

REVIEW ARTICLE

Genetic alterations in Schimke immuno-osseous dysplasia: Pathogenic mechanisms and therapeutic prospects

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Abstract

Schimke immuno-osseous dysplasia (SIOD) is an ultra-rare autosomal recessive multisystem disorder caused by biallelic pathogenic variants in *SMARCAL1*, which encodes an adenosine triphosphate-dependent annealing helicase involved in replication-fork remodeling and chromatin dynamics. Loss of *SMARCAL1* function leads to replication-associated genomic instability, transcriptional dysregulation, and telomere dysfunction, collectively underlying the triad of steroid-resistant nephrotic syndrome, spondyloepiphyseal dysplasia, and T-cell immunodeficiency, as well as vascular and malignant complications. In this review, we summarize the spectrum of *SMARCAL1* genetic alterations in SIOD, ranging from missense and truncating variants to gross deletions, and discuss their molecular consequences at the protein and cellular levels. We highlight current disease models, including patient-derived induced pluripotent stem cells (iPSCs) and inducible *SMARCAL1* knockdown iPSC systems, which have revealed mechanistic links between replication stress and dysregulated expression of master differentiation genes. Finally, we evaluate the state of the art and realistic prospects for gene therapy in SIOD. Although no gene therapy trial for SIOD is currently active, advances in iPSC modeling, clustered regularly interspaced short palindromic repeats-mediated gene correction, and successful ex vivo hematopoietic stem cell gene therapy in related monogenic immunodeficiencies position *SMARCAL1* as a plausible, though challenging, therapeutic target. Key obstacles include multi-organ involvement, strict control of *SMARCAL1* dosage due to its role in genome stability, and the extreme rarity of the disorder, which limits the feasibility of clinical trials.

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1. Introduction

Schimke immuno-osseous dysplasia (SIOD; MIM #242900) is an ultra-rare autosomal recessive multisystem disease. Clinically, SIOD is characterized by a triad consisting of

disproportionate short stature with spondyloepiphyseal dysplasia, steroid-resistant nephrotic syndrome leading to progressive renal failure, and T-cell immunodeficiency with lymphopenia^{1,2} (Figure 1).

Beyond this clinical triad, SIOD manifests with a broad, heterogeneous spectrum of additional features. These include diffuse skin hyperpigmentation, characteristic facial gestalt, and a markedly elevated risk of vascular complications such as premature atherosclerosis, hypertension, and cerebrovascular events.³⁻⁷ Notably, affected individuals also show increased susceptibility to malignancies, particularly lymphomas and bone tumors,

likely reflecting underlying genome-maintenance defects.^{1,3}

The molecular basis of SIOD is established in most affected individuals and involves biallelic pathogenic variants in the SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A-like 1 (*SMARCAL1*) gene.^{1,3,8-10} *SMARCAL1* encodes an adenosine triphosphate (ATP)-dependent annealing helicase that plays a central role in replication-fork remodeling, maintenance of stalled forks, and the cellular response to replication stress. Loss of *SMARCAL1* function impairs fork stability, induces transcriptional dysregulation, and causes telomere dysfunction, providing a mechanistic basis for the multisystem features of SIOD.

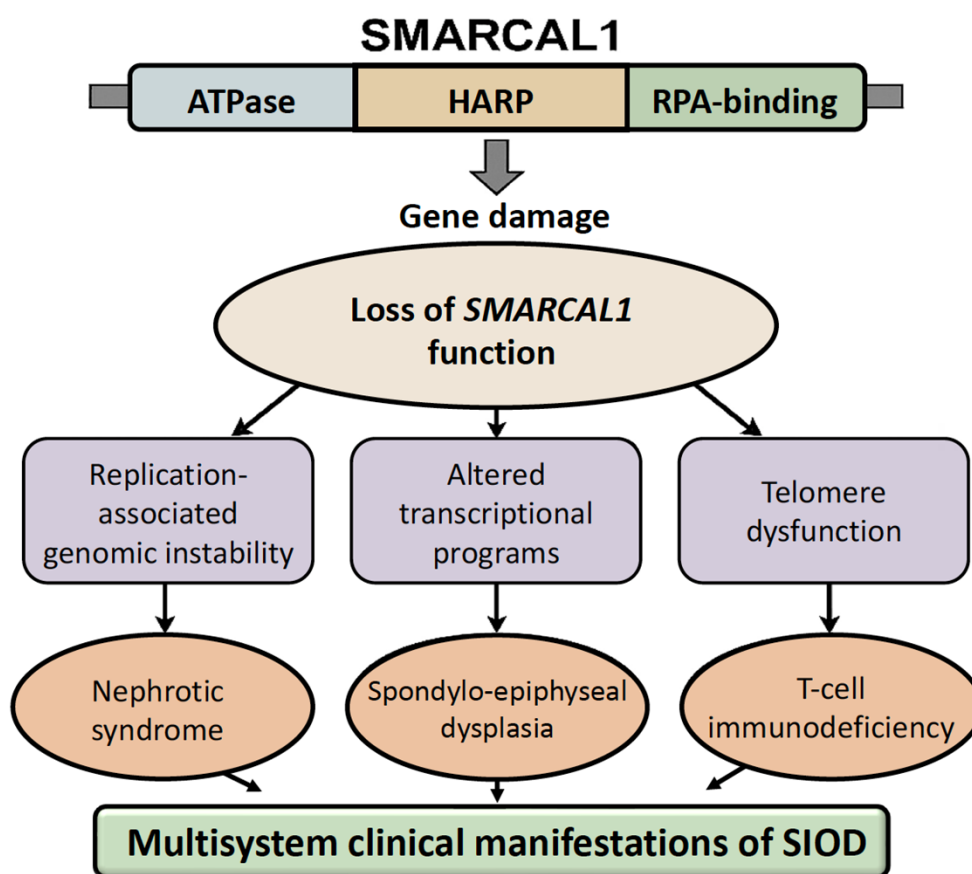


Figure 1. Domain organization of *SMARCAL1* and the cellular and clinical consequences of its loss. The schematic illustrates the major functional domains of *SMARCAL1*, including the ATPase domain, HARP domain, and RPA-binding region. In response to DNA damage, loss of *SMARCAL1* function leads to replication-associated genomic instability, altered transcriptional programs, and telomere dysfunction. These defects give rise to distinct pathological outcomes, including nephrotic syndrome, spondyloepiphyseal dysplasia, and T-cell immunodeficiency. Loss of *SMARCAL1* disrupts replication-fork stability and telomere maintenance, explaining the core multisystem clinical manifestations of SIOD. Created with MS PowerPoint 2024.

Abbreviations: ATP: Adenosine triphosphate; HARP: HepA-related protein; RPA: Replication protein A; SIOD: Schimke immuno-osseous dysplasia.

Given the severe prognosis, limited treatment options, and the growing success of gene therapy approaches for monogenic immune and renal diseases, the concept of *SMARCAL1*-targeted gene therapy has become increasingly compelling.¹¹ In this review, we summarize the spectrum of *SMARCAL1* genetic alterations, their cellular and molecular consequences, current SIOD disease models, and emerging prospects for gene therapy, with an emphasis on replication-associated mechanisms, genome stability, and translational strategies relevant to both clinicians and researchers.

2. Literature search and methodological approach

This review is based on a structured literature search combined with targeted manual curation to ensure comprehensive and transparent coverage of current knowledge on SIOD and *SMARCAL1* biology.

Peer-reviewed biomedical literature was searched in PubMed, Web of Science, and Scopus. Given the ultra-rare nature of SIOD, no restrictions on publication year were applied to capture both foundational studies and recent advances. Search queries combined disease-specific, mechanistic, and translational terms, including “Schimke immuno-osseous dysplasia,” “SIOD,” and “*SMARCAL1*,” together with “replication stress,” “replication fork,” “genome stability,” “chromatin remodeling,” and “telomere maintenance,” as well as emerging therapeutic keywords such as “gene therapy,” “CRISPR,” “base editing,” “prime editing,” “induced pluripotent stem cells,” and “hematopoietic stem cell gene therapy.” Additional focused searches addressed specific aspects of *SMARCAL1* function, including replication protein A (RPA) interaction, annealing helicase activity, replication-fork remodeling, and alternative lengthening of telomeres.

Eligible publications included peer-reviewed original research articles and authoritative review papers describing molecular functions of *SMARCAL1*, genotype–phenotype correlations in SIOD, or experimental and translational gene therapy approaches relevant to replication stress-associated disease. Non-peer-reviewed materials and studies lacking mechanistic or translational relevance were excluded.

The initial search yielded approximately 150 records. After removal of duplicates, 112 articles were screened based on titles and abstracts, and 52 publications were selected for full-text evaluation. Of these, 41 core studies were synthesized in the main body of the review. To meet journal requirements and strengthen clinical and translational context, additional relevant publications identified through manual reference screening were

incorporated, resulting in a final reference list of 67 cited works.

Due to the limited size and heterogeneity of the SIOD literature, data were synthesized narratively rather than through formal meta-analysis, with emphasis on integrating molecular mechanisms, clinical manifestations, and implications for emerging gene therapy strategies.

3. *SMARCAL1* structure, function, and role in genome stability

3.1. *SMARCAL1* protein structure

The *SMARCAL1* protein is a member of the SNF2 family of ATP-dependent chromatin-remodeling enzymes and contains several conserved functional regions essential for maintaining replication-fork stability. The N-terminal portion includes a conserved ATPase domain characteristic of SNF2-like remodelers, which provides the energy required for DNA translocation and fork remodeling.^{12,13} Adjacent to this region lies the HepA-related protein (HARP) domain, responsible for the annealing helicase activity that allows *SMARCAL1* to regress and stabilize stalled replication forks.¹⁴

A crucial structural element is the RPA-binding motif, which mediates interaction with RPA on single-stranded DNA exposed at stalled forks. This interaction is required for *SMARCAL1* recruitment to sites of replication stress and for precise regulation of its fork-regression activity.^{15,16} In particular, RPA binding spatially restricts *SMARCAL1* activity to RPA-coated DNA structures, thereby preventing aberrant remodeling.¹⁵

The *SMARCAL1* protein contains a DExx/HELICc ATPase module typical of SNF2-family remodelers, two HARP domains required for annealing helicase activity, an N-terminal regulatory region integrating replication stress signals, and a conserved RPA-binding motif. This motif enables direct recognition of RPA-coated single-stranded DNA and restricts *SMARCAL1* activity to appropriate substrates, preventing aberrant remodeling. Ataxia telangiectasia and Rad3-related kinase (ATR)-dependent phosphorylation of *SMARCAL1* reduces its catalytic activity under high replication stress, thereby preventing excessive fork regression and fork collapse.¹⁷

In addition to interaction-dependent regulation, *SMARCAL1* activity is modulated by phosphorylation events within the replication stress response network, including ATR-dependent phosphorylation that prevents excessive fork remodeling under high-stress conditions¹⁸ (Figure 2).

Together, these structural features enable *SMARCAL1*

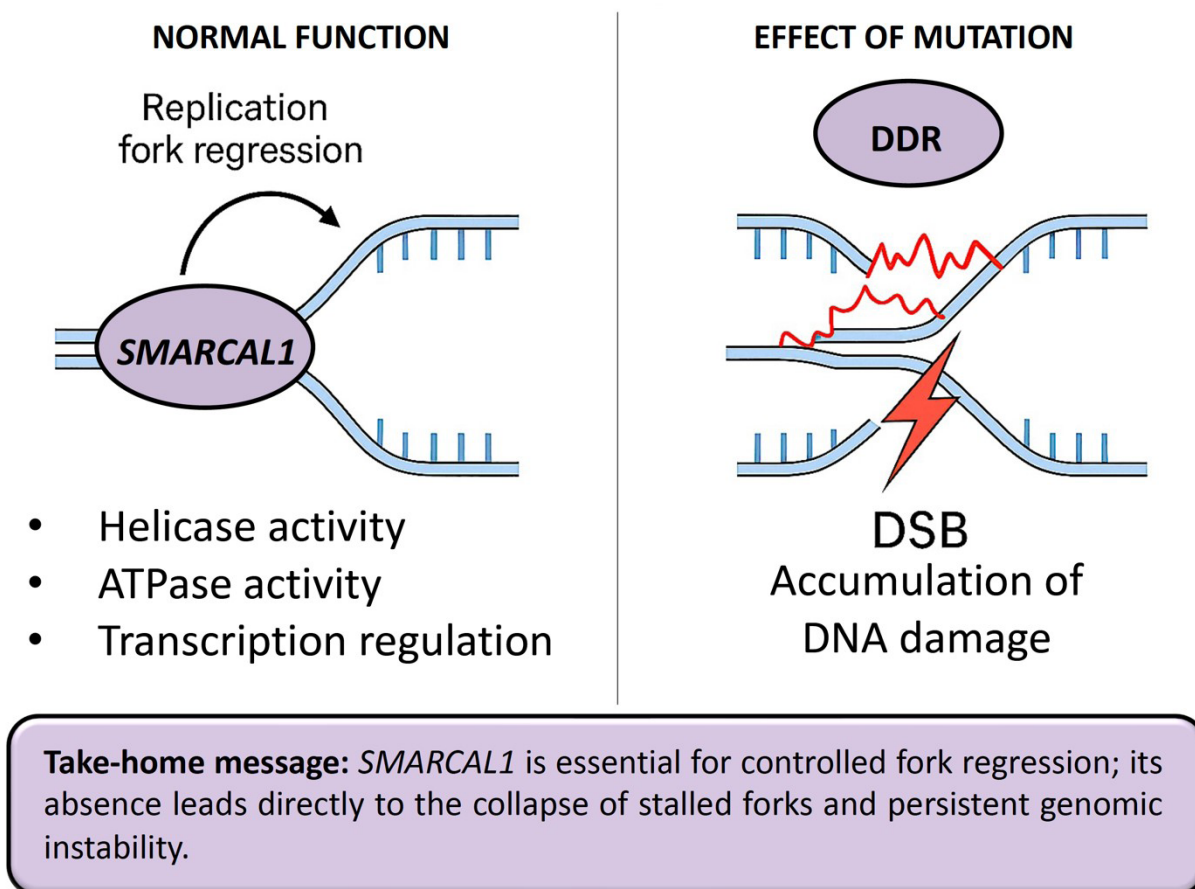


Figure 2. Normal *SMARCAL1* function at stalled replication forks and the consequences of *SMARCAL1* mutation. (A) Under normal conditions, *SMARCAL1* promotes replication fork regression and contributes to helicase and adenosine triphosphatase (ATPase) activities, as well as transcriptional regulation, thereby maintaining replication fork stability. (B) Mutations in *SMARCAL1* impair fork remodeling, leading to aberrant DNA structures, activation of the DNA damage response (DDR), and accumulation of double-strand breaks (DSBs), ultimately resulting in persistent genomic instability. Created with MS PowerPoint 2024.

to coordinate ATP-dependent remodeling, annealing helicase activity, and precise RPA-mediated targeting, making it a central factor in replication-fork metabolism and maintenance of genome stability.

3.2. Function in replication stress response

Under conditions of replication stress, such as fork stalling due to DNA damage, nucleotide depletion, or the formation of secondary DNA structures, *SMARCAL1* plays a central role in maintaining fork integrity. The protein is recruited to RPA-coated single-stranded DNA at stalled forks, where it remodels fork structures through ATP-dependent annealing helicase activity.^{15,16}

A key function of *SMARCAL1* is fork regression, a process that converts stalled forks into four-way junctions, allowing lesion bypass or repair. This mechanism stabilizes perturbed replication intermediates and prevents

uncontrolled fork collapse.^{15,19} *SMARCAL1* also contributes to the restart of stalled forks by cooperating with other fork remodelers and DNA translocases, ensuring proper progression once obstacles are removed.²⁰

Importantly, *SMARCAL1* acts as a safeguard against the formation of double-strand breaks (DSBs) during replication. By stabilizing abnormal fork structures and regulating the extent of fork remodeling, *SMARCAL1* prevents excessive or inappropriate processing that would otherwise lead to DSBs.^{18,19} Loss of *SMARCAL1* function results in profound defects in replication-fork maintenance, such as the accumulation of aberrant replication intermediates due to impaired remodeling,^{14,19} genome instability and chromosomal fragility, reflecting susceptibility of stalled forks to collapse,^{19,21} and hyperactivation of DNA-damage response pathways, particularly ATR signaling triggered by persistent

replication stress.^{18,21}

These molecular defects explain many of the cellular and clinical features of SIOD, including impaired proliferation, transcriptional dysregulation, telomere fragility, and increased risk of malignancy.

3.3. Chromatin, telomeres, and transcription

SMARCAL1 plays a crucial role not only in replication fork remodeling but also in maintaining chromatin architecture and telomere integrity. Its activity at telomeres is particularly important in cells that rely on the alternative lengthening of telomeres (ALT) pathway. In these contexts, *SMARCAL1* resolves replication stress arising from repetitive telomeric DNA and secondary structures; loss of *SMARCAL1* leads to telomere attrition, replication-associated damage, and telomere–telomere or telomere–chromosome fusions.^{22–24} These defects destabilize telomere structure and promote the accumulation of dysfunctional telomeric intermediates, contributing to genomic instability—a hallmark of SIOD cellular pathology.

At ALT telomeres, *SMARCAL1* resolves replication stress arising from repetitive sequences and secondary structures. Its loss results in telomere fragility, dysfunctional intermediates, and telomere–telomere fusions, demonstrating its essential role in maintaining telomere integrity in ALT-dependent cells.²⁵

Beyond its telomeric functions, *SMARCAL1* deficiency disrupts global chromatin organization. SIOD cellular models demonstrate altered accessibility and transcriptional dysregulation, especially in genes involved in extracellular matrix formation and tissue differentiation. Notably, reduced expression of elastin and aberrant regulation of master differentiation genes have been documented in both patient-derived induced pluripotent stem cell (iPSC) models and inducible *SMARCAL1* knockdown systems.^{5,15,26} These transcriptional abnormalities likely result from persistent replication stress that interferes with chromatin remodeling and proper maintenance of transcription.

Together, the converging chromatin, telomeric, and transcriptional defects associated with *SMARCAL1* loss help explain the multi-organ phenotype of SIOD, including vascular fragility, skeletal dysplasia, and impaired cellular differentiation.^{27,28}

4. Spectrum of *SMARCAL1* genetic alterations in Schimke immuno-osseous dysplasia

4.1. Types of variants

Pathogenic variants in *SMARCAL1* encompass a wide

spectrum of mutation types, consistent with the molecular heterogeneity and clinical variability of SIOD. Reported variant classes include:

- (i) Missense mutations, which often reduce but do not completely abolish *SMARCAL1* enzymatic activity, and are associated with intermediate or milder phenotypes.^{1,8,29}
- (ii) Nonsense and frameshift mutations, typically resulting in truncated proteins subject to nonsense-mediated decay, and generally leading to severe, early-onset SIOD.^{1,3,8,30}
- (iii) Splice-site alterations, producing aberrant transcripts or exon skipping and generating variable phenotypes depending on the degree of residual protein function.^{8,29}
- (iv) Large deletions (copy-number variants [CNVs]) removing part or all of the *SMARCAL1* locus, frequently associated with the most severe and rapidly progressive forms of SIOD.^{10,29,31}
- (v) Rare regulatory-region variants, which may reduce *SMARCAL1* transcription without altering its coding sequence and are suspected contributors to atypical or attenuated presentations.^{8,29}

Recent studies further underscore the clinical significance of large *SMARCAL1* deletions, identifying multi-exon or whole-gene losses in patients with profound immunodeficiency, early renal failure, and rapidly progressive multi-organ involvement. These findings demonstrate the importance of incorporating multiplex ligation-dependent probe amplification or sequencing-based CNV analysis into SIOD diagnostics^{10,31} (Table 1). The phenotypic severity gradient is shown in Figure 3.

4.2. Genotype–phenotype correlations

The clinical spectrum of SIOD ranges from severe early-onset forms with rapid multi-organ deterioration to milder, slowly progressive variants. Numerous cohort studies and case series have demonstrated that disease severity strongly correlates with the underlying *SMARCAL1* variant type.^{1,3,8,10,29}

Truncating variants (nonsense and frameshift mutations) and large deletions typically abolish *SMARCAL1* function, resulting in markedly reduced or absent protein levels. These mutations are consistently associated with severe SIOD, often presenting in early childhood with profound immunodeficiency, rapid progression to end-stage renal disease, and increased susceptibility to vascular and malignant complications.^{1,2,3,8,10,26,31}

In contrast, missense variants frequently preserve partial ATPase or annealing helicase activity, thereby allowing residual protein function. Patients carrying

Table 1. Summary of the major classes of *SMARCAL1* mutations and their molecular and clinical consequences

Type of mutation	Molecular mechanism	Consequences for the <i>SMARCAL1</i> protein	Typical clinical phenotype	Notes
Missense	Single-nucleotide change → amino acid substitution	Partial loss of function; destabilization of ATPase or HARP domains; reduced helicase activity	Mild to moderate SIOD; later onset; less severe immunodeficiency	Most common mutation type. Common example: p.R586W (partial ATPase impairment)
Nonsense	Introduction of a premature stop codon	Truncated protein → degradation via nonsense-mediated decay	Severe SIOD; rapid progression of renal failure; profound immunodeficiency	Typically results in a complete loss of function. Typical example: p.Y620*
Frameshift	Insertions/deletions causing a reading-frame shift	Usually introduces premature stop → degradation of mRNA or protein	Severe phenotype, often early-onset SIOD	Frequently causes full loss of function. Typical example: c.2470_2471del
Splice-site mutations	Disruption of mRNA splicing	Exon loss or aberrant protein formation	Variable phenotype, ranging from moderate to severe	Often underdetected in diagnostics. Representative example: c.2070+1G>A
Large deletions (CNVs)	Loss of part or the entire <i>SMARCAL1</i> gene	Absence of <i>SMARCAL1</i> protein	Very severe phenotype; rapid multi-organ deterioration	Rare; requires MLPA/CNV analysis. Examples include multi-exon deletions affecting exons 3–11

Abbreviations: ATP: Adenosine triphosphate; CNV: Copy number variation; HARP: HepA-related protein; MLPA: Multiplex ligation-dependent probe amplification; RPA: Replication protein A; SIOD: Schimke immuno-osseous dysplasia.

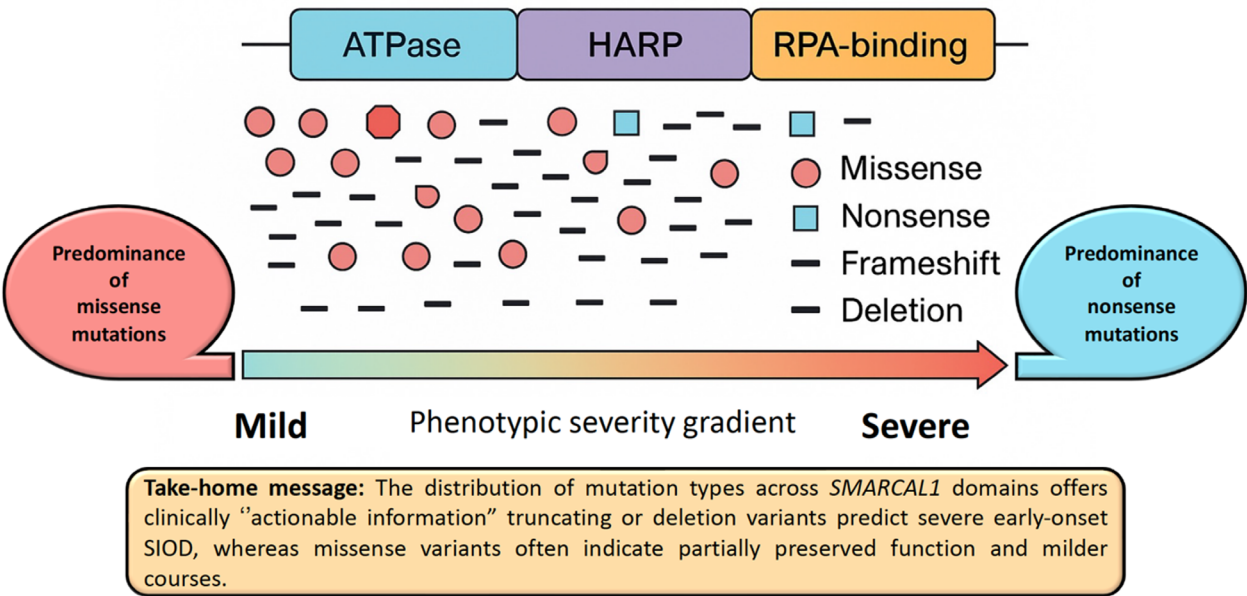


Figure 3. Spectrum of *SMARCAL1* mutations across functional domains and their clinical severity. The schematic depicts the localization of different classes of *SMARCAL1* mutations: missense, nonsense, frameshift, and deletions within the ATPase, HARP, and RPA-binding domains. A gradient from mild to severe phenotypes is shown, indicating that milder clinical presentations are typically associated with a predominance of missense variants. In contrast, more severe phenotypes are associated with a higher frequency of nonsense mutations and other truncating variants. This distribution highlights the relationship between mutation type, domain involvement, and phenotypic severity. Created with MS PowerPoint 2024.

Abbreviations: ATP: Adenosine triphosphate; HARP: HepA-related protein; RPA: Replication protein A; SIOD: Schimke immuno-osseous dysplasia.

biallelic missense variants often present with intermediate or atypical SIOD phenotypes, including later disease onset, milder immunodeficiency, and variable skeletal or renal involvement.^{1,8,10,29} Functional studies confirm that different missense mutations reduce *SMARCAL1* stability or catalytic efficiency to varying degrees, explaining the observed phenotypic heterogeneity.^{15,26}

Splice-site variants show variable expressivity, depending on whether aberrant splicing allows production of a partially functional protein. Some patients display moderate SIOD, whereas others mirror the severity of truncating mutations.^{8,29} Additionally, emerging evidence suggests that regulatory region variants, though rare, may contribute to attenuated or atypical presentations by reducing gene expression rather than by structural disruption of *SMARCAL1*.^{8,29}

Together, these correlations highlight the importance of detailed variant classification, including CNV detection and transcript analysis, in predicting prognosis and tailoring clinical management.

5. Organ system consequences of *SMARCAL1* deficiency

SMARCAL1 deficiency produces multisystem pathology due to the protein's essential roles in replication-fork stabilization, chromatin organization, telomere integrity,

and transcriptional regulation. Replication stress in vulnerable, highly proliferative, or structurally specialized cell types such as podocytes, chondrocytes, lymphocytes, and endothelial cells leads to the characteristic organ damage observed in SIOD.^{1,3,8,10} The organ system consequences of *SMARCAL1* deficiency are summarized in Table 2.

5.1. Kidneys

Kidney disease is one of the dominant and earliest manifestations of SIOD. Most patients develop steroid-resistant nephrotic syndrome, histologically characterized by focal segmental glomerulosclerosis and progressive mesangial expansion.^{1,3,6,8,30}

Mechanistically, *SMARCAL1* deficiency induces replication stress in podocytes and renal endothelial cells, both of which rely heavily on genome stability throughout development and maintenance. Impaired fork remodeling leads to accumulated DNA damage, loss of podocyte integrity, altered barrier function, and progressive interstitial fibrosis.^{14,15,18,19,21} These mechanisms are consistent with the early onset and rapid progression to renal failure observed in many patients.^{3,10}

Diagnostic workup of SIOD-related kidney disease includes laboratory evaluation of nephrotic-range proteinuria, a kidney biopsy typically showing focal

Table 2. Organ system consequences of *SMARCAL1* deficiency

Organ system	Underlying cellular mechanism	Major clinical features	Potential benefit from future gene-corrected HSC/iPSC therapy	Key references
Kidney	Replication stress in podocytes and endothelium; genomic instability; loss of filtration barrier integrity	Steroid-resistant nephrotic syndrome, FSGS, rapid progression to ESRD	Likely requires iPSC-derived renal progenitor replacement; HSC correction unlikely to benefit renal pathology directly	1,3,6,8,10,14,15,19,30
Skeletal system	Impaired chondrocyte proliferation; dysregulated differentiation programs	Spondyloepiphyseal dysplasia, growth failure	Potentially responsive to iPSC-derived chondrocyte progenitors; limited impact from HSC therapy	3,5,26,32
Immune system	Defective DDR; impaired lymphocyte proliferation; potential V(D)J defects	T-cell lymphopenia, recurrent infections	High expected benefit from HSC gene therapy; could restore T-cell development	1,3,8,29
Cardiovascular system	Endothelial replication stress; reduced elastin expression	Atherosclerosis, hypertension, stroke	Possible partial benefit via endothelial iPSC-derived cell therapies; low expected impact from HSC correction	3,5,7
Cancer	Telomere instability; accumulation of replication-associated breaks	Lymphomas, osteosarcoma	Unclear; restoring <i>SMARCAL1</i> may reduce replication-stress burden, but long-term data are needed	1,21-24

Abbreviations: DDR: DNA damage response; ESRD: End-stage renal disease; FSGS: Focal segmental glomerulosclerosis; HSC: Hematopoietic stem cell; iPSC: Induced pluripotent stem cell; V(D)J: Variable–diversity–joining.

segmental glomerulosclerosis, and genetic testing confirming pathogenic *SMARCAL1* variants.

5.2. Skeletal system

Skeletal abnormalities, including spondyloepiphyseal dysplasia, disproportionate short stature, and vertebral anomalies, are hallmark features of SIOD.^{3,5,32} Growth-plate chondrocytes are rapidly dividing cells, rendering them highly susceptible to replication stress. Loss of *SMARCAL1* disrupts chromatin architecture and alters transcription of genes controlling differentiation and extracellular matrix production, including elastin and other developmental regulators.^{5,26} These combined defects impair chondrocyte proliferation and maturation, leading to an abnormal growth plate structure and skeletal dysplasia.

5.3. Immune system

A characteristic immunologic feature of SIOD is T-cell lymphopenia, accompanied by susceptibility to infections and reduced adaptive immune competence.^{1,3,8} The immunodeficiency arises from *SMARCAL1*'s role in maintaining genome stability during rapid lymphocyte proliferation. Its deficiency causes persistent replication-associated DNA damage, impaired DNA damage response signaling, reduced proliferation and survival of developing T cells, and potential disruption of V(D)J recombination and T-cell receptor repertoire formation.^{1,8,29} Together, these defects compromise T-cell homeostasis and immune function.

5.4. Cardiovascular system and cancer

Vascular disease is frequent and often severe in SIOD. Patients commonly develop premature atherosclerosis, hypertension, vascular stiffness, and are at high risk for stroke.^{3,5,7} *SMARCAL1*-deficient endothelial cells exhibit heightened replication stress and transcriptional dysregulation, including reduced elastin expression, a critical determinant of vascular elasticity.⁵ Moreover, chronic replication stress, telomere dysfunction, and genome instability increase susceptibility to malignancies, including lymphomas and osteosarcoma.^{1,21-24} These cancers align with *SMARCAL1*'s central function in telomere maintenance and protection of stalled replication forks.

6. Current treatment as a baseline for gene therapy

Current therapeutic management is primarily supportive and aims to mitigate the clinical manifestations and complications arising from progressive renal dysfunction. As the disorder is rooted in a defined genetic defect, available interventions are unable to correct the underlying

molecular pathology. Instead, clinical care focuses on controlling secondary complications and maintaining organ function for as long as possible.^{33,34} Supportive management typically includes metabolic stabilization, infection prevention, and renal replacement strategies. Key components of current supportive treatment include (i) nephrotic syndrome control, encompassing the management of proteinuria, edema, and lipid abnormalities; (ii) dialysis and kidney transplantation, which provide essential renal replacement in advanced stages of kidney failure and remain the principal life-prolonging interventions; (iii) infection prophylaxis, which is necessary due to the heightened susceptibility to infectious complications inherent to the disease and further exacerbated by immunosuppressive therapy following transplantation; and (iv) growth and orthopedic therapy aimed at addressing extra-renal manifestations and improving long-term quality of life.

In recent years, novel strategies have sought to improve transplantation outcomes by combining kidney transplantation with the induction of mixed hematopoietic chimerism. This approach aims to achieve partial immune tolerance, thereby reducing the need for long-term immunosuppressive therapy. Although such protocols have shown promising potential for minimizing immunological complications, they remain fundamentally supportive rather than curative.^{35,36} Crucially, they do not address the primary genetic cause of the disease, leaving the underlying mechanism unaltered.

This limitation underscores the urgent need for therapeutic approaches that act at the molecular level. Gene therapy offers a unique opportunity to directly correct the genetic defect, with the potential to halt disease progression and provide lasting clinical benefit. In this context, current management strategies serve primarily as a clinical baseline against which the efficacy, durability, and transformative potential of gene-based interventions can be evaluated.^{37,38}

7. Disease models supporting gene therapy development

The development of effective gene therapy strategies for SIOD relies heavily on robust cellular models that accurately reproduce the molecular defects associated with *SMARCAL1* loss. Advances in iPSC technology, inducible knockdown systems, and precise genome editing approaches have enabled detailed investigation of *SMARCAL1* biology and provided a platform for testing therapeutic correction methods.

7.1. Patient-derived induced pluripotent stem cells

A key resource for modeling SIOD is the patient-derived

iPSCline SDASi001-A, which carries compound pathogenic *SMARCAL1* mutations and retains full pluripotency.³⁹ These cells provide a renewable and genetically accurate human model for dissecting replication-stress phenotypes, studying chromatin and transcriptional abnormalities, evaluating telomere dysfunction, testing clustered regularly interspaced short palindromic repeats (CRISPR)-based gene correction, and differentiating corrected cells into renal, skeletal, and hematopoietic lineages relevant to SIOD pathology. As SIOD affects multiple organ systems, patient-derived iPSCs are particularly valuable for identifying cell-type-specific vulnerabilities and testing multi-lineage therapeutic approaches.

7.2. Inducible *SMARCAL1* knockdown induced pluripotent stem cell models

Complementing patient-derived cells, inducible *SMARCAL1* knockdown iPSC systems recapitulate severe SIOD phenotypes in a controlled genetic background.^{26,40} These models allow temporal regulation of *SMARCAL1* suppression, enabling researchers to distinguish defects arising during early development from those caused by acute loss of function. Knockdown iPSCs demonstrate pronounced replication stress, accumulation of aberrant replication intermediates, transcriptional dysregulation affecting master differentiation genes, and impaired lineage commitment. Such systems have been critical for establishing mechanistic links between replication-fork instability and developmental defects characteristic of SIOD.

7.3. Clustered regularly interspaced short palindromic repeats editing of *SMARCAL1*

Multiple studies confirm that *SMARCAL1* is amenable to CRISPR-based genome editing, including classical CRISPR-Cas9 with homology-directed repair (HDR), base editors, and prime editing strategies.^{15,19,20,41-43}

These technologies have been successfully applied in human cell lines, including iPSCs and hematopoietic stem and progenitor cells. Their application to SIOD models enables precise correction of patient-specific *SMARCAL1* mutations, functional rescue of replication-stress phenotypes, evaluation of dosage sensitivity, and assessment of long-term genomic stability following gene repair.⁴⁴⁻⁴⁶

Moreover, the success of *ex vivo* gene therapy for other monogenic immune disorders such as X-linked severe combined immunodeficiency, adenosine deaminase severe combined immunodeficiency, and Wiskott-Aldrich syndrome demonstrates that hematopoietic stem cell (HSC)-targeted strategies are feasible and clinically

translatable.^{47,48} The combination of SIOD iPSC models, inducible knockdown systems, and advanced CRISPR platforms provides a strong experimental foundation for future *SMARCAL1*-targeted therapies.

8. Strategies for Schimke immuno-osseous dysplasia gene therapy

8.1. *Ex vivo* hematopoietic stem cell gene therapy

A compelling rationale for pursuing *ex vivo* gene therapy targeting HSCs in SIOD stems from the presence of severe T-cell immunodeficiency, a core clinical manifestation of the disease. The success of HSC-based gene therapy in multiple primary immunodeficiencies, including X-linked severe combined immunodeficiency, adenosine deaminase severe combined immunodeficiency, and Wiskott-Aldrich syndrome, demonstrates both feasibility and long-term safety when appropriately regulated.^{47,49,50} These precedents provide a strong translational foundation for applying similar strategies to SIOD, despite its rarity. In principle, *ex vivo* HSC gene therapy may be preferable for patients whose disease burden is dominated by immunological dysfunction with preserved renal and skeletal function, whereas iPSC-based regenerative or multi-lineage correction strategies may be more suitable for individuals with advanced multi-organ involvement. Defining these criteria clearly will be essential for future clinical translation.^{51,52}

A standard *ex vivo* HSC gene therapy workflow would involve:

- (i) Isolation of autologous CD34⁺ hematopoietic stem and progenitor cells from peripheral blood or bone marrow.^{53,54}
- (ii) Genetic correction of *SMARCAL1*, either by lentiviral vector-mediated gene addition, or CRISPR-based gene repair, including HDR, base editing, or prime editing, depending on variant type.^{55,56}
- (iii) Reinfusion of corrected HSCs following myeloablative or reduced-intensity conditioning to allow engraftment (Figure 4).

Such an approach aims to restore T-cell development and function, thereby improving immune competence and reducing the burden of infection. However, gene therapy for SIOD poses unique challenges that differ from classical immunodeficiencies:

- (i) *SMARCAL1* dosage sensitivity: Because *SMARCAL1* regulates replication-fork stability, both under- and overexpression can be harmful. Overexpression, in particular, may disrupt fork remodeling and increase replication stress,

necessitating tight control of transgene levels.⁵⁷

- (ii) Oncogenic risk: As *SMARCAL1* is intimately involved in genome stability, inappropriate expression or insertional mutagenesis could potentiate genomic instability or neoplastic transformation.⁵⁷
- (iii) Multisystem involvement: Restoring immune function alone will not resolve SIOD's renal, skeletal, and vascular phenotypes, though HSC gene therapy may address immunologic morbidity.⁵⁸

Despite these challenges, *ex vivo* gene therapy remains the most realistic first-step approach toward an eventual

SMARCAL1-targeted treatment, owing to the accessibility of HSCs and prior success treating related diseases.

8.2. *Ex vivo* induced pluripotent stem cell correction and regenerative therapy

Ex vivo correction of patient-derived iPSCs represents a versatile strategy for treating the multisystem manifestations of SIOD. Given that iPSCs can be differentiated into virtually any somatic lineage, they provide a platform for both mechanistic studies and regenerative applications.⁵⁹ A typical iPSC-based therapeutic approach would include:

- (i) Reprogramming patient somatic cells into iPSCs, as demonstrated in the SIOD iPSC

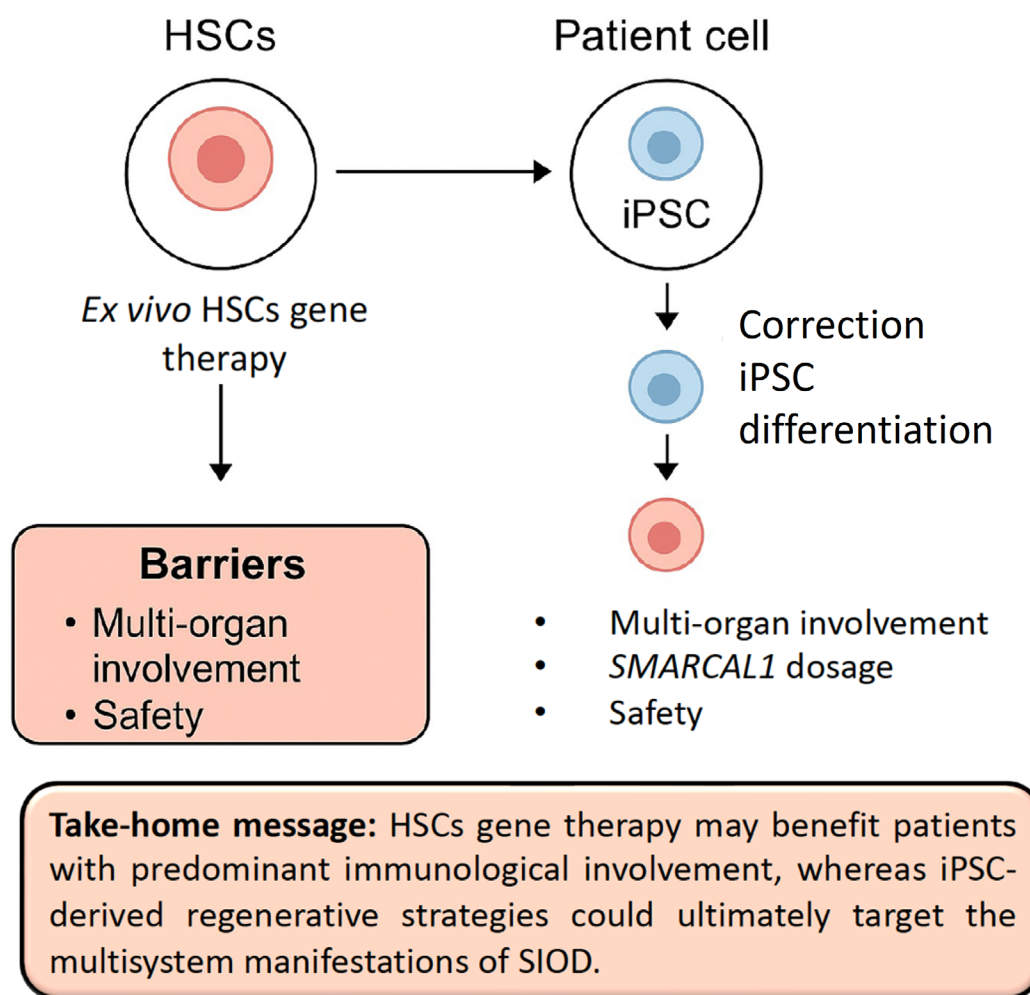


Figure 4. Potential gene therapy and induced pluripotent stem cell (iPSC)-based therapeutic strategies for *SMARCAL1* deficiency and associated barriers. The left panel illustrates an *ex vivo* hematopoietic stem cell (HSC) gene therapy approach, in which HSCs are corrected and potentially transplanted back into the patient. This strategy is challenged by the multi-organ nature of *SMARCAL1*-related disease and safety concerns. The right panel shows an iPSC-based approach in which patient cells are reprogrammed into iPSCs, genetically corrected, and differentiated into the desired cell types. Barriers to this method include multi-organ involvement, the need for precise control of *SMARCAL1* dosage, and overarching safety considerations. Created with MS PowerPoint 2024.

line SDASi001-A, which carries compound *SMARCAL1* mutations while maintaining full pluripotency.³⁹

- (ii) Correcting the pathogenic *SMARCAL1* variants using CRISPR-Cas9 with HDR, base-editing tools, or prime editing strategies capable of precise, low-DSB correction.⁴¹⁻⁴³
- (iii) Differentiating the corrected iPSCs into cell types directly affected in SIOD, such as renal progenitors, chondrocytes, or hematopoietic lineages, to test functional rescue of replication stress, transcriptional dysregulation, and telomere instability.^{26,39}

Such models uniquely allow the assessment of *SMARCAL1* dosage sensitivity, which is critical given the protein's tight regulation of replication-fork remodeling and genome stability.^{15,19,20} Beyond mechanistic studies, iPSC-derived, gene-corrected progenitors could eventually support organ-specific regenerative therapies, although clinical translation remains distant.

8.3. *In vivo* gene therapy

Direct *in vivo* gene delivery is theoretically attractive for a multisystem disorder like SIOD, but it remains a long-term goal due to substantial biological and technical challenges,^{60,61} such as:

- (i) Multi-organ targeting: SIOD affects kidneys, skeleton, immune cells, vasculature, and other tissues, demanding broad and efficient *in vivo* delivery beyond the capability of current vector systems.⁶²
- (ii) Narrow *SMARCAL1* dosage window: Both under- and overexpression of *SMARCAL1* can induce replication stress and genomic instability, making *in vivo* expression control particularly risky.^{15,19,20,22-24}
- (iii) Vector immunogenicity: Even in immunodeficient patients, immune responses against viral vectors or Cas proteins may reduce efficiency or preclude repeat dosing. This challenge is well documented in the broader field of gene therapy.⁴⁷⁻⁴⁹

Due to these limitations, *in vivo* gene therapy for SIOD remains a long-term prospect, likely requiring future advances in vector engineering, tissue-specific regulation, and ultra-precise genome-editing technologies.

9. Discussion

Schimke immuno-osseous dysplasia poses unique challenges for therapeutic development, particularly in gene therapy. The disorder's complexity stems from the fundamental role of *SMARCAL1* in genomic maintenance,

which makes both deficiency and misexpression harmful. At the same time, emerging technologies, including refined iPSC platforms, low-DSB genome editors, and advances in HSC gene therapy, are creating new opportunities for translational progress.

9.1. Major challenges

A central obstacle in SIOD is its multisystem nature, with clinically significant involvement of the kidneys, immune system, skeleton, and vasculature. This broad tissue distribution reflects the essential role of *SMARCAL1* in replication-fork remodeling and transcriptional regulation, underscoring the need for widespread cellular correction to achieve complete disease modification.^{1,3,8}

Another critical barrier is the strict *SMARCAL1* dosage requirement. Both insufficient and excessive *SMARCAL1* activity can destabilize replication forks and increase genomic stress, raising the risk of unintended toxicity in gene therapy settings. This dosage sensitivity mandates highly precise expression control in any therapeutic strategy.^{15,19,20}

Patients with SIOD also have an elevated baseline cancer risk, consistent with defects in replication-fork stability, telomere maintenance, and DNA damage responses. Cases of lymphoma and osteosarcoma have been reported and align with mechanistic studies linking *SMARCAL1* loss to telomere dysfunction and genomic instability.²¹⁻²⁴ Any intervention must therefore avoid compounding oncogenic risk.

Additional challenges include the extremely low prevalence of SIOD, which limits clinical trial feasibility, and the tendency toward late diagnosis, often after irreversible renal or vascular damage has developed.^{3,10,30}

Schimke immuno-osseous dysplasia presents substantial therapeutic challenges due to its multisystem pathology, which simultaneously affects renal, immune, skeletal, and vascular tissues and therefore requires therapeutic approaches that address both immune dysfunction and broader replication-stress-related cellular damage.⁶³⁻⁶⁵ Collectively, these challenges highlight the need for therapies that are not only effective but also biologically nuanced and scalable despite the disease's rarity.

9.2 Genetic causation and epigenetic modifiers in Schimke immuno-osseous dysplasia

Schimke immuno-osseous dysplasia is unequivocally initiated by biallelic pathogenic variants in *SMARCAL1* and thus represents a monogenic autosomal recessive disorder. However, clinical and experimental observations

indicate that disease expression cannot be fully explained by DNA sequence alone, suggesting the contribution of additional non-genetic layers that modulate penetrance and tissue specificity.

Recent conceptual frameworks emphasize that, while the central dogma remains valid, heritable biological information may extend beyond nucleotide sequence. In this context, Cao *et al.*⁶⁶ propose that chromatin-encoded, structurally embedded regulatory states can transmit biological information without violating the DNA-to-RNA-to-protein paradigm.⁶⁶ This perspective is particularly relevant for SIOD, in which the primary genetic lesion affects genome maintenance processes rather than a single downstream pathway.

Within this framework, *SMARCAL1* mutations may initiate persistent alterations in chromatin organization and replication-associated regulatory states that are mitotically stable and lineage-specific, thereby shaping phenotypic variability independently of genotype. Importantly, this view does not redefine SIOD as an epigenetic disorder but positions epigenetic mechanisms as secondary modifiers of a genetically defined disease.

Accordingly, phenotypic variability in SIOD is likely multilayered, integrating sequence-based causation with replication-associated regulatory memory. Incorporating this model refines our understanding of disease variability in SIOD and aligns it with emerging concepts of information flow in human genetics.⁶⁶

9.3. Future perspectives

Despite these obstacles, several promising avenues for therapeutic development are emerging.

9.3.1. Refined induced pluripotent stem cell-based correction platforms

Patient-derived iPSCs and inducible *SMARCAL1* knockdown systems enable detailed mechanistic studies and provide platforms for preclinical correction testing. These models allow the controlled assessment of *SMARCAL1* dosage, evaluation of transcriptional rescue, and generation of corrected progenitors relevant to kidney, skeletal, or hematopoietic tissues.^{26,39}

9.3.2. Advanced genome-editing technologies

Low-DSB editing technologies, such as base editing and prime editing, offer safer alternatives to classical CRISPR-Cas9 by reducing DNA breaks and associated genomic instability. Their recent successes in HSCs and iPSC systems support their future applications in SIOD.⁴¹⁻⁴³

9.3.3. Tailored hematopoietic stem cell gene correction approaches

Hematopoietic stem cell gene therapy remains the most immediate clinical possibility, supported by decades of progress in treating primary immunodeficiencies. Optimized protocols for CRISPR- or vector-based correction of HSCs may restore T-cell immunity while mitigating dosage risks.⁴⁷⁻⁴⁹ Such approaches could substantially improve immunologic outcomes even if multisystem correction is not yet achievable.

9.3.4. Integration with tolerance-inducing transplant strategies

Emerging transplantation approaches, such as mixed hematopoietic chimerism, may synergize with gene-corrected HSCs, reducing the need for long-term immunosuppression and improving engraftment outcomes.^{67,68}

9.3.5. Deeper exploration of *SMARCAL1* in cancer biology

Given *SMARCAL1*'s fundamental role in genome stability, further investigation into its functions in DNA replication, telomere biology, and chromatin dynamics may help identify both therapeutic opportunities and safeguards. Insights from cancer biology may reveal novel ways to modulate replication stress without inducing genomic instability.²²⁻²⁴

9.3. Summary

In summary, SIOD presents substantial therapeutic challenges due to its multisystem pathology, the essential nature of *SMARCAL1* in replication-fork dynamics, and inherent cancer susceptibility. Nevertheless, rapid advances in iPSC modeling, precision genome editing, and stem-cell-based therapies provide a strong foundation for future treatment strategies. Continued refinement of these technologies, alongside a deeper mechanistic understanding of *SMARCAL1*, offers realistic potential to translate gene therapy into clinical benefit for this ultra-rare disorder. Overall, this work consolidates mechanistic and clinical findings, highlights knowledge gaps, outlines methodological priorities, and provides conceptual frameworks to guide future mechanistic studies, gene-editing experiments, and translational SIOD research.

9.4. Key unanswered questions

Several critical questions remain unanswered and should guide future research directions:

- (i) Which thresholds of *SMARCAL1* expression

restore function without inducing replication stress?

- (ii) Are dedicated SIOD animal models needed to evaluate the long-term safety of gene correction?
- (iii) What are the longitudinal cancer risks in SIOD, and how would gene therapy modify them?
- (iv) What standardized functional assays should be used to measure *SMARCAL1* restoration *in vitro*?

Addressing these questions will be pivotal for translating experimental correction strategies into clinically viable therapies.

10. Conclusion

SMARCAL1 deficiency disrupts replication-fork stability, chromatin organization, and transcription, leading to the characteristic multisystem manifestations of SIOD. Advances in disease modeling, especially iPSC platforms and inducible *SMARCAL1* knockdown systems, have deepened our understanding of SIOD pathogenesis and paved the way to targeted gene correction strategies.

Although significant challenges remain, including dosage sensitivity and the need for multisystem correction, emerging genome-editing technologies and progress in *ex vivo* HSC approaches offer the most promising path toward future therapeutic development.

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