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Rothmund-Thomson Syndrome

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Summary

Clinical characteristics

Rothmund-Thomson syndrome (RTS) is characterized by a rash that progresses to poikiloderma; sparse hair, eyelashes, and/or eyebrows; small size; skeletal and dental abnormalities; juvenile cataracts; and an increased risk for cancer, especially osteosarcoma. A variety of benign and malignant hematologic abnormalities have been reported in affected individuals. The rash of RTS typically develops between ages three and six months (occasionally as late as age two years) as erythema, swelling, and blistering on the face, subsequently spreading to the buttocks and extremities. The rash evolves over months to years into the chronic pattern of reticulated hypo- and hyperpigmentation, telangiectasias, and punctate atrophy (collectively known as poikiloderma) that persist throughout life. Hyperkeratotic lesions occur in approximately one third of individuals. Skeletal abnormalities can include radial ray defects, ulnar defects, absent or hypoplastic patella, and osteopenia.

Diagnosis/testing

The diagnosis of RTS is established by clinical findings (in particular, the characteristic rash) and/or the identification of biallelic pathogenic variants in *ANAPC1* or *RECQL4* on molecular genetic testing.

Management

Treatment of manifestations: Pulsed dye laser to the telangiectatic component of the rash for cosmetic management; surgical removal of cataracts; standard treatment for cancer and/or hematologic concerns.

Surveillance: Annual general physical, dermatologic, and eye examination; monitoring of health and growth, skin for lesions with unusual color or texture, for cataracts. Prompt skeletal radiographic examination when clinical suspicion of osteosarcoma is present (bone pain, swelling or enlarging lesion on a limb); however, surveillance screening for osteosarcoma is not routinely recommended.

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Agents/circumstances to avoid: Excessive exposure to heat or sunlight; growth hormone for those with short stature with normal growth hormone levels.

Genetic counseling

RTS is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible if the *ANAPC1* or *RECQL4* pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Rothmund-Thomson syndrome (RTS) **should be suspected** in individuals with the classic rash of RTS.

Acute phase

- Starts in infancy, usually between ages three and six months
- Erythema on the cheeks and face
- Spreads to involve the extensor surfaces of the extremities
- Typically sparing of the trunk and abdomen; possible involvement of the buttocks

Chronic phase

- Gradually develops over a period of months to years
- Reticulated hyper- and hypopigmentation, telangiectasias, and areas of punctate atrophy (i.e., poikiloderma)
- Persists throughout life

If the rash is atypical (either in appearance, distribution, or pattern of onset and spread), a diagnosis of *probable* RTS can be made if two of the following additional features of RTS are present:

- Sparse scalp hair, eyelashes, and/or eyebrows
- Small size, usually symmetric for height and weight
- Gastrointestinal disturbance as young children, usually consisting of chronic vomiting and diarrhea, sometimes requiring feeding tubes
- Dental abnormalities that include rudimentary or hypoplastic teeth, enamel defects, delayed tooth eruption
- Nail abnormalities such as dysplastic or poorly formed nails
- Hyperkeratosis, particularly of the soles of the feet
- Cataracts, usually juvenile, bilateral
- Skeletal abnormalities including radial ray defects, ulnar defects, absent or hypoplastic patella, osteopenia, abnormal trabeculation
- Cancers including skin cancers (basal cell carcinoma and squamous cell carcinoma) and in particular osteosarcoma

Establishing the Diagnosis

The diagnosis of RTS **is established** in a proband with the classic rash of RTS with onset, spread, and appearance described above and/or biallelic pathogenic variants in *ANAPC1* or *RECQL4* identified on molecular genetic testing (see Table 1).

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

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

Option 1

When the phenotypic findings suggest the diagnosis of Rothmund-Thomson syndrome, molecular genetic testing approaches can include use of a **multigene panel** or **single gene testing**.

A multigene panel that includes *ANAPC1* and *RECQL4* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Note: As *ANAPC1* has only recently been identified as a gene associated with RTS [Ajeawung et al 2019], the ordering clinician may need to contact the laboratory to request testing of this gene.

Single-gene testing. If a multigene panel is not available, single-gene testing could be performed:

- If the individual presents with skeletal abnormalities or osteosarcoma, recommend starting with *RECQL4* testing.
- For individuals with early-onset juvenile cataracts without skeletal defects or osteosarcoma, recommend starting with *ANAPC1* testing.

Sequence analysis of either gene can detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no pathogenic variant is detected in either gene by the sequencing method used, gene-targeted deletion/duplication analysis may be considered; however, no exon or whole-gene deletions/duplications have thus far been identified as a cause of RTS.

Option 2

When the diagnosis of Rothmund-Thomson syndrome is unclear because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in Rothmund-Thomson Syndrome (RTS)

Gene [1, 2]	Proportion of RTS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
ANAPC1	10%	14/14 [6, 7]	Unknown [8]
RECQL4	60%	>99% [6, 9]	Unknown [8]
Unknown [10]	30%	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Data derived from the subscription-based professional view of the Human Gene Mutation Database [Stenson et al 2017]
7. The most frequently detected pathogenic variant, c.2705-198C>T [Ajeawung et al 2019], is deep intronic and may not be detected by routine analysis.
8. No data on detection rate of gene-targeted deletion/duplication analysis are available.
9. Some pathogenic variants are in short introns of *RECQL4*; therefore, sequencing should encompass these intronic regions [Wang et al 2002].
10. In nearly 40% of individuals with the typical clinical findings of RTS, molecular genetic testing fails to identify a pathogenic variant in *RECQL4*. These individuals have been designated as having type 1 RTS. A proportion of probands with type 1 RTS will have pathogenic variants in *ANAPC1* (7 of 9 families tested by Ajeawung et al [2019]). The existence of one or more additional causative genes is likely [Wang et al 2003, Ajeawung et al 2019].

Clinical Characteristics

Clinical Description

Rothmund-Thomson syndrome (RTS) is a genetic disorder associated with a characteristic skin rash in combination with certain other findings detailed in this section. One subset of affected individuals defined by the lack of *RECQL4* pathogenic variants (historically referred to as type 1 RTS) is predisposed to developing juvenile cataracts but not osteosarcoma when followed over time. The other, larger subset of individuals with RTS and *RECQL4* pathogenic variants (historically referred to as type 2 RTS) is at increased risk of developing osteosarcoma and other cancers, and these individuals are also more likely to have skeletal abnormalities [Wang et al 2003]. It is important to keep in mind that there are phenotypic overlaps between types 1 and 2, and some individuals have not had any abnormality found on molecular genetic testing thus far.

Variability. Individuals with RTS can exhibit few or many of the associated clinical features. The severity of the features (e.g., rash) also varies.

Skin. Children with RTS typically develop a rash between ages three and six months but occasionally as late as age two years. The skin changes begin as erythema, swelling, and occasionally blistering on the face, then spread to the buttocks and extremities. Gradually over a period of months to years the skin changes become chronic, with reticulated hypo- and hyperpigmentation, telangiectasias, and punctate atrophy (collectively referred to as poikiloderma) that persist throughout life.

Hyperkeratotic lesions occur in approximately one third of individuals.

Uncommon but reported findings [Mak et al 2006] include the following:

- Calcinosis, the formation of calcium deposits in the skin, usually at the site of an injury

  Note: Calcinosis cutis differs from osteoma cutis, which is true bone formation.

- Porokeratosis, a sign of disordered keratinization. This has been reported in one person with RTS, and thus may or may not be a related finding.

Teeth. Many individuals with RTS also have dental abnormalities including rudimentary or hypoplastic teeth, microdontia, delayed eruption, supernumerary and congenitally missing teeth, ectopic eruption, and increased incidence of caries [Haytaç et al 2002].

Hair. Children with RTS may have sparse scalp hair or even total alopecia. Eyelashes and/or eyebrows may also be sparse or absent.

Growth. Most individuals with RTS are the result of a full-term pregnancy but tend to have low birth weight and length for gestational age. They remain small throughout their lives, usually below the fifth percentile for both weight and height. Growth hormone levels are usually normal.

Skeleton. A study of 28 individuals with RTS examined by skeletal survey found that 75% had at least one major skeletal abnormality [Mehollin-Ray et al 2008]. Findings included abnormal trabeculation with longitudinal and transverse metaphyseal striations, dysplastic changes in the phalanges, absent or malformed bones (e.g., aplastic radii, malformed ulnae, hypoplastic thumbs), fused bones, osteopenia, and hypoplastic or absent patella. These skeletal findings are more often seen in individuals with type 2 RTS, caused by pathogenic variants in *RECQL4*.

In a study of metabolic bone disease in 29 individuals with a clinical diagnosis of RTS, a significant proportion were found to have decreased bone mineral density as well as history of fractures [Cao et al 2017]. Additionally, the presence of pathogenic variants in *RECQL4* and low bone mineral density correlated with the history of increased risk of fractures [Cao et al 2017].

Gastrointestinal. Some infants or young children with RTS have feeding difficulties or other gastrointestinal problems including chronic emesis or diarrhea. Although feeding tubes are occasionally required, most of these problems resolve spontaneously during childhood [Wang et al 2001].

Hematologic. Benign and malignant hematologic abnormalities including isolated anemia and neutropenia, myelodysplasia, aplastic anemia, and leukemia have been reported in individuals with RTS [Knoell et al 1999, Porter et al 1999, Narayan et al 2001, Pianigiani et al 2001].

Cataract. The prevalence of juvenile cataracts has been reported in some series to be as high as 50%, with onset usually between ages three and seven years. In an international cohort of 41 individuals with RTS (age range 9 months to 42 years), the prevalence of cataracts was found to be much lower (<10%) [Wang et al 2001]. Earlier onset (as early as the first few months of life) and later onset (teens or adulthood) have also been reported. Most of the reports of early-onset, bilateral juvenile cataracts come from descriptions from Europe; these individuals are more likely to represent type 1 RTS, caused by pathogenic variants in *ANAPC1* [Ajeawung et al 2019]

Cancer. The overall prevalence of cancers in adults with RTS is unknown.

- **Osteosarcoma** is the most commonly reported malignancy [Wang et al 2003]. In a cohort of those with RTS, the prevalence of osteosarcoma was 30% [Wang et al 2001]. The median age at diagnosis, 11 years, was slightly younger than that seen in the general population. Families in which more than one sib had RTS and osteosarcoma have been identified [Lindor et al 2000, Wang et al 2001]. Osteosarcoma is associated with type 2 RTS.
- **Skin cancer.** Individuals with RTS are also at increased risk of developing skin cancer, including basal cell carcinoma and squamous cell carcinoma [Borg et al 1998] and melanoma [Howell & Bray 2008]. The prevalence of skin cancers in individuals with RTS is estimated from the literature to be 5%. Skin cancer

can occur at any age, although it often occurs earlier than in the general population. The mean age for epithelial tumors has been estimated at 34.4 years [Stinco et al 2008]. Piquero-Casals et al [2002] report on a consanguineous Brazilian family with classic features of RTS including poikiloderma and bilateral cataracts. All three affected sibs developed cutaneous squamous cell carcinoma in adulthood (age 35-48 years). The cancers occurred on non-sun-exposed surfaces. Skin cancer occurs in individuals with both type 1 and type 2 RTS.

- **Second malignancy.** A few individuals with RTS have been reported to have a second malignancy. One developed non-Hodgkin lymphoma nine years after chemotherapy for osteosarcoma [Spurney et al 1998], and another developed Hodgkin lymphoma eight years after therapy for osteosarcoma [Wang et al 2001]. In general, follow-up time for individuals with RTS and osteosarcoma has been too short to draw conclusions about the risk of secondary malignancy.
- **Multiple primary cancers** have also been reported in individuals with RTS. For example, one affected individual developed anaplastic large-cell lymphoma at age nine years, diffuse large-cell B lymphoma and osteosarcoma at age 14 years, and acute lymphoblastic leukemia at age 21 years. Whether the latter cancers represent secondary malignancies is not known [Simon et al 2010].
- **Chemotherapy effects.** Because RTS is felt to be a chromosome instability syndrome, those treated for malignancy may in theory be more sensitive to the effects of chemotherapy and at a higher risk for second malignancy. However, from the limited number of individuals reported, it appears that most individuals with RTS and cancer treated with chemotherapy have not had significantly increased toxicities, although some individuals may experience increased mucositis with doxorubicin treatment [Hicks et al 2007, Simon et al 2010]. Other individuals have reported increased toxicities after treatment with high-dose methotrexate, but side effect profiles vary significantly among individuals and appear to be specific to the individual.

Other. Infertility has been described in affected males and females; however, a few affected females have had normal pregnancies, and a few males have produced offspring.

Immunologic function appears to be intact. However, there are several isolated reports of individuals with RTS who have concomitant immune dysfunction. These include an individual who had humoral immune deficiency associated with granulomatous skin lesions [De Somer et al 2010], an affected individual with IgG_4 deficiency and recurrent sinopulmonary infections [Kubota et al 1993], and another affected individual with low serum immunoglobulin (IgG and IgA) levels who presented with herpes encephalitis [Ito et al 1999]. One individual with RTS and severe combined immunodeficiency (T-B+NK- phenotype with agammaglobulinemia) underwent successful hematopoietic stem cell transplantation [Broom et al 2006].

Most individuals with RTS appear to have normal intelligence.

Life span. In the absence of malignancy, life span is probably normal, although follow-up data in the published literature are limited. Death from metastatic osteosarcoma and other cancers has been reported in a number of children and adults with RTS.

Phenotype Correlations by Gene

Osteosarcoma and skeletal defects are more often found in individuals with RTS associated with *RECQL4* pathogenic variants (type 2 RTS) [Wang et al 2001, Wang et al 2003, Mehollin-Ray et al 2008], while bilateral juvenile cataracts are more often associated with *ANAPC1* pathogenic variants (type 1 RTS) [Ajeawung et al 2019].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

"Poikiloderma congenitale," the name given by M Sidney Thomson to the disorder he described in 1923, has been used in the literature to describe RTS in the past.

Prevalence

RTS is a rare disorder. Since its original description by Auguste Rothmund in Austria in 1868, fewer than 500 individuals have been described in the English-language literature.

RTS has been described in all ethnicities. No population appears to be at higher or lower risk for the disorder. However, specific pathogenic variants may exist within certain ethnic groups.

The population prevalence and carrier frequency of RTS are unknown [Larizza et al 2013].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ANAPC1*.

Other phenotypes associated with germline pathogenic variants in *RECQL4*:

- RAPADILINO (*ra*dial *ra*y defect; *pa*tellae hypoplasia or aplasia and cleft or highly arched *pa*late; *di*arrhea and d*i*slocated joints; *li*ttle size and *li*mb malformation; *no*se slender and *no*rmal intelligence) syndrome (OMIM 266280) is characterized by pre- and postnatal growth retardation. Cervical spine segmentation defects have been reported. Failure to thrive results from feeding problems and juvenile diarrhea of unknown cause [Siitonen et al 2003]. Since its original description in Finland [Kääriäinen et al 1989], only 14 Finnish and two non-Finnish individuals have been reported [Vargas et al 1992, Kant et al 1998, Jam et al 1999, Siitonen et al 2003]. Osteosarcoma was reported in one of the 16 individuals. Lymphoma appears to be a frequent complication in individuals with RAPADILINO syndrome; it occurred in four individuals before age 35 years [Siitonen et al 2009].

  The Finn-specific *RECQL4* splice site variant IVS7+2delT associated with RAPADILINO syndrome leads to in-frame skipping of exon 7 that is predicted to remove 44 amino acids just before the conserved helicase domain, apparently without altering transcription of the helicase domain itself. Nine of the 14 affected Finnish individuals are homozygous for IVS7+2delT and five are compound heterozygotes for IVS7+2delT and a nonsense variant in extra-helicase exons 5, 18, and 19, thus sparing in all cases the helicase domain, which is therefore thought to play a role in poikiloderma and predisposition to osteosarcoma [Siitonen et al 2003].

- **Baller-Gerold syndrome (BGS)** is characterized by craniosynostosis (coronal suture most commonly involved), upper-limb anomalies (most commonly radial ray defects), short stature, and poikiloderma. Patellar hypoplasia or aplasia may become apparent in childhood. Eleven different *RECQL4* pathogenic variants have been reported in seven families with BGS with seven variants having been detected only in association with BGS. One case of lymphoma has been reported in an individual with Baller-Gerold syndrome [Debeljak et al 2009].

Differential Diagnosis

The differential diagnosis of Rothmund-Thomson syndrome (RTS) includes the disorders summarized in Table 2, which can exhibit features of poikiloderma but are otherwise clinically distinct from RTS.

Table 2. Disorders That Can Exhibit Features of Poikiloderma to Consider in the Differential Diagnosis of Rothmund-Thomson Syndrome (RTS)

Disorder	Gene(s)	MOI	Overlapping Clinical Features of Disorder	Distinguishing Clinical Features of Disorder
Bloom syndrome [1]	*BLM*	AR	• Rash characterized by an erythematous, sun-sensitive lesion of the face; not true poikiloderma • Loss of lower eyelashes & blister & fissure formation of lower lip common • Café au lait macules or paired hypopigmented & hyperpigmented macules in some • Most common cause of death: cancer (at younger-than-usual ages) • Severe pre- & postnatal growth deficiency w/↓ subcutaneous fat	• Recurrent infections (otitis media & pneumonia) • Chronic pulmonary disease • Diabetes mellitus
Werner syndrome	*WRN*	AR	• Initial findings (usually in 3rd decade): loss & graying of hair, alopecia, scleroderma-like skin changes • Skin ulcers (4th decade) • Cancer predisposition	• Premature appearance of features assoc w/normal aging • Normal development until end of 1st decade • 1st symptom: no growth spurt during early teen years • Initial signs: (3rd decade) hoarseness followed by bilateral ocular cataracts, type 2 diabetes mellitus, hypogonadism, & osteoporosis in 4th decade
Ataxia-telangiectasia	*ATM*	AR	• ↑ risk of malignancy, particularly leukemia & lymphoma • Unusual sensitivity to ionizing radiation	• Progressive cerebellar ataxia beginning ages 1-4 yrs • Oculomotor apraxia • Frequent infections • Choreoathetosis • Telangiectasias of the conjunctivae • Immunodeficiency
Fanconi anemia	>20 genes [2]	AR AD XL	• Abnormal skin pigmentation • ↑ risk of malignancy: 10%-30% incidence of hematologic malignancies (primarily acute myeloid leukemia); 25%-30% incidence of nonhematologic malignancies (solid tumors, particularly of head & neck, skin, GI tract, & genital tract)	• Bone marrow failure in 1st decade; 90% estimated cumulative incidence of bone marrow failure by age 40-50 yrs • Physical abnormalities: short stature; malformations of thumbs, forearms, skeletal system, eye, kidneys & urinary tract, ear, heart, GI system, oral cavity, & CNS; hearing loss; hypogonadism; DD

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Overlapping Clinical Features of Disorder	Distinguishing Clinical Features of Disorder
Xeroderma pigmentosum	*DDB2* *ERCC1* *ERCC2* *ERCC3* *ERCC4* *ERCC5* *POLH* *XPA* *XPC*	AR	• Sun sensitivity (sunburn w/ blistering; persistent erythema on minimal sun exposure in ~60%; severe, marked freckle-like pigmentation of face before age 2 yrs) • Greatly ↑ risk of cutaneous neoplasms (basal cell carcinoma, squamous cell carcinoma, melanoma) • Xerosis (dry skin) • Poikiloderma • Loss of lashes	• Median age of onset of non-melanoma skin cancer: <10 yrs • Neurologic manifestations in ~25% • Photophobia • Keratitis • Atrophy of skin of eyelids
Kindler syndrome	*FERMT1*	AR	• Acral bullae at birth & after minor trauma • Diffuse poikiloderma w/striate & reticulate atrophy • Widespread eczematoid dermatitis • Keratotic papules of hands, feet, elbows, knees • Marked photosensitivity	• Esophageal & urethral strictures • Webbing of fingers & toes • No ↑ risk for cataract or malignancy
Dyskeratosis congenita	*ACD* *CTC1* *DKC1* *NHP2* *NOP10* *PARN* *RTEL1* *TERC* *TERT* *TINF2* *WRAP53*	XL AD AR	• Lacy reticular pigmentation of neck & upper chest • Nail dystrophy • ↑ risk of leukemia & skin cancers	• Bone marrow failure • Oral leukoplakia w/variable onset • Not assoc w/radial ray defects or cataracts
Poikiloderma with neutropenia	*USB1*	AR	• Rash • Less common finding: acute myeloid leukemia	• Onset of rash differs from that seen in RTS: more eczematous, starting peripherally & spreading centrally • Rash affecting the trunk • Not assoc w/radial ray abnormalities • Clinically significant neutropenia w/ recurrent sinopulmonary infection • Less common finding: bone marrow failure • Paronychias common

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Overlapping Clinical Features of Disorder	Distinguishing Clinical Features of Disorder
Hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis	*FAM111B*	AD	• Poikiloderma (typically beginning in 1st 6 mos & mainly facial) • Chronic erythematous & scaly skin lesions on extremities (distinct from chronic poikiloderma of extremities seen in RTS) • Sclerosis of digits • Mild palmoplantar keratoderma • Scalp hair, eyelashes, &/or eyebrows typically sparse • Nail dysplasia in some	• Hypohidrosis w/heat intolerance • Mild lymphedema of extremities • Muscle contractures usually seen in childhood; can be present by age 2 yrs • In most: progressive weakness of proximal & distal muscles of all 4 limbs • In some adults: progressive interstitial pulmonary fibrosis that can be life threatening w/in 3-4 yrs after respiratory symptoms appear

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; DD = developmental delay; GI = gastrointestinal; MOI = mode of inheritance; XL = X-linked

1. A greatly increased frequency of sister chromatid exchanges (SCEs) in cells exposed to bromodeoxyuridine (BrdU) is diagnostic. Bloom syndrome is the only disorder in which such evidence of hyper-recombination is known to occur.

2. See Phenotypic Series: Fanconi Anemia for a list of genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Rothmund-Thomson syndrome (RTS), the evaluations in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Rothmund-Thomson Syndrome (RTS)

System/Concern	Evaluation	Comment
Skin	Dermatologic eval	
Skeletal	Baseline skeletal radiographic exam by age 5 yrs to identify underlying skeletal abnormalities; baseline DXA scan to assess bone mineral density if indicated	Obtain DXA if osteopenia is seen on skeletal survey or there is a history of fractures.
Hematologic	Baseline CBC w/differential	Individuals w/clinical evidence of anemia or cytopenias should be evaluated by CBC & bone marrow biopsy if clinically indicated.
Vision	Ophthalmologic exam to evaluate for cataracts	
Other	Consultation w/clinical geneticist &/or genetic counselor	

CBC = complete blood count; DXA = dual-energy x-ray absorptiometry

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Rothmund-Thomson Syndrome (RTS)

Manifestation/Concern	Treatment	Considerations/Other
Skin rash	Pulsed dye laser has been used for cosmetic management of the telangiectatic component of rash.	
Hematologic concerns	Individuals w/hematologic abnormalities should be treated in standard manner by hematologist familiar w/RTS.	
Cataract	Visually significant cataracts require surgical removal.	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Cancer	Affected individuals who develop cancer should be treated per standard chemotherapy &/or radiation regimens.	Doses should be modified only if individual experiences significantly ↑ toxicities.

Surveillance

Table 5. Recommended Surveillance for Individuals with Rothmund-Thomson Syndrome (RTS)

System/Concern	Evaluation	Frequency
General	Eval by physician familiar w/RTS for overall health maintenance & monitoring of growth	Annual
Skin	Eval by dermatologist w/close monitoring of skin for lesions w/unusual color or texture, as individuals w/RTS are at ↑ risk for skin cancers	Annually or more frequently if indicated
Eyes (for those w/o cataracts)	Eye exams for screening purposes	Annually
Skeletal [1]	Skeletal radiographic exam	Promptly if clinical suspicion of osteosarcoma is present (incl bone pain, swelling, or enlarging lesion on a limb) due to the high risk for this potentially lethal malignancy

1. Surveillance screening for osteosarcoma is not routinely recommended for individuals with RTS [Walsh et al 2017].

Agents/Circumstances to Avoid

Exposure to heat or sunlight may exacerbate the rash in some individuals.

Avoidance of excessive sun exposure decreases the risk for skin cancer.

Given the theoretic potential for tumorigenesis, growth hormone (GH) therapy is not recommended for individuals with normal GH levels. For individuals with documented GH deficiency, standard treatment with growth hormone is appropriate.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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

Other

Given the theoretic potential for tumorigenesis, growth hormone (GH) therapy is not recommended for individuals with normal GH levels. For individuals with documented GH deficiency, routine treatment with growth hormone is appropriate.

Genetic Counseling

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

Mode of Inheritance

Rothmund-Thomson syndrome (RTS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a proband with confirmed biallelic pathogenic variants in *ANAPC1* or *RECQL4* are obligate heterozygotes (i.e., presumed to be carriers of one *ANAPC1* or *RECQL4* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for an *ANAPC1* or *RECQL4* pathogenic variant and allow reliable recurrence risk assessment. (Although a *de novo* pathogenic variant has not been reported in RTS to date, *de novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are apparently asymptomatic, although this issue has not been carefully studied.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are apparently asymptomatic, although this issue has not been carefully studied.

Offspring of a proband

- The offspring of an individual with RTS are obligate heterozygotes (carriers) for a pathogenic variant in *ANAPC1* or *RECQL4*.
- The carrier frequency for RTS is unknown; however, given the rarity of the disorder, the likelihood that an affected individual will have children with a carrier is very low. Exceptions include areas in which a founder variant in *ANAPC1* may be present (e.g., in western Austria, where Rothmund originally described RTS; and in the Mennonite population).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ANAPC1* or *RECQL4* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *RECQL4* or *ANAPC1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

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

Prenatal Testing and Preimplantation Genetic Testing

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

Ultrasound examination. Ultrasound examination at 16 to 18 weeks' gestation may detect forearm reduction defects; however, given the variability of clinical findings, the absence of skeletal abnormalities on ultrasound examination in a fetus at risk does not exclude the possibility of RTS.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Resources

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

- **National Library of Medicine Genetics Home Reference**
  Rothmund-Thomson syndrome
- **Rothmund-Thomson Syndrome Foundation**
  RTS Foundation
  4307 Woodward Court
  Chantilly VA 20151
  Email: rtssupport@rtsplace.org
  www.rtsplace.org

Molecular Genetics

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

Table A. Rothmund-Thomson Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ANAPC1	2q13	Anaphase-promoting complex subunit 1		ANAPC1	ANAPC1
RECQL4	8q24.3	ATP-dependent DNA helicase Q4	RECQL4 database	RECQL4	RECQL4

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

Table B. OMIM Entries for Rothmund-Thomson Syndrome (View All in OMIM)

268400	ROTHMUND-THOMSON SYNDROME, TYPE 2; RTS2
603780	RECQ PROTEIN-LIKE 4; RECQL4
608473	ANAPHASE-PROMOTING COMPLEX, SUBUNIT 1; ANAPC1
618625	ROTHMUND-THOMSON SYNDROME, TYPE 1; RTS1

Molecular Pathogenesis

Rothmund-Thomson syndrome (RTS) is caused by pathogenic variants in *ANAPC1* or *RECQL4*; it is often classified as a disorder of DNA repair and replication.

ANAPC1 encodes the APC1 protein, which is the largest subunit of the anaphase-promoting complex/cyclosome (APC/C). APC/C is an E3 ubiquitin ligase that targets specific proteins for degradation. It helps to control cellular transition at distinct phases of the cell cycle. The phenotypes seen in individuals with type 1 RTS may thus be the result of defective cell cycling [Ajeawung et al 2019]. The APC/C has also been shown to play a role in DNA replication and repair, senescence, and cell differentiation.

RECQL4 encodes ATP-dependent DNA helicase Q4, a member of the RecQ DNA helicase family, categorized by a 3'-5' polarity of unwinding double-stranded DNA and RNA-DNA hybrids to produce single-stranded DNA templates. RecQ helicases are DNA helicases (enzymes that promote DNA unwinding, allowing many basic cellular processes to occur) that play a role in maintaining chromosome integrity at various stages of DNA processing (replication, recombination, repair, telomere maintenance) but also in translation, RNA processing, mtDNA maintenance, and chromosome segregation [Croteau et al 2014, Lu et al 2014]. Since they act in virtually all aspects of DNA metabolism, perturbation of their expression and biochemical activity leads to genomic instability, resulting in disease and cancer predisposition [Bochman 2014].

Pathogenic variants in *ANAPC1* have been found in a proportion of individuals with type 1 RTS and pathogenic variants in *RECQL4* has been found in individuals with type 2 RTS (see Clinical Description). How *ANAPC1* and *RECQL4* may potentially interact is currently unknown.

Mechanism of disease causation. RTS occurs via a loss-of-function mechanism.

Table 6. Rothmund-Thomson Syndrome: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
ANAPC1	The most frequently detected pathogenic variant, c.2705-198C>T, is deep intronic & may not be detected by routine analysis [Ajeawung et al 2019].
RECQL4	Some pathogenic variants are in short introns of *RECQL4*; therefore, sequencing should encompass these intronic regions [Wang et al 2002].

1. Genes are listed in alphabetic order.

Table 7. Rothmund-Thomson Syndrome: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
ANAPC1	NM_022662.3 NP_073153.1	c.2705-198C>T	--	Frequently identified variant (11/14 disease alleles) that results in introduction of a pseudoexon [Ajeawung et al 2019]

Table 7. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
RECQL4	NM_004260.3 NP_004251.3	c.2269C>T	p.Gln757Ter	Most common pathogenic variant in *RECQL4* [Author, personal communication]
		c.1573delT	p.Cys525AlafsTer33	2nd most common pathogenic variant in *RECQL4* [Author, personal communication]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes are listed in alphabetic order.

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Chapter Notes

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Dr Wang's web page

Dr Plon is a board-certified geneticist with expertise in cancer genetics and the control of genomic stability. She directs the Baylor Cancer Genetics Clinic at Texas Children's Hospital/Baylor College of Medicine and is actively involved in genetic evaluation and counseling for families at increased risk for cancer.

Dr Plon's web page

Revision History

- 4 June 2020 (ha) Revision: added *ANAPC1* as a cause of RTS; edits to Diagnosis, Management, Genetic Counseling, and Molecular Genetics
- 3 January 2019 (ha) Comprehensive update posted live

- 11 August 2016 (bp) Revision: POIKTMP added to Differential Diagnosis
- 3 December 2015 (me) Comprehensive update posted live
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- 7 April 2009 (me) Comprehensive update posted live
- 2 October 2006 (cd) Revision: deletion/duplication analysis clinically available
- 26 September 2006 (me) Comprehensive update posted live
- 5 January 2005 (sp) Revision: Genetically Related Disorders
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