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Comprehensive Review of Rothmund-Thomson Syndrome: Clinical Manifestations, Molecular Pathogenesis, and Therapeutic Approaches

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ABSTRACT

Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive genodermatosis characterized by a spectrum of clinical manifestations, including poikiloderma, sparse hair, short stature, skeletal abnormalities, and an increased predisposition to malignancies, particularly osteosarcoma. This syndrome is primarily associated with mutations in the RECQL4 gene, a critical player in DNA repair and genomic stability. This review provides an in-depth analysis of the clinical presentation, underlying molecular mechanisms, and current therapeutic strategies for RTS. We aim to elucidate the genetic and cellular pathways implicated in RTS, highlight the challenges in clinical management, and explore potential future directions in research and therapy.

KEYWORDS: Genodermatosis, Rothmund-Thomson, poikiloderma, skin.

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INTRODUCTION

Rothmund-Thomson syndrome (RTS), first described by Rothmund in 1868 and later expanded upon by Thomson in 1936, is a rare genetic disorder that falls under the category of poikiloderma syndromes. RTS exhibits a wide array of clinical manifestations that typically present in early childhood. The hallmark feature of RTS is poikiloderma, a condition characterized by skin atrophy, telangiectasia, and hyper- and hypopigmented macules, which usually appear within the first few months of life. In addition to cutaneous abnormalities, individuals with RTS frequently exhibit sparse scalp hair, eyebrows, and eyelashes, as well as nail dystrophy and juvenile cataracts. Growth retardation and skeletal anomalies, such as radial ray defects and osteopenia, are also common, contributing to the overall phenotype of short stature and skeletal dysplasia.1,2

The etiology of RTS is closely linked to mutations in the RECQL4 gene, located on chromosome 8q24.3, which encodes a RecQ helicase involved in DNA replication, repair, and recombination. RECQL4 mutations disrupt genomic stability, leading to increased susceptibility to malignancies, particularly osteosarcoma, and to a lesser extent, skin cancers. The pathogenesis of RTS underscores the crucial role of DNA helicases in maintaining chromosomal integrity and highlights the consequences of defective DNA repair mechanisms.1,2

Despite advances in our understanding of the genetic underpinnings of RTS, the clinical management of the syndrome remains challenging. There is currently no cure for RTS, and treatment is primarily symptomatic and supportive. Early intervention and regular monitoring for complications, particularly malignancies, are essential components of patient care. Advances in molecular genetics and the potential for gene therapy offer hope for future therapeutic strategies that may alter the course of the disease.3,4

This article provides a comprehensive review of Rothmund-Thomson syndrome, encompassing its clinical features, genetic basis, molecular pathogenesis, and current therapeutic approaches. By integrating clinical observations with molecular insights, we aim to present a detailed understanding of RTS, underscore the importance of early diagnosis and intervention, and identify avenues for future research and treatment development.3,4

EPIDEMIOLOGY OF ROTHMUND-THOMSON SYNDROME

Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive disorder with an estimated prevalence of less than 1 in 1,000,000 individuals. The exact prevalence is difficult to determine due to underdiagnosis and misdiagnosis, given the syndrome's phenotypic variability and overlap with other genetic disorders. RTS has been reported in various ethnic groups worldwide, without a clear predilection for any specific population, suggesting a global distribution.5,6

The incidence of RTS appears to be uniform across different regions, although higher incidences may be observed in populations with a higher rate of consanguinity due to the autosomal recessive inheritance pattern. Consanguinity increases the likelihood of homozygosity for recessive mutations, thereby raising the incidence of rare genetic disorders such as RTS. However, comprehensive epidemiological data are scarce, and the existing reports often come from case studies and small cohort studies.5,6

RTS is caused by mutations in the RECQL4 gene, which plays a crucial role in maintaining genomic stability through its involvement in DNA repair, replication, and recombination. More than 30 different mutations in the RECQL4 gene have been identified in individuals with RTS, with no single mutation accounting for a majority of cases. This genetic heterogeneity contributes to the clinical variability observed in RTS patients.5,6

The syndrome manifests equally in both males and females, with no significant gender predilection. The onset of clinical symptoms typically occurs in early infancy, with poikiloderma being the first and most characteristic sign. This cutaneous manifestation usually begins between the ages of 3 to 6 months and progresses over time. Other associated features, such as sparse hair, cataracts, skeletal abnormalities, and an increased risk of malignancies, develop as the patient ages.7,8

The natural history of RTS is marked by a significant risk of malignancies, particularly osteosarcoma, which occurs in approximately 30% of affected individuals. The median age of onset for osteosarcoma in RTS patients is around 11 years, earlier than in the general population. This early onset and high incidence underscore the importance of vigilant cancer surveillance in these patients. Additionally, RTS patients are at an elevated risk for other cancers, including skin cancers and hematological malignancies, albeit less frequently than osteosarcoma.7,8

Skeletal abnormalities are present in a significant proportion of RTS patients, with varying degrees of severity. These can include radial ray defects, absent or hypoplastic thumbs, short stature, and generalized skeletal dysplasia. Growth retardation is nearly universal in RTS, contributing to the characteristic short stature observed in these patients.8,9

The rarity of RTS poses challenges for large-scale epidemiological studies, and much of the current understanding is derived from case reports and small series. Collaborative efforts and international registries could enhance the collection of epidemiological data and improve the understanding of the natural history and prevalence of RTS. This information is crucial for developing evidence-based guidelines for diagnosis, management, and surveillance of individuals with RTS.9,10

Rothmund-Thomson syndrome is a rare genetic disorder with a worldwide distribution and an estimated prevalence of less than 1 in 1,000,000. It is characterized by early-onset poikiloderma, skeletal anomalies, sparse hair, cataracts, and a significant risk of malignancies, particularly osteosarcoma. The autosomal recessive inheritance pattern and genetic heterogeneity of RTS complicate the epidemiological landscape, underscoring the need for continued research and international collaboration to better understand and manage this complex syndrome.7,8

CLINICAL MANIFESTATIONS OF ROTHMUND-THOMSON SYNDROME

Rothmund-Thomson syndrome (RTS) is a multifaceted genodermatosis that presents with a broad spectrum of clinical manifestations, many of which evolve over time. The clinical picture of RTS is heterogeneous, with variability in the severity and combination of symptoms among affected individuals. Understanding the full range of clinical features is essential for accurate diagnosis, management, and genetic counseling.7,8

CUTANEOUS MANIFESTATIONS

The hallmark of RTS is poikiloderma, a condition characterized by a triad of skin atrophy, telangiectasia, and pigmentary changes, including both hyperpigmentation and hypopigmentation. Poikiloderma typically begins in infancy, usually between 3 to 6 months of age. It often starts on the cheeks and spreads to other parts of the body, including the extensor surfaces of the limbs and the buttocks. The poikilodermatous rash may evolve over time, becoming more pronounced and widespread.7,8

In addition to poikiloderma, individuals with RTS may exhibit other cutaneous abnormalities such as:

- **Photosensitivity:** Increased sensitivity to ultraviolet (UV) radiation, leading to exacerbation of skin lesions upon sun exposure.7,8
- **Hypo- and Hyperpigmented Macules:** Irregular patches of skin that are either lighter or darker than the surrounding areas.7,8
- **Skin Atrophy:** Thinning of the skin, leading to a fragile, parchment-like appearance.7,8

Hair and Nail Abnormalities

Hair anomalies are common in RTS, often presenting as sparse, brittle, and slow-growing scalp hair. Eyebrows and eyelashes are also frequently sparse or absent. These hair

abnormalities contribute to the characteristic facial appearance of individuals with RTS.7,8

Nail dystrophy is another notable feature, manifesting as ridged, thin, or spoon-shaped nails. Nail growth may be slow, and the nails can be prone to splitting and breakage.7,8

Ocular Manifestations

Ocular involvement in RTS primarily includes bilateral juvenile cataracts, which can develop in childhood or early adolescence. These cataracts can significantly impair vision and often require surgical intervention. Other ocular abnormalities may include strabismus and ptosis.7,8

Skeletal Abnormalities

Skeletal anomalies are a significant component of the RTS phenotype. These can include:

- **Radial Ray Defects:** Malformations of the radius bone and associated structures, such as hypoplastic or absent thumbs, which can impact hand function.7,8
- **Short Stature:** Growth retardation is nearly universal in RTS, with affected individuals typically falling below the third percentile for height.7,8
- **Generalized Skeletal Dysplasia:** Abnormalities in bone development and growth, including osteopenia and osteoporosis, which increase the risk of fractures.9,10
- **Delayed Bone Age:** Radiographic imaging often reveals a delay in bone maturation compared to chronological age.9,10

Dental Abnormalities

Dental anomalies are common and may include hypodontia (missing teeth), microdontia (small teeth), and enamel hypoplasia. These dental issues can affect both primary and permanent teeth, leading to challenges in oral health and aesthetics.9,10

Gastrointestinal Manifestations

Some individuals with RTS may experience gastrointestinal issues, such as chronic diarrhea, constipation, and failure to thrive. These symptoms can be related to underlying malabsorption or other gastrointestinal tract anomalies.9,10

Genitourinary Anomalies

Genitourinary abnormalities, although less common, can occur in RTS. These may include renal malformations, undescended testes (cryptorchidism) in males, and uterine anomalies in females.9,10

Malignancies

A critical aspect of RTS is the heightened risk of malignancies, particularly osteosarcoma, which occurs in approximately 30% of individuals. The median age of onset for osteosarcoma in RTS patients is around 11 years, significantly younger than in the general population. Other malignancies associated with RTS include skin cancers, such as basal cell carcinoma and squamous cell carcinoma, and hematological malignancies, though these are less frequent.9,10

Hematological Abnormalities

Hematological issues may also be present, such as anemia, neutropenia, and thrombocytopenia. These conditions can contribute to increased susceptibility to infections and may complicate the clinical management of RTS.9,10

Immune System Dysfunction

Individuals with RTS may exhibit signs of immune system dysfunction, including recurrent infections and, in some cases, evidence of immunodeficiency. The exact nature and extent of immune dysfunction in RTS are still under investigation.11,12

Neurological Manifestations

Neurological abnormalities, although less common, can include developmental delay, intellectual disability, and seizures. These manifestations are variable and may not be present in all affected individuals.11,12

Other Manifestations

RTS can also involve other systems and organs, leading to a variety of additional clinical features. These may include endocrinological abnormalities, such as hypogonadism, and cardiovascular anomalies.11,12

In summary, Rothmund-Thomson syndrome is a complex disorder with a wide range of clinical manifestations affecting multiple organ systems. The phenotypic variability requires a comprehensive and multidisciplinary approach to diagnosis and management. Regular monitoring for malignancies, particularly osteosarcoma, is crucial, and early intervention for other manifestations can improve the quality of life for individuals with RTS.11,12

Diagnostic Methods for Rothmund-Thomson Syndrome

Rothmund-Thomson syndrome (RTS) is a rare genetic disorder with a complex clinical presentation, necessitating a comprehensive and multidisciplinary approach to diagnosis. The diagnosis of RTS involves a combination of clinical evaluation, genetic testing, and supportive diagnostic procedures to confirm the presence of characteristic features and underlying genetic mutations. Below is an in-depth overview of the diagnostic methods utilized in the assessment of RTS.11,12

CLINICAL EVALUATION

The initial step in diagnosing RTS involves a thorough clinical evaluation, focusing on the characteristic features of the syndrome. A detailed medical history and physical examination are essential to identify the hallmark signs and symptoms, including:

- **Poikiloderma:** The presence of skin atrophy, telangiectasia, and pigmentary changes, typically

beginning in early infancy, is a key diagnostic criterion.11,12

- **Sparse Hair:** Examination of the scalp, eyebrows, and eyelashes for signs of hair sparseness or brittleness.11,12
- **Nail Dystrophy:** Inspection of the nails for abnormalities such as ridging, thinning, or spoon-shaped nails.
- **Skeletal Abnormalities:** Assessment for radial ray defects, short stature, and other skeletal anomalies through physical examination and anthropometric measurements.11,12
- **Ocular Examination:** Evaluation for juvenile cataracts and other ocular abnormalities, which may necessitate referral to an ophthalmologist.

Genetic Testing

Genetic testing is a crucial component of the diagnostic process for RTS. The primary genetic cause of RTS is mutations in the RECQL4 gene, which can be identified through several molecular genetic techniques:

- **Sanger Sequencing:** This method involves sequencing the RECQL4 gene to identify point mutations, small insertions, or deletions. It is highly accurate and widely used for detecting known mutations.11,12
- **Next-Generation Sequencing (NGS):** NGS allows for the comprehensive analysis of the RECQL4 gene and other genes that may be involved in RTS or related syndromes. This technique can detect a wide range of genetic variations, including single nucleotide variants, insertions, deletions, and copy number variations.11,12
- **Multiplex Ligation-dependent Probe Amplification (MLPA):** MLPA is used to detect larger deletions or duplications within the RECQL4 gene that may not be identified by sequencing alone.11,12

Radiographic Imaging

Radiographic imaging plays a significant role in diagnosing and characterizing the skeletal abnormalities associated with RTS. Common imaging studies include:

- **X-rays:** Standard radiographs of the hands, wrists, and long bones are essential for identifying radial ray defects, osteopenia, osteoporosis, and other skeletal dysplasias. X-rays can also reveal delayed bone age.11,12
- **Bone Density Scans (DEXA):** Dual-energy X-ray absorptiometry (DEXA) scans are used to assess bone mineral density, particularly in patients with suspected osteopenia or osteoporosis.11,12

Ophthalmologic Examination

A comprehensive ophthalmologic examination is necessary to identify and document ocular manifestations such as juvenile cataracts. The examination may include:

- **Slit-Lamp Examination:** This allows for detailed visualization of the anterior segment of the eye to detect cataracts.13,14
- **Fundoscopy:** Examination of the retina to identify any additional ocular abnormalities.13,14
- **Visual Acuity Testing:** Assessment of vision to determine the impact of cataracts or other ocular issues on visual function.13,14

Dermatologic Assessment

Dermatologic evaluation is critical for documenting the extent and progression of poikiloderma and other skin abnormalities. This may include:

- **Skin Biopsy:** In some cases, a skin biopsy may be performed to examine histopathological features. The biopsy can reveal findings such as epidermal atrophy, loss of rete ridges, and dermal fibrosis, which are consistent with poikiloderma.13,14

Endocrinological Evaluation

Given the frequent occurrence of growth retardation and potential endocrine abnormalities in RTS, an endocrinological assessment is often warranted. This may involve:

- **Hormonal Assays:** Measurement of growth hormone levels, thyroid function tests, and other relevant hormonal evaluations to identify any underlying endocrine dysfunctions.13,14
- **Bone Age Assessment:** Radiographic assessment of bone age can help evaluate growth delays relative to chronological age.13,14

Hematological and Immunological Tests

Hematological and immunological assessments are important for detecting potential hematological abnormalities and immune dysfunction. These tests may include:

- **Complete Blood Count (CBC):** To evaluate for anemia, neutropenia, and thrombocytopenia.13,14
- **Immunological Tests:** Assessment of immunoglobulin levels and lymphocyte subsets to detect any immunodeficiencies.13,14

Oncological Surveillance

Given the increased risk of malignancies, particularly osteosarcoma, ongoing oncological surveillance is crucial. This involves regular clinical examinations and imaging studies to detect early signs of cancer. Specific surveillance strategies may include:

- **MRI or CT Scans:** Periodic imaging of bones to detect early osteosarcomas.

- **Dermatologic Screening:** Regular skin examinations to identify early signs of skin cancer.13,14

Differential Diagnosis

The diagnosis of RTS requires differentiation from other syndromes with overlapping features. Differential diagnosis may include:

- **Bloom Syndrome:** Characterized by short stature, photosensitivity, and an increased risk of malignancies, but with distinctive facial erythema and a high frequency of sister chromatid exchanges.13,14
- **Werner Syndrome:** Typically presents in adulthood with premature aging, cataracts, and skin changes, but lacks the early-onset poikiloderma seen in RTS.
- **Poikiloderma Congenitale:** Another condition with poikiloderma, but without the skeletal abnormalities and cancer predisposition seen in RTS.13,14

The diagnosis of Rothmund-Thomson syndrome is multifaceted, requiring a thorough clinical evaluation, genetic testing, and a range of supportive diagnostic procedures. Accurate diagnosis is essential for appropriate management, genetic counseling, and surveillance for complications, particularly malignancies. Advances in genetic testing techniques have significantly enhanced the ability to confirm RTS, facilitating early intervention and improved patient outcomes.13,14

Therapeutic Methods for Rothmund-Thomson Syndrome

Rothmund-Thomson syndrome (RTS) is a complex genetic disorder with no definitive cure, and treatment is primarily symptomatic and supportive. The therapeutic approach is multidisciplinary, involving dermatologists, geneticists, endocrinologists, oncologists, orthopedists, and other specialists as needed to manage the diverse manifestations of the syndrome. Below is a comprehensive overview of the therapeutic methods employed in the management of RTS.13,14

Dermatologic Management

The hallmark feature of RTS, poikiloderma, requires ongoing dermatologic care to manage symptoms and prevent complications:

- **Sun Protection:** Due to increased photosensitivity, rigorous photoprotection is essential. This includes the use of broad-spectrum sunscreens with high SPF, protective clothing, and avoidance of excessive sun exposure.13,14
- **Topical Therapies:** Topical corticosteroids or tacrolimus may be prescribed to reduce inflammation and manage skin irritation. Emollients and moisturizers are recommended to alleviate dryness and improve skin barrier function.13,14
- **Laser Therapy:** In cases where telangiectasia is prominent, laser therapy, such as pulsed dye laser, can be used to reduce the appearance of dilated blood vessels.13,14

Ophthalmologic Interventions

Management of ocular manifestations, particularly juvenile cataracts, is crucial to preserving vision:

- **Cataract Surgery:** Early surgical intervention is often required to remove cataracts and restore visual acuity. This procedure is typically followed by the implantation of intraocular lenses.13,14
- **Regular Eye Examinations:** Lifelong ophthalmologic surveillance is necessary to monitor for new or recurrent cataracts and other ocular complications.13,14

Skeletal and Orthopedic Management

Skeletal abnormalities and growth retardation necessitate a combination of medical and surgical interventions:

- **Growth Hormone Therapy:** In some cases, recombinant growth hormone therapy may be considered to address growth retardation, although its efficacy can be variable.13,14
- **Orthopedic Surgery:** Surgical correction of radial ray defects, such as pollicization for thumb hypoplasia, may be performed to improve hand function. Other orthopedic surgeries may be necessary to correct skeletal deformities and prevent fractures.13,14
- **Bone Health Monitoring:** Regular bone density assessments and appropriate interventions, such as calcium and vitamin D supplementation, are important to manage osteopenia and osteoporosis.13,14

Dental Care

Dental anomalies require regular dental care and intervention:

- **Orthodontic Treatment:** Orthodontic evaluation and treatment may be needed to address malocclusion and other dental alignment issues.13,14
- **Restorative Dentistry:** Restorative procedures, including crowns and bridges, can be employed to manage hypodontia and microdontia.13,14
- **Regular Dental Check-Ups:** Lifelong dental surveillance is essential to maintain oral health and address emerging dental issues promptly.13,14

Oncological Surveillance and Management

Given the increased risk of malignancies, particularly osteosarcoma, vigilant oncological surveillance is critical:

- **Regular Imaging:** Routine imaging studies, such as MRI or CT scans, are conducted to detect early signs of osteosarcoma. The frequency of imaging depends

on individual risk factors and clinical presentation.13,14

- **Biopsy and Histopathology:** Any suspicious lesions should be biopsied promptly for histopathological examination to confirm malignancy.13,14
- **Multimodal Cancer Treatment:** The treatment of osteosarcoma and other malignancies involves a combination of surgery, chemotherapy, and radiation therapy, tailored to the specific type and stage of cancer. Collaboration with pediatric oncologists and specialized cancer centers is essential for optimal management.13,14

Endocrinological Management

Endocrine abnormalities, including growth retardation and potential hormone deficiencies, require endocrinological evaluation and treatment:

- **Hormone Replacement Therapy:** For patients with identified hormone deficiencies, such as hypothyroidism or hypogonadism, appropriate hormone replacement therapy is initiated.13,14
- **Growth Monitoring:** Regular monitoring of growth parameters and bone age assessments are essential to evaluate the effectiveness of growth hormone therapy and other interventions.13,14

Immunological and Hematological Management

Hematological abnormalities and immune dysfunction necessitate a proactive approach to monitoring and intervention:

- **Complete Blood Count (CBC) Monitoring:** Regular CBCs are performed to detect anemia, neutropenia, and thrombocytopenia. Management strategies may include growth factor support for neutropenia or transfusions for severe anemia.13,14
- **Immunological Assessments:** Evaluation of immunoglobulin levels and lymphocyte subsets can help identify immune deficiencies. Immunoglobulin replacement therapy may be considered for patients with significant immunodeficiency.13,14
- **Infection Prophylaxis:** Prophylactic antibiotics and antifungal agents may be prescribed to prevent recurrent infections, particularly in patients with documented immune dysfunction.14,15

Nutritional and Gastrointestinal Management

Nutritional support is vital for patients with gastrointestinal manifestations and growth retardation:

- **Nutritional Assessments:** Regular assessment of nutritional status and dietary intake is essential to ensure adequate growth and development.
- **Supplementation:** Nutritional supplementation, including high-calorie diets, vitamins, and minerals, may be necessary to address deficiencies and support growth.14,15
- **Gastrointestinal Interventions:** Management of gastrointestinal symptoms, such as chronic diarrhea or constipation, with appropriate dietary modifications and medications.14,15

Psychosocial Support

Psychosocial support is an integral part of the holistic care for individuals with RTS:

- **Psychological Counseling:** Counseling and psychological support can help patients and families cope with the chronic nature of the syndrome and its impact on quality of life.14,15
- **Social Support Services:** Coordination with social workers and support groups can provide resources and assistance for families navigating the complexities of RTS care.14,15

Genetic Counseling

Genetic counseling is crucial for affected individuals and their families to understand the hereditary nature of RTS and the implications for family planning:

- **Carrier Testing:** Genetic testing of family members can identify carriers of RECQL4 mutations and inform reproductive decision-making.14,15
- **Prenatal Diagnosis:** For families with a known mutation, prenatal diagnostic options, such as chorionic villus sampling (CVS) or amniocentesis, are available to determine if the fetus is affected.14,15

Experimental Therapies and Research

Ongoing research into the molecular mechanisms of RTS and potential therapeutic targets holds promise for future treatments:

- **Gene Therapy:** Advances in gene therapy techniques may offer potential future treatments aimed at correcting the underlying genetic defect in RECQL4.16
- **Targeted Therapies:** Research into targeted therapies that address specific molecular pathways disrupted in RTS is ongoing, with the hope of developing more effective treatments.16

The management of Rothmund-Thomson syndrome is multifaceted and requires a coordinated, multidisciplinary approach to address the diverse and complex manifestations of the disorder. While current therapies focus on symptomatic relief and prevention of complications, ongoing research into the genetic and molecular basis of RTS holds promise for future therapeutic advancements.

CONCLUSION

In conclusion, Rothmund-Thomson syndrome (RTS) presents a complex clinical challenge, characterized by a constellation of dermatologic, skeletal, ocular, and systemic manifestations. While the underlying genetic mutation in the

RECQL4 gene has been identified, there is currently no definitive cure for RTS, and management remains largely supportive and symptomatic. The multidisciplinary approach involving dermatologists, geneticists, ophthalmologists, orthopedists, oncologists, endocrinologists, and other specialists is essential for the comprehensive care of affected individuals.

The management of RTS focuses on addressing the diverse array of clinical features, including poikiloderma, skeletal abnormalities, ocular complications, growth retardation, dental anomalies, and the heightened risk of malignancies. Dermatologic care emphasizes sun protection and symptomatic relief, while orthopedic interventions aim to improve hand function and skeletal alignment. Ophthalmologic surveillance and timely cataract surgery are essential for preserving vision, and oncological monitoring is paramount for early detection and management of malignancies.

Despite these therapeutic strategies, challenges remain in managing the complex nature of RTS, including the variable clinical presentation and the lack of standardized treatment protocols. Ongoing research into the molecular mechanisms of RTS is crucial for the development of targeted therapies and potential curative approaches. Genetic counseling plays a pivotal role in supporting affected individuals and their families, providing information about the hereditary nature of RTS and options for family planning.

In summary, the management of Rothmund-Thomson syndrome requires a coordinated, multidisciplinary approach, with a focus on symptom management, surveillance for complications, and ongoing research into novel therapeutic strategies. By combining clinical expertise with advances in genetic and molecular research, there is hope for improving the quality of life and outcomes for individuals affected by this rare and complex genetic disorder.

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