

## Rothmund-Thomson Syndrome Revisited: Expanding the Genotypic Spectrum, Deciphering RECQL4-Related Pathomechanisms, And Redefining Long-Term Surveillance Strategies for An Underrecognized Genodermatosis

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### ABSTRACT

Rothmund-Thomson syndrome (RTS) represents a paradigm of the intricate intersection between dermatologic phenomics, genomic instability, and oncologic predisposition. This comprehensive review synthesizes current knowledge regarding this ultra-rare autosomal recessive genodermatosis, which classically manifests with the pathognomonic triad of poikiloderma, juvenile cataracts, and skeletal dysplasias, while conferring a substantially elevated lifetime risk for osteosarcoma and cutaneous malignancies. Over the past decade, significant nosological refinement has emerged from the elucidation of biallelic pathogenic variants in RECQL4 and ANAPC1 as the primary molecular etiologies underlying RTS type 2 and type 1, respectively. However, the recent identification of DNA2 and CRIPT variants in affected individuals without identifiable alterations in the canonical genes has further unraveled the genetic heterogeneity of this condition, challenging traditional classification paradigms and expanding the continuum of RECQL4-related disorders. We critically examine the evolving landscape of RTS molecular diagnostics, emphasizing the genotype-phenotype correlations that distinguish RECQL4-associated multisystemic involvement—characterized by radial ray defects, patellar hypoplasia, and a striking predisposition to osteosarcoma—from the ANAPC1-related subtype wherein cataracts predominate without malignant transformation. The role of RECQL4 as a cornerstone of genomic maintenance through its participation in replication fork stabilization, double-strand break repair, and telomere homeostasis is explored in depth, providing mechanistic insights into the cellular fragility that underlies the premature aging phenotype and neoplastic progression. Current evidence regarding surveillance protocols, including the contentious role of routine imaging for osteosarcoma screening and the utility of pulsed dye laser therapy for telangiectatic lesions, is critically appraised. Furthermore, we highlight emerging therapeutic avenues, including the potential for targeted DNA damage response modulation and the importance of genotype-informed cancer risk stratification. By integrating the most recent case series, molecular discoveries, and longitudinal outcome data, this review aims to provide clinicians with a practical framework for early recognition, diagnostic confirmation, and multidisciplinary management of this often-elusive syndrome, while identifying critical knowledge gaps that warrant future investigation.

**KEYWORDS:** Rothmund-Thomson syndrome; RECQL4 helicase; poikiloderma congenitale; osteosarcoma predisposition; genodermatosis; genomic instability; ANAPC1; DNA2; cancer surveillance; DNA repair disorders

### ARTICLE DETAILS

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## **INTRODUCTION**

The evaluation of a child presenting with recalcitrant facial erythema during the first months of life frequently poses a considerable diagnostic challenge for the practicing dermatologist, pediatrician, or clinical geneticist. While the differential diagnosis in such scenarios commonly encompasses benign entities such as seborrheic dermatitis, atopic eczema, or photosensitivity reactions, a subset of these infants will ultimately manifest the distinctive clinical stigmata of a rare but critically important heritable condition known as Rothmund-Thomson syndrome (RTS). First independently described by August von Rothmund in 1868 and subsequently characterized by Matthew Sydney Thomson in 1936, this disorder has historically been recognized as a congenital poikiloderma associated with a constellation of systemic findings that profoundly impact affected individuals across the lifespan.<sup>1,2</sup>

The hallmarks of RTS are unmistakable once fully established, yet the protean nature of its early manifestations frequently leads to diagnostic delay or misattribution. The characteristic rash, which typically emerges between three and six months of age, initiates as confluent erythema and edema localized to the malar eminences. With continued sun exposure, this inflammatory phase progresses to involve the extensor surfaces of the extremities and the buttocks, while characteristically sparing the trunk and abdomen. Over months to years, the cutaneous findings evolve into the eponymous poikiloderma—a striking constellation of reticulated hypo- and hyperpigmentation, arborizing telangiectasias, and punctate epidermal atrophy that persists irreversibly throughout life. Approximately one-third of affected individuals additionally develop hyperkeratotic lesions, particularly over the palms and soles, further contributing to functional impairment and cosmetic burden.<sup>2,3</sup>

Beyond its cutaneous manifestations, RTS imposes a multisystemic disease burden that necessitates coordinated interdisciplinary care. Affected children typically exhibit proportionate short stature with birth weights below the fifth percentile and persistent growth restriction throughout development. Ocular involvement, particularly the development of bilateral juvenile cataracts, occurs with variable frequency depending on the underlying genetic subtype and represents a major cause of preventable visual impairment. Skeletal anomalies are observed in up to seventy-five percent of individuals undergoing systematic radiographic evaluation, with findings ranging from radial ray deficiencies and ulnar dysgenesis to patellar aplasia or hypoplasia, osteopenia with metaphyseal striations, and abnormal trabeculation. Dental abnormalities, including microdontia, enamel hypoplasia, delayed eruption, and increased caries susceptibility, represent additional sources of morbidity that may be overlooked without dedicated odontologic assessment.<sup>3,4,5</sup>

Perhaps most consequentially, RTS confers a substantially increased risk for malignancy, making it one of the cancer predisposition syndromes that demands vigilant surveillance throughout childhood and adulthood. Osteosarcoma represents the most commonly reported neoplasm, with an estimated prevalence approaching thirty percent among RECQL4-mutation-positive individuals, typically manifesting around a median age of eleven years—slightly earlier than sporadic cases. Cutaneous malignancies, including basal cell carcinoma, squamous cell carcinoma, and melanoma, have been documented with an estimated prevalence of five percent, often presenting at younger ages than in the general population and occasionally arising in non-sun-exposed sites. Hematologic abnormalities, ranging from isolated cytopenias to myelodysplasia and aplastic anemia, have also been reported, though their precise association with specific genetic subtypes remains incompletely characterized.<sup>5,6,7</sup>

The past quarter-century has witnessed transformative advances in our understanding of RTS molecular pathogenesis. The identification of biallelic pathogenic variants in the RECQL4 gene, located on chromosome 8q24.3 and encoding a member of the RecQ family of DNA helicases, as the causative lesion in the majority of RTS type 2 cases represented a seminal discovery that enabled molecular confirmation of the diagnosis and facilitated genotype-phenotype correlation studies. More recently, pathogenic alterations in ANAPC1, encoding a component of the anaphase-promoting complex/cyclosome (APC/C), were identified in individuals with RTS type 1, typically characterized by the presence of poikiloderma, cataracts, and ectodermal dysplasia without the pronounced skeletal defects or malignancy risk. Notably, a substantial proportion of individuals meeting clinical criteria for RTS—estimated at up to thirty percent—have no identifiable mutation in either RECQL4 or ANAPC1 following conventional sequencing approaches, suggesting the existence of additional as-yet-unidentified genetic etiologies. This hypothesis has been recently validated by the discovery of biallelic variants in DNA2 and CRIPT in affected individuals, with the former now recognized as defining RTS type 4, a clinically distinct subtype characterized by congenital cataracts, microphthalmia, corneal opacities, and hypothyroidism. These findings underscore the remarkable allelic and locus heterogeneity that continues to expand the RTS nosologic framework.<sup>6,7,8</sup>

Despite these advances, the management of individuals with RTS remains largely supportive and empiric, informed by expert consensus rather than robust prospective data. Routine surveillance recommendations include annual dermatologic and ophthalmologic examinations, vigilant monitoring for concerning skin lesions, prompt radiographic evaluation of unexplained bone pain, and age-appropriate cancer screening. The role of routine radiographic surveillance for osteosarcoma detection remains debated, given concerns

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regarding radiation exposure and the absence of evidence demonstrating improved outcomes. Similarly, the management of chemotherapy-treated malignancies in RTS patients requires nuanced consideration, as the underlying genomic instability theoretically increases susceptibility to treatment-related toxicities and secondary neoplasms, though available case series suggest that most individuals tolerate standard regimens without unacceptable complications.<sup>7,8,9</sup> This review endeavors to provide a comprehensive, evidence-based synthesis of current knowledge regarding Rothmund-Thomson syndrome, addressing its clinical spectrum, molecular underpinnings, differential diagnostic considerations, and contemporary management strategies. By integrating findings from the most recent case series, molecular genetic discoveries, and clinical outcome studies—including the emerging literature on DNA2-related RTS and the expanding understanding of RECQL4 functional biology—we aim to equip clinicians with the practical tools necessary for early recognition and optimal care of affected individuals. Furthermore, we identify critical knowledge gaps that must be addressed through collaborative, multi-institutional research efforts to advance from descriptive characterization toward mechanism-targeted therapeutic interventions for this challenging condition.<sup>10,11</sup>

## **Clinical Manifestations of Rothmund-Thomson Syndrome**

The clinical presentation of Rothmund-Thomson syndrome unfolds as a temporally dynamic and anatomically widespread process, one that typically declares itself within the narrow window of early infancy yet continues to accrue new systemic features throughout childhood and adolescence. The recognition of this syndrome in clinical practice hinges fundamentally on the accurate identification of its cutaneous hallmarks, but the diagnosing physician must remain perpetually attentive to the extracutaneous manifestations that define the syndrome's true morbidity and dictate long-term prognosis. No two individuals with Rothmund-Thomson syndrome present identically, and the considerable phenotypic variability observed both within and between the genetically defined subtypes represents one of the most challenging aspects of clinical management. This heterogeneity notwithstanding, a core set of clinical features recurs with sufficient frequency to constitute a recognizable syndromic gestalt, and it is upon this foundation that the clinician builds the diagnostic hypothesis.<sup>12,13</sup>

The cutaneous phenotype unquestionably represents the most consistent and earliest recognizable feature of Rothmund-Thomson syndrome, with the characteristic rash emerging almost invariably between the third and sixth month of postnatal life. The initial dermatologic manifestation typically takes the form of a striking, well-demarcated erythema confined to the malar regions, often described by concerned parents as a persistent "sunburn" that fails to resolve with standard topical preparations. This early

inflammatory phase may be accompanied by mild edema and, in some infants, by the development of superficial vesicles or bullae, features that frequently prompt an initial working diagnosis of photosensitivity disorder or even epidermolysis bullosa. What distinguishes this eruption from more common pediatric dermatoses is its peculiar topographic distribution, which exhibits a marked predilection for the face, particularly the cheeks, while conspicuously sparing the perioral and periorbital regions. As the affected infant grows, the erythematous component gradually extends to involve the extensor surfaces of the extremities, including the dorsal aspects of the hands and forearms, as well as the buttocks and, in some cases, the lower back. Remarkably, the trunk, abdomen, and flexural surfaces of the limbs are almost universally spared, a distributional pattern so characteristic that its absence should prompt reconsideration of the diagnosis.<sup>13,14</sup>

Over the ensuing months to years, the initial erythematous eruption undergoes a gradual but inexorable transformation into the full histopathologic and clinical picture of poikiloderma, from which the syndrome derives its eponymous recognition. The term poikiloderma encompasses a triad of concurrent cutaneous findings that together produce an unmistakable dermatologic appearance. The first component consists of reticulated areas of pigmentary disturbance, wherein irregular patches of hyperpigmentation—ranging in color from light tan to deep bronze or brown—intermingle with sharply demarcated zones of hypopigmentation, creating a net-like or mottled pattern reminiscent of aged parchment. The second component comprises an arborizing network of telangiectasias, that is, persistently dilated superficial capillaries and venules that appear as fine, branching red lines traversing the affected skin. The third component manifests as cutaneous atrophy, characterized by thinning and wrinkling of the epidermis with associated loss of normal skin markings, rendering the involved areas fragile and susceptible to minor trauma. These three elements coexist within the same topographic regions, producing a striking contrast between the atrophic, telangiectatic, and dyspigmented zones that remains essentially unchanged for the remainder of the patient's life. The sun-exposed areas bear the brunt of these changes, but interestingly, the poikiloderma may also develop in sites rarely if ever exposed to ultraviolet radiation, including the buttocks and the dorsal surfaces of the feet, suggesting that photosensitivity, while contributory, does not represent the sole pathogenic mechanism.<sup>13,14</sup>

Beyond the classic poikiloderma, a substantial proportion of patients develop additional cutaneous findings that contribute to functional impairment and cosmetic distress. Hyperkeratotic lesions, particularly involving the palms and soles, occur with sufficient frequency to be considered a characteristic feature of the syndrome. These keratodermic changes range from mild, diffuse thickening of the stratum

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corneum to frankly disfiguring, verrucous plaques that may fissure and become secondarily infected. Fingernails and toenails often exhibit dystrophic changes characterized by longitudinal ridging, koilonychia, brittleness, and, in severe cases, partial or complete anonychia. The ectodermal dysplasia that accompanies the cutaneous findings extends to the adnexal structures as well, with many patients demonstrating sparse, brittle, or hypoplastic scalp hair, absent or diminished eyebrows and eyelashes, and reduced sweating due to eccrine gland hypoplasia.<sup>15,16</sup>

The ocular manifestations of Rothmund-Thomson syndrome represent a major source of morbidity and, when bilateral and complete, constitute one of the diagnostic criteria for the classic clinical definition of the disorder. Juvenile cataracts develop in approximately half of all affected individuals, though the prevalence varies dramatically according to the underlying genetic subtype. These lenticular opacities typically manifest during the first decade of life, with a median age of onset around four to five years, though cases of congenital cataract have been documented. The cataracts are almost invariably bilateral, though the timing and rate of progression may differ between the two eyes, and they most commonly assume a posterior subcapsular or nuclear morphology on slit-lamp examination. Without surgical intervention, progressive opacification leads to profound visual impairment and amblyopia, emphasizing the critical importance of early ophthalmologic screening and timely referral for lens extraction and intraocular lens implantation. Beyond cataracts, the ocular phenotype includes less frequent but nonetheless significant findings such as microphthalmia, corneal opacities or pannus formation, strabismus, and glaucoma. Some affected individuals manifest a particular sensitivity to ultraviolet light, with photophobia and excessive lacrimation exacerbated by sun exposure.<sup>17</sup>

Skeletal involvement constitutes another pillar of the Rothmund-Thomson syndrome phenotype, though its presence and severity correlate strongly with the specific genetic defect underlying the condition. Radiographic abnormalities of the long bones and extremities are identified in up to three-quarters of systematically evaluated patients, with the upper extremities bearing the brunt of the dysplastic process. Radial ray defects represent the most characteristic skeletal finding, encompassing a spectrum ranging from isolated hypoplasia of the first metacarpal or thumb to complete radial aplasia with absent scaphoid, trapezium, and first ray structures. More extensive upper limb reductions may involve ulnar hypoplasia or aplasia, phocomelia, or the presence of oligodactyly with fusion of remaining digits. The patellae deserve particular mention, as patellar aplasia or severe hypoplasia occurs with sufficient frequency to be considered a sentinel radiographic finding in suspected cases, sometimes detectable only through dedicated knee imaging in the preschool years. Additional skeletal anomalies documented in the literature include metaphyseal

chondrodysplasia with characteristic cupping and fraying of the metaphyses, osteoporosis with reduced bone mineral density and increased fracture risk, osteolytic lesions, scoliosis, and congenital dislocations of the hips. Dental and craniofacial anomalies round out the skeletal phenotype, with microdontia, taurodontism, enamel hypoplasia, delayed tooth eruption, and an exceptionally high caries burden frequently necessitating coordinated pediatric dental care.<sup>17</sup>

Perhaps the most clinically consequential manifestation of Rothmund-Thomson syndrome lies in its profound predisposition to malignancy, a feature that places this condition squarely within the family of inherited cancer susceptibility syndromes. Osteosarcoma represents the most common and best-characterized neoplasm associated with the syndrome, with an estimated cumulative risk approaching thirty percent among individuals harboring biallelic RECQL4 mutations. The median age at osteosarcoma diagnosis in this population is approximately eleven years, notably younger than the typical adolescent peak observed in sporadic cases, and the tumors frequently arise in atypical skeletal locations including the distal femur, proximal tibia, humerus, and, interestingly, the mandible or other craniofacial bones. Histologically, these osteosarcomas are most commonly of the conventional high-grade osteoblastic subtype, though chondroblastic and fibroblastic variants have also been described. The prognosis for RECQL4-associated osteosarcoma appears comparable to that of sporadic osteosarcoma when treated with contemporary multimodal regimens incorporating neoadjuvant chemotherapy, wide surgical resection, and adjuvant therapy, though the underlying genomic instability may theoretically increase susceptibility to chemotherapy-related secondary malignancies.<sup>17,18</sup>

Cutaneous malignancies constitute the second major category of neoplasia in Rothmund-Thomson syndrome, affecting approximately five percent of patients, typically in the second to fourth decades of life. Basal cell carcinoma appears most frequently, often arising within poikilodermatous skin on sun-exposed areas of the face, neck, and dorsal hands, though cases arising on the buttocks or lower back have been documented, suggesting that ultraviolet radiation, while contributory, is not strictly necessary for carcinogenesis in this population. Squamous cell carcinoma and melanoma have also been reported, and multiple primary cutaneous malignancies may develop in the same individual over time. The management of these lesions follows standard oncologic principles, but the diffuse nature of the poikilodermatous field renders complete surveillance challenging and necessitates regular, systematic skin examinations by an experienced dermatologist.<sup>19</sup>

Hematologic abnormalities represent a less frequent but potentially life-threatening component of the Rothmund-Thomson syndrome phenotype. Isolated cytopenias, particularly thrombocytopenia and anemia, have been

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documented in various case series, and some affected individuals progress to more severe bone marrow failure syndromes including myelodysplasia and aplastic anemia. The pathogenesis of hematologic involvement remains incompletely understood, but the role of RECQL4 in maintaining hematopoietic stem cell genomic integrity provides a plausible mechanistic link. Patients presenting with unexplained bruising, pallor, fatigue, or recurrent infections warrant prompt hematologic evaluation including complete blood count with differential and, when indicated, bone marrow aspiration and biopsy.<sup>19</sup>

Additional systemic manifestations, while less consistently observed, contribute meaningfully to the overall disease burden and quality-of-life impairment in affected individuals. Gastrointestinal involvement, including chronic diarrhea, malabsorption, and protein-losing enteropathy, has been reported in a minority of patients, sometimes necessitating nutritional support. Endocrine abnormalities, ranging from hypothyroidism and growth hormone deficiency to precocious puberty and insulin-dependent diabetes mellitus, occur sporadically and should prompt age-appropriate screening. Renal anomalies, including horseshoe kidney, renal agenesis, and medullary cystic disease, have been documented in isolated case reports. Finally, and perhaps most subtly, some individuals with Rothmund-Thomson syndrome manifest features suggestive of premature aging, including early graying of the hair, skin atrophy beyond the poikilodermatous areas, and, in rare instances, premature coronary artery disease or cerebrovascular events.<sup>19</sup>

### **Diagnosis of Rothmund-Thomson Syndrome**

The diagnostic journey for an individual suspected of having Rothmund-Thomson syndrome typically begins at the dermatology or clinical genetics clinic, though in many cases the path to confirmation winds through multiple specialties over several years. There exists no single gold-standard test that establishes the diagnosis in every instance, and the clinician must therefore integrate information gleaned from the physical examination, the detailed patient history, targeted laboratory investigations, and ultimately molecular genetic analysis to arrive at a definitive conclusion. The diagnostic process is further complicated by the considerable phenotypic overlap between Rothmund-Thomson syndrome and several other heritable conditions characterized by poikiloderma, photosensitivity, and skeletal anomalies, making the accurate distinction among these entities a matter of substantial clinical importance.<sup>20</sup>

The clinical diagnostic criteria for Rothmund-Thomson syndrome have evolved over time, with the most widely accepted framework requiring the presence of the characteristic poikiloderma plus at least two of the following major extracutaneous findings: juvenile bilateral cataracts, skeletal abnormalities including radial ray defects or patellar anomalies, short stature, and premature aging features. However, practicing clinicians must recognize that these

criteria were developed before the era of routine molecular testing and that they may fail to capture the full spectrum of individuals with genetically confirmed disease, particularly those with milder or atypical presentations. Indeed, some patients with biallelic RECQL4 mutations present with only poikiloderma and an isolated skeletal abnormality but no cataracts or growth restriction, yet they remain at demonstrable risk for malignancy and therefore warrant the same surveillance protocols as syndromic patients. This observation underscores the limitations of purely phenotype-based diagnostic schemas and argues strongly for the incorporation of molecular testing into the initial evaluation of any child with unexplained poikiloderma, regardless of whether the full clinical criteria are satisfied.<sup>21</sup>

The physical examination of a child suspected to have Rothmund-Thomson syndrome must be systematic and thorough, paying particular attention to several key domains. The cutaneous evaluation should document the precise distribution and morphology of the poikilodermatous changes, noting the presence or absence of associated hyperkeratosis, edema, or photosensitivity. A complete ocular examination including slit-lamp biomicroscopy is essential to detect early lenticular opacities that may not yet be visually significant, as well as to identify other anterior segment abnormalities such as corneal pannus or iris hypoplasia. The skeletal survey, while not strictly diagnostic, provides invaluable information regarding the presence of radial ray defects, patellar abnormalities, metaphyseal dysplasia, and other osseous anomalies that support the clinical diagnosis and guide orthopedic management. Growth parameters should be plotted on standardized growth charts, and the clinician should remain attentive to subtle dysmorphic facial features including a beaked nose, frontal bossing, and micrognathia, which, while not pathognomonic, occur with sufficient frequency to contribute to the diagnostic gestalt.<sup>21</sup>

The laboratory evaluation of suspected Rothmund-Thomson syndrome begins with a thorough hematologic assessment, including a complete blood count with manual differential and examination of peripheral blood smear. The presence of unexplained cytopenias, particularly thrombocytopenia or anemia, raises the possibility of evolving bone marrow failure and warrants further investigation with bone marrow aspiration and biopsy when clinically indicated. Baseline liver and renal function tests, thyroid studies, and fasting glucose levels provide a benchmark against which future changes can be measured and help identify endocrinopathies that may require intervention. Radiographic imaging, beyond the initial skeletal survey, should be guided by clinical symptoms rather than performed routinely, though a baseline chest radiograph and abdominal ultrasound may be considered to exclude occult congenital anomalies.<sup>21</sup>

The definitive diagnosis of Rothmund-Thomson syndrome rests on molecular genetic confirmation, and the approach to

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genetic testing has become increasingly sophisticated over the past decade. For the patient whose clinical presentation strongly suggests the syndrome, the recommended first-tier test is sequencing of the RECQL4 gene, given that biallelic pathogenic variants in this locus account for approximately two-thirds of molecularly confirmed cases. The spectrum of RECQL4 mutations documented in Rothmund-Thomson syndrome is remarkably diverse, encompassing missense and nonsense mutations, small insertions and deletions, and larger genomic rearrangements, with the majority of pathogenic alterations residing within the highly conserved helicase domain. Deletion or duplication analysis via multiplex ligation-dependent probe amplification should be considered when conventional sequencing fails to identify a second pathogenic variant in a patient with strong clinical suspicion, as some affected individuals carry one detectable point mutation in trans with a whole-exon deletion that escapes routine sequencing detection.<sup>21</sup>

For those patients in whom RECQL4 sequencing and deletion analysis return negative results, the diagnostic evaluation proceeds to sequencing of ANAPC1, which encodes a core component of the anaphase-promoting complex. Pathogenic variants in ANAPC1 define Rothmund-Thomson syndrome type 1 and are typically associated with a milder phenotype characterized by poikiloderma, cataracts, and ectodermal dysplasia without the pronounced skeletal abnormalities or malignancy risk observed in RECQL4-associated disease. More recently, the diagnostic algorithm has expanded to include DNA2 and CRIPT sequencing for the small subset of patients who remain without molecular diagnosis after comprehensive evaluation of the canonical genes. DNA2-related disease, now designated as Rothmund-Thomson syndrome type 4, presents with congenital cataracts, microphthalmia, corneal opacities, and hypothyroidism, representing a clinically distinct entity that nonetheless shares the eponymous poikiloderma. The recognition of this genetic heterogeneity has important implications for genetic counseling, as the recurrence risk, prenatal testing options, and cancer surveillance recommendations differ meaningfully among the various molecular subtypes.<sup>21</sup>

The differential diagnosis of Rothmund-Thomson syndrome encompasses a broad array of genodermatoses and acquired conditions that must be systematically excluded before a confident diagnosis can be rendered. Poikiloderma congenitale, the descriptive term for the cutaneous findings, appears in several other heritable disorders including dyskeratosis congenita, Clericuzio-type poikiloderma with neutropenia, and hereditary sclerosing poikiloderma. Dyskeratosis congenita, caused by pathogenic variants in telomere biology genes including TERT, TERC, DKC1, and TINF2, shares the triad of poikiloderma, nail dystrophy, and oral leukoplakia but can be distinguished by the presence of bone marrow failure, pulmonary fibrosis, and liver disease, complications that are not typical features of Rothmund-

Thomson syndrome. Clericuzio syndrome, resulting from biallelic mutations in USB1, presents with poikiloderma, chronic neutropenia, and recurrent infections but lacks the cataracts and skeletal anomalies seen in Rothmund-Thomson syndrome. Kindler syndrome, a subtype of epidermolysis bullosa caused by FERMT1 mutations, features poikiloderma in combination with acral blistering, photosensitivity, and progressive poikiloderma, but mucosal involvement and gingival fragility help distinguish this entity. The Nijmegen breakage syndrome, Bloom syndrome, and ataxia-telangiectasia all include poikiloderma within their phenotypic spectra but can be differentiated by their associated neurologic features, immunodeficiencies, and specific chromosomal instability patterns on cytogenetic testing.<sup>21</sup>

### **Treatment of Rothmund-Thomson Syndrome**

The management of Rothmund-Thomson syndrome is by necessity multidisciplinary, supportive, and tailored to the individual patient's constellation of manifestations, as no disease-modifying therapy currently exists to address the underlying molecular pathology. The treatment paradigm therefore focuses on proactive surveillance for known complications, symptomatic relief of existing symptoms, and the prevention of secondary sequelae through patient and family education. A coordinated care team typically includes a dermatologist, ophthalmologist, orthopedist, pediatric oncologist, clinical geneticist, dentist, endocrinologist, and, when appropriate, a psychologist or social worker to address the psychosocial dimensions of living with a visible and potentially disabling chronic condition.<sup>22</sup>

Cutaneous management represents a cornerstone of supportive care, with sun protection assuming paramount importance given the exacerbating effect of ultraviolet radiation on the poikilodermatous changes. Patients and their families must receive thorough education regarding daily application of broad-spectrum sunscreens with a sun protection factor of at least fifty, preferably those containing physical blocking agents such as zinc oxide or titanium dioxide, which provide more reliable protection than chemical filters in this photosensitive population. Protective clothing, wide-brimmed hats, and ultraviolet-protective sunglasses should become routine components of the patient's wardrobe, and outdoor activities should be scheduled during early morning or late afternoon hours whenever possible to minimize peak ultraviolet exposure. For those patients troubled by the telangiectatic component of the poikiloderma, pulsed dye laser therapy has emerged as a safe and effective intervention, delivering selective photothermolysis to dilated superficial vessels while sparing the surrounding atrophic epidermis. Multiple treatment sessions are typically required to achieve satisfactory cosmetic results, and patients should be counseled that the underlying predisposition to vessel dilation may lead to recurrence over time, necessitating maintenance sessions. Hyperkeratotic lesions of the palms

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and soles respond variably to topical keratolytics including urea-based preparations and salicylic acid ointments, though severe cases may require periodic manual debridement by a podiatrist or dermatologist. Emollients and barrier creams help maintain skin hydration and reduce the risk of fissuring and secondary infection in chronically dry, atrophic skin.<sup>22</sup> Ophthalmologic management in Rothmund-Thomson syndrome requires regular surveillance by a pediatric ophthalmologist experienced in the evaluation of lens abnormalities. For patients who develop progressive cataracts, the decision to proceed with surgical extraction depends on the degree of visual impairment and the patient's age and developmental status. Lensectomy with intraocular lens implantation represents the standard of care in developed countries, though the choice of surgical technique and the timing of implantation must be individualized based on the patient's age, the presence of coexisting ocular anomalies, and the surgeon's experience. Postoperative visual rehabilitation with glasses or contact lenses and amblyopia therapy when indicated maximizes functional outcomes. For those patients with corneal opacities or pannus, management focuses on maintaining ocular surface health with lubricating drops and, in severe cases, considering corneal transplantation. Photophobia, a common complaint even in the absence of significant lens opacity, can be alleviated with tinted lenses and brimmed headwear.<sup>22</sup>

Skeletal management encompasses both the treatment of congenital anomalies and the surveillance for acquired abnormalities. Radial ray defects and other upper extremity reductions may benefit from early referral to a hand surgeon or orthopedic specialist, with surgical reconstruction considered for those patients whose functional impairment is substantial. Osteoporosis and reduced bone mineral density should be addressed with adequate calcium and vitamin D supplementation, weight-bearing exercise as tolerated, and, in severe cases, consultation with a metabolic bone specialist regarding bisphosphonate therapy. The management of patellar abnormalities is primarily supportive, with physical therapy to strengthen surrounding musculature and, for patients with recurrent patellofemoral instability, consideration of patellar realignment procedures. Growth hormone therapy has been administered to some patients with short stature and documented growth hormone deficiency, though the response is variable and long-term follow-up studies are limited.<sup>22</sup>

Cancer surveillance constitutes perhaps the most critical element of the treatment plan, given the substantial malignancy risk conferred by the underlying genomic instability. For children and adolescents with confirmed RECQL4-related Rothmund-Thomson syndrome, consensus guidelines recommend a baseline whole-body magnetic resonance imaging at the time of diagnosis or by age five to six years, followed by annual skeletal surveys or whole-body MRI to screen for occult osteosarcoma. The optimal interval

and modality remain subjects of active debate, as some experts advocate for more frequent imaging given the aggressive nature of osteosarcoma, while others express concern regarding cumulative radiation exposure from serial radiographs and the high false-positive rate of MRI. The author's practice, informed by consultation with pediatric oncologists and radiologists, favors annual whole-body MRI without contrast through age eighteen years, supplemented by prompt radiographic evaluation of any focal bone pain, swelling, or limp that develops between scheduled screenings. Cutaneous cancer surveillance requires annual full-body skin examination by a dermatologist, with particular attention to the poikilodermatous areas and any enlarging or changing pigmented lesions. The threshold for biopsy should be lower than in the general population, given the increased risk of malignancy and the atypical presentations that cutaneous neoplasms may adopt in this setting. Patients should be counseled regarding self-skin examination and instructed to report any new or changing lesions promptly. Hematologic surveillance through annual complete blood counts helps detect early cytopenias or myelodysplasia, with bone marrow evaluation reserved for those patients who develop unexplained persistent abnormalities.<sup>22</sup>

Dental management requires early and ongoing involvement of a pediatric dentist familiar with the care of ectodermal dysplasia patients. Preventive measures including topical fluoride application, dental sealants, and meticulous oral hygiene instruction reduce the risk of caries in patients with enamel hypoplasia. Regular panoramic radiographs screen for dental anomalies and allow for timely extraction of retained primary teeth or orthodontic referral when needed. Anesthesia considerations are important for those patients requiring surgical dental extractions or other procedures, as the underlying genomic instability does not contraindicate the use of standard anesthetic agents but does warrant attention to airway anatomy and the potential for difficult intubation in patients with mandibular hypoplasia.<sup>22</sup>

### **CONCLUSIONS**

Rothmund-Thomson syndrome represents a fascinating yet sobering example of how a single defective molecular pathway can produce a cascade of clinical consequences affecting nearly every organ system. The elucidation of RECQL4, ANAPC1, DNA2, and CRIPT as causative genes has transformed our understanding of this condition from a purely descriptive clinicopathological entity into a molecularly defined disorder with clear genotype-phenotype correlations that inform prognosis and guide surveillance. However, substantial knowledge gaps remain, and the thirty percent of affected individuals who continue to lack a molecular diagnosis following comprehensive genetic testing represent both a clinical challenge and a research opportunity that should drive continued efforts at gene discovery.

# Rothmund-Thomson Syndrome Revisited: Expanding the Genotypic Spectrum, Deciphering RECQL4-Related Pathomechanisms, And Redefining Long-Term Surveillance Strategies for An Underrecognized Genodermatosis

From a practical clinical perspective, the most important message for practicing physicians is that early recognition saves lives. The infant with unexplained facial erythema that fails to respond to standard treatments, particularly when accompanied by growth restriction or skeletal anomalies, deserves consideration of Rothmund-Thomson syndrome and referral for genetic evaluation. The diagnosis, once confirmed, transforms the patient from a collection of seemingly unrelated symptoms into an individual with a predictable natural history and a defined set of surveillance needs that, when faithfully implemented, can significantly reduce morbidity and mortality. The prognosis for individuals with Rothmund-Thomson syndrome has improved meaningfully over recent decades, not because of any breakthrough therapy but because of heightened awareness, earlier diagnosis, and more systematic surveillance for treatable complications.

Looking forward, the next decade promises continued advances in our understanding of this rare condition. The development of patient registries and natural history studies will provide the longitudinal data needed to refine surveillance protocols and to identify prognostic biomarkers that distinguish patients at highest risk for specific complications. The application of advanced genomic technologies, including optical genome mapping and long-read sequencing, may resolve the diagnostic odyssey for those patients who remain without molecular diagnosis after conventional testing. And while disease-modifying therapies remain a distant hope, the elucidation of RECQL4 function in DNA replication and repair raises the possibility that targeted modulation of the DNA damage response might someday ameliorate the cellular fragility that underlies the clinical phenotype. Until that day arrives, the clinician's most powerful tools remain a high index of suspicion, a thorough understanding of the syndrome's protean manifestations, and a commitment to the multidisciplinary, lifelong care that these complex patients require and deserve.

## REFERENCES

- I. Ho SKL, Tong GPY, Leung LT, Cheng SSW, Fu ECH, Lo IFM, et al. RECQL4-related Rothmund-Thomson syndrome: A case series and literature review. *Cancer Genet.* 2025;292-293:131-136.
- II. Wang LL, Plon SE. Rothmund-Thomson Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1999 Oct 6 [updated 2020 Jun 4].
- III. Larizza L, Roversi G, Volpi L. Rothmund-Thomson syndrome. *Orphanet J Rare Dis.* 2010;5:2.
- IV. Martins DJ, Di Lazzaro Filho R, Bertola DR, Hoch NC. Rothmund-Thomson syndrome, a disorder far from solved. *Front Aging.* 2023;4:1292691.
- V. Vennos EM, James WD. Rothmund-Thomson syndrome: review of the world literature. *J Am Acad Dermatol.* 1992;27(5 Pt 1):750-762.
- VI. Orphanet. Rothmund-Thomson syndrome [Internet]. Paris: Orphanet; 2025 [cited 2026 May 11]. Available from: <https://www.orpha.net/en/disease/detail/2909>
- VII. Piquero-Casals J, Okubo AY, Nico MM. Rothmund-Thomson syndrome in three siblings and development of cutaneous squamous cell carcinoma. *Pediatr Dermatol.* 2002;19(4):312-316.
- VIII. Hafner J, Trueb RM. Rothmund-Thomson syndrome. In: Hafner J, Trueb RM, editors. *Management of Rare Skin Diseases.* Berlin: Springer; 2020. p. 145-152.
- IX. Potozkin JR, Geronemus RG. Treatment of the poikilodermatous component of the Rothmund-Thomson syndrome with the flashlamp-pumped pulsed dye laser: a case report. *Pediatr Dermatol.* 1991;8(2):162-165.
- X. Kaufmann S, Jones KL, Peabody J, Tolo V. Growth hormone deficiency in the Rothmund-Thomson syndrome. *Am J Med Genet.* 1985;23(4):861-868.
- XI. Unraveling syndrome-driven osteosarcoma: genetic insights and therapeutic frontiers. *Orphanet J Rare Dis.* 2026;21:45.
- XII. Porter WM, Hardman CM, Creamer D, Morar N, Whittaker SJ. Haematological disease in siblings with Rothmund-Thomson syndrome. *Clin Exp Dermatol.* 1999;24(6):452-454.
- XIII. Pianigiani E, De Aloe G, Andreassi A, Fimiani M. Rothmund-Thomson syndrome (Thomson-type) and myelodysplasia. *Pediatr Dermatol.* 2001;18(5):422-425.
- XIV. Simons A, Kallenberg CGM, de Vries EGE. Rothmund-Thomson syndrome and malignant disease. A case report and review of the literature. *Clin Exp Dermatol.* 1982;7(5):455-460.
- XV. Mackay HL, Stone HR, Ellis K, Ronson GE, Walker AK, Starowicz K, et al. USP50 suppresses alternative RecQ helicase use and deleterious DNA2 activity during replication. *bioRxiv.* 2024.
- XVI. Alsabbagh MM. Rothmund-Thomson syndrome: A review of clinical and molecular aspects. *J Dermatol Dermatol Surg.* 2020;24(1):5-11.
- XVII. Gilissen C, Hoischen A, Brunner HG, Veltman JA. Disease gene identification strategies for exome sequencing. *Eur J Hum Genet.* 2012;20(5):490-497.
- XVIII. Ripperger T, Bielack SS, Borkhardt A, Brecht IB, Burkhardt B, Calaminus G, et al. Update on Recommendations for Cancer Screening and Surveillance in Children with Genomic Instability Disorders. *Clin Cancer Res.* 2024;30(22):5009-5020.

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- XIX. Colombo EA, Fontana L, Roversi G, Catusi I, Garzo M, Baldo C, et al. ANAPC1 mutations cause a Rothmund-Thomson syndrome-like condition. Clin Genet. 2019;96(5):418-428.
- XX. Sznajder Y, Saragoni C, Garavelli L, Van Maldergem L. Atypical Rothmund-Thomson syndrome in a patient with compound heterozygous mutations in RECQL4 gene and phenotypic features in RECQL4 syndromes. Eur J Pediatr. 2008;167(2):175-181.
- XXI. Simon T, Kohlschuetter A, Bielack S, Langer T. Rothmund-Thomson syndrome and osteosarcoma: a review of the literature and report of two cases. Klin Padiatr. 2012;224(4):256-260.
- XXII. Mills KD, Ferguson DO, Alt FW. The role of DNA breaks in genomic instability and tumorigenesis. Immunol Rev. 2003;194:77-95.