors that disrupt protein-DNA interactions? Cell. 1997;88:737–40. [PubMed: 9118215]
38. 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: 11113849]
39. 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. [PMC free article: PMC2791023] [PubMed: 19841479]
40. 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: 9843216]
41. Ramanan AV, Hussain K, Hird M, Gaspar HB. Short limbed skeletal dysplasia associated with combined immunodeficiency and congenital subglottic stenosis: a new constellation of features. Clin Dysmorphol. 2000;9:173–6. [PubMed: 10955476]
42. 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: 11023514]
43. 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: 26499378]
44. 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: 2066860]
45. 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: 15367289]
46. Urbán Z, Riazi S, Seidl TL, Katahira J, Smoot LB, Chitayat D, Boyd CD, Hinek A. Connection between elastin haploinsufficiency and increased cell proliferation in patients with supravalvular aortic stenosis and Williams-Beuren syndrome. Am J Hum Genet. 2002;71:30–44. [PMC free article: PMC384991] [PubMed: 12016585]
47. Yuan J, Ghosal G, Chen J. The annealing helicase HARP protects stalled replication forks. Genes Dev. 2009;23:2394–9. [PMC free article: PMC2764499] [PubMed: 19793864]
48. Yusufzai T, Kadonaga JT. HARP is an ATP-driven annealing helicase. Science. 2008;322:748–50. [PMC free article: PMC2587503] [PubMed: 18974355]
49. 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. [PMC free article: PMC2764493] [PubMed: 19793863]
50. 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. [PMC free article: PMC3184066] [PubMed: 21914180]

Suggested Reading

1. Schimke RN, Horton WA, King CR. Chondroitin-6-sulphaturia, defective cellular immunity, and nephrotic syndrome. Lancet. 1971;2:1088–9. [PubMed: 4106927]

Chapter Notes

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