Baylor College of Medicine

ROTHMUND THOMSON SYNDROME FOUNDATION

Texas Children's Cancer Center

# Welcome to the 2020 Webinar #1

**Dr. Lisa L. Wang – The History of RTS Research and Clinical Studies**

# Mission Statement

- Promote awareness of Rothmund-Thomson Syndrome and related syndromes to the general public and to healthcare professionals
- Provide education and support to affected families worldwide
- Provide education to healthcare professionals who may encounter patients affected with these disorders
- Promote research aimed at understanding the molecular and cellular basis of RTS and the clinical manifestations
- Raise funds through events and contributions that will support the overall efforts of the group

# Ideas for Future RTS Webinars

- Coping with a rare disease during the COVID pandemic
- Dermatology challenges with Dr. Moise Levy
- The differences between Type 1 and Type 2 RTS and genetic testing
- Orthopedic issues and challenges
- Cancer concerns, monitoring and treatment

# RTSF Medical Advisory and Board Members

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# The Future of RTS Research

Lisa L. Wang, MD
Texas Children's Hospital
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Houston, TX

&

John Kimmel,
Founder and Chair, Rothmund-Thomson Syndrome Foundation
Chantilly, VA

ROTHMUND THOMSON SYNDROME FOUNDATION

*Pediatrics*

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# 1st RTS "Sharing and Caring" Conference

October 17-19, 2007
Houston, TX

- Day 1: Educational Lectures
  - Genetics of RTS (Sharon E. Plon, MD, PhD)
  - Dermatologic Manifestations of RTS (Mo Levy, MD)
  - RTS and Bone Disease (Lisa L. Wang, MD)
  - Radiologic Findings in RTS (Amy Mehollin-Ray, MD)
  - Sharing and Caring Session—Families
- Day 2:
  - RTS Support Group Planning

# 1st RTS Conference 2007


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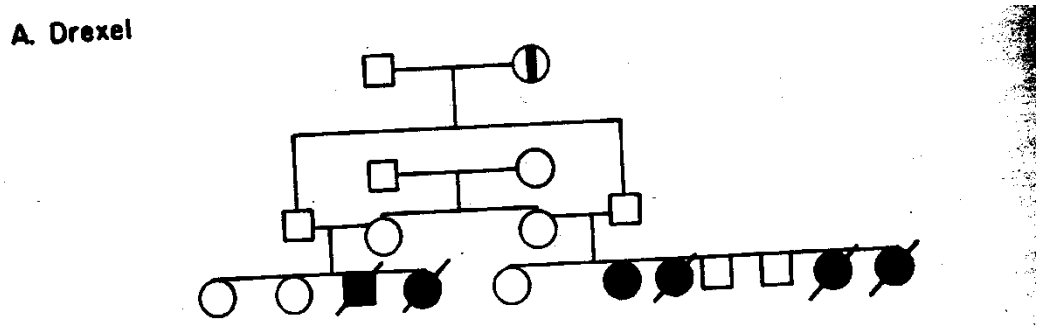
# Outline

- History of RTS and RTS Research
- Milestones in RTS Research
- Current and Future Goals

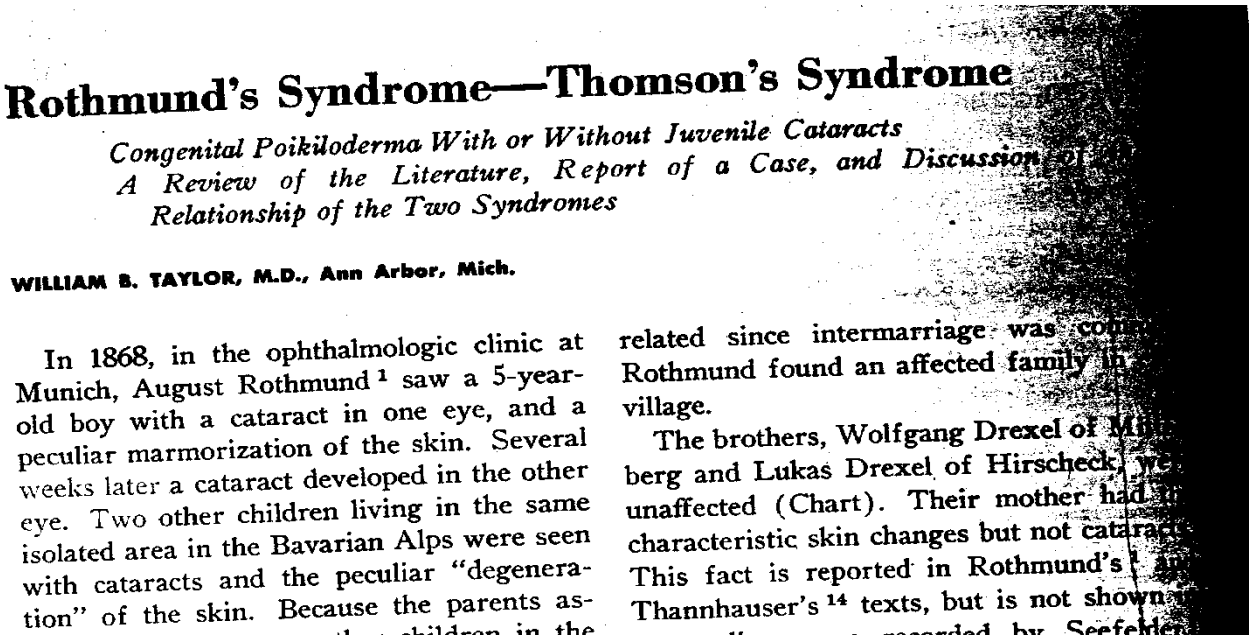
# History of RTS

- **1868:** Auguste Rothmund first described the characteristic rash and cataracts in inbred Austrian families




- **1923:** M. Sydney Thomson described the rash and *skeletal anomalies* in sisters; coined term “poikiloderma congenitale”

- **1957:** William Taylor united the two disorders, proposed eponym "Rothmund-Thomson Syndrome"



**Rothmund's Syndrome—Thomson's Syndrome**

*Congenital Poikiloderma With or Without Juvenile Cataracts*
*A Review of the Literature, Report of a Case, and Discussion of the*
*Relationship of the Two Syndromes*

WILLIAM B. TAYLOR, M.D., Ann Arbor, Mich.

In 1868, in the ophthalmologic clinic at Munich, August Rothmund [1] saw a 5-year-old boy with a cataract in one eye, and a peculiar marmorization of the skin. Several weeks later a cataract developed in the other eye. Two other children living in the same isolated area in the Bavarian Alps were seen with cataracts and the peculiar "degeneration" of the skin. Because the parents as-

related since intermarriage was co
Rothmund found an affected family in
village.

The brothers, Wolfgang Drexel of M
berg and Lukas Drexel of Hirscheck, we
unaffected (Chart). Their mother had
characteristic skin changes but not cataract
This fact is reported in Rothmund's [1] an
Thannhauser's [14] texts, but is not shown

Taylor WB, AMA Arch Dermatol;75:236-244 (1957)

# How we got started

- Patient diagnosed with osteosarcoma (OS) in 1999
- Also carried diagnosis of Rothmund-Thomson Syndrome (RTS)
- Sister also had RTS and  died of metastatic OS
- **QUESTION:  Is there any link between these two  rare diseases?**

# History of Baylor College of Medicine (BCM) RTS Study

- **First IRB Protocol**
  - H-7207: "The Molecular Basis of Familial Cancer Predisposition Syndromes"
  - Includes subjects with RTS and other disorders
  - Includes family members
  - First subject enrolled 01/19/1999
  - Yearly recontact letters
- **Second IRB Protocol** approved 08/22/2000
  - H-9106: "The Molecular Basis and Clinical Spectrum of Rothmund-Thomson Syndrome"

# History of BCM RTS Study

- **General Clinical Research Center (GCRC) Study** approved 09/20/2000
  - Includes subjects with a diagnosis of RTS
  - First subject enrolled 07/25/2001
  - 36 subjects enrolled - came to Texas Children's Hospital
  - Comprehensive evaluation including Genetics, Dermatology, Ophthalmology, Oncology, labs, skeletal surveys

➢ With these protocols approved and in place, we could begin to collect medical information and biologic samples to start generating data.

# 1: Defining the syndrome

American Journal of Medical Genetics 102:11–17 (2001)

## Clinical Manifestations in a Cohort of 41 Rothmund-Thomson Syndrome Patients

Lisa L. Wang,[1] Moise L. Levy,[1,2] Richard A. Lewis,[1,3,4] Murali M. Chintagumpala,[1] Dorit Lev,[5] Maureen Rogers,[6] and Sharon E. Plon[1,3]*

[1]*Department of Pediatrics, Baylor College of Medicine, Houston, Texas*
[2]*Department of Dermatology, Baylor College of Medicine, Houston, Texas*
[3]*Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas*
[4]*Department of Ophthalmology, Baylor College of Medicine, Houston, Texas*
[5]*Institute of Medical Genetics, Wolfson Medical Center, Holon, Israel*
[6]*Children's Hospital Medical Centre, Westmead NSW, Australia*

**Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive genodermatosis characterized by a poikilodermatous rash starting in infancy, small stature, skeletal abnormalities, juvenile cataracts, and predisposition to specific cancers. We have identified a contemporary cohort of 41 patients to better define the clinical profile, diagnostic criteria, and management of patients with RTS. Patients with the diagnosis of RTS were ascertained by referrals from dermatology, ophthalmology, genetics, and oncology or from direct contact with the patient's family. Medical information was obtained from interviews with physicians, patients, and their parents and a review of medical records. The age range at ascertainment was 9 months to 42 years (28 males and 13 females; M:F, 2:1). All subjects displayed a characteristic rash. Thirteen subjects had osteosarcoma (OS) (32%), eight had radial defects (20%), seven had gastrointestinal findings (17%), two had cataracts (6%), and one had skin cancer (2%). Twenty-two of 28 patients without OS were less than 15 years old and thus remain at significant risk for this tumor. This case-series study reveals a clinical profile of RTS that includes a higher prevalence of OS and fewer cataracts, compared to previous reports. We describe the frequency of clinical anomalies in a contemporary cohort of RTS patients and revises guidelines for diagnosis and management of RTS.** 

**KEY WORDS: cancer; cataract; chromosomal instability; genetics; osteosarcoma; poikiloderma; radial ray defect; rash**

### INTRODUCTION

Rothmund-Thomson syndrome (RTS) (OMIM 268400) is a rare autosomal recessive disorder first described in 1868 by German ophthalmologist Auguste Rothmund in inbred family members who had a peculiar rash and bilateral juvenile cataracts [Rothmund, 1868]. Sydney Thomson, a British dermatologist, coined the term "poikiloderma congenitale" in 1923 for patients with a similar rash and skeletal anomalies, but no cataracts [Thomson, 1923]. In 1957, William Taylor suggested that the two disorders were the same and proposed the combined eponym Rothmund-Thomson syndrome [Taylor, 1957].

RTS is characterized primarily by a sun-sensitive rash that usually begins between 3 and 6 months, but may appear soon after birth or as late as 2 years. The

2001

# Summary of Clinical Findings in 41 RTS Subjects Baylor College of Medicine Study

| | | |
|---|---|---|
| **Rash** | **41/41** | **100%** |
| **Small stature** | **25/38** | **66%** |
| **Skeletal dysplasia** | **15/20** | **75%** |
| **Radial ray defect** | **8/40** | **20%** |
| **Sparse scalp hair** | **15/30** | **50%** |
| **Sparse brows/lashes** | **19/26** | **73%** |
| **Cataracts** | **2/32** | **6%** |
| **Skin cancer** | **1/41** | **2%** |
| **Osteosarcoma** | **13/41** | **32%** |

Wang *et al* (2001) Am J Med Genet; 102:11-17

# Clinical Diagnostic Criteria for RTS

## DEFINITE RTS

- **Characteristic rash with or without other features:**
  - ***Acute phase:*** **Begins in infancy (usually 3-6 months) as erythema/blisters on cheeks, often sun-sensitive, spreads to extensor surfaces of extremities, buttocks**
  - ***Chronic phase:*** **Poikiloderma consisting of reticulated hypo- and hyper-pigmentation, atrophy, telangiectases**

Wang *et al* (2001) Am J Med Genet; 102:11-17

# Clinical Diagnostic Criteria for RTS

## PROBABLE RTS

- ***Atypical rash*** **plus two or more features of RTS**

- **Positive family history of RTS**
- **Osteosarcoma**
- **Skin malignancy**
- **Radial ray defect**
- **Other skeletal dysplasias**
- **Juvenile cataract**

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- **Small stature**
- **Sparse scalp hair**
- **Sparse brows and/or lashes**
- **Dental abnormalities**
- **Nail abnormalities**

Wang *et al* (2001) Am J Med Genet; 102:11-17

# Genetic Basis of RTS

- When we started our research, the cause of RTS was unknown.
- It was known to be an inherited disorder and transmitted in an **autosomal recessive** pattern.
- In 1999, a gene for RTS was discovered.

# 2: Finding the cause of RTS

## Kitao *et al*. (1999) Nature Genetics; 22: 82-84

*letter*

### Mutations in *RECQL4* cause a subset of cases of Rothmund-Thomson syndrome

Saori Kitao[1], Akira Shimamoto[1], Makoto Goto[2], Robert W. Miller[3], William A. Smithson[4], Noralane M. Lindor[4] & Yasuhiro Furuichi[1]

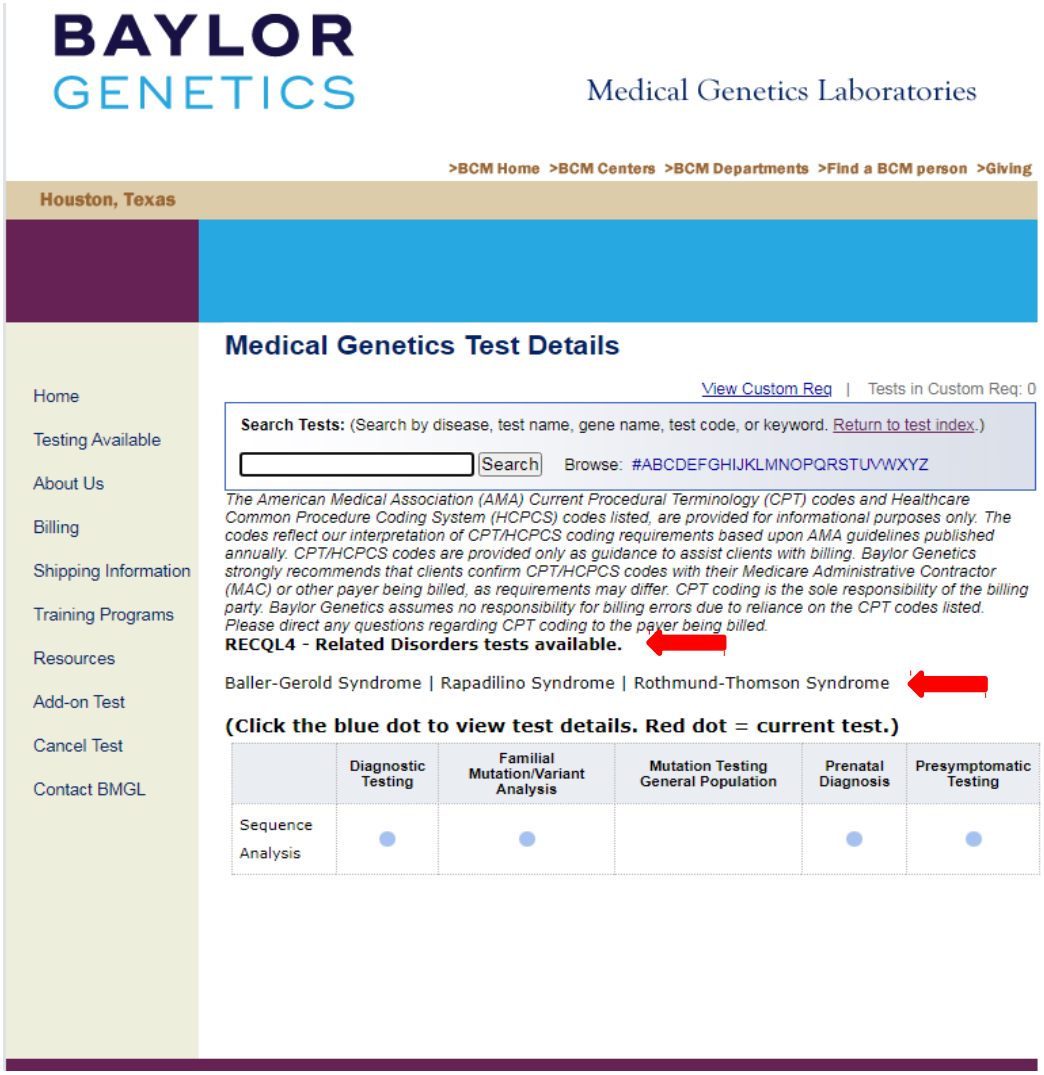
**Rothmund-Thomson syndrome (RTS; also known as poikiloderma congenitale) is a rare, autosomal recessive genetic disorder characterized by abnormalities in skin and skeleton, juvenile cataracts, premature ageing and a predisposition to neoplasia[1–4]. Cytogenetic studies indicate that cells from**

The coding sequence of *RECQL4*, consisting of 3,627 bases and encoding a protein with 1,208 amino acids, has been published[18]; exon and intron junctions have also recently been identified (unpublished data). We amplified all exon regions of *RECQL4* from patients by PCR and compared their sequences

- 3 out of 7 RTS cases had mutations in ***RECQL4***

# 3: Sequence RTS patients to see how many have mutations in *RECQL4*

- Mutation testing done initially in the lab as part of research
- Helped to develop a clinical test for RTS
- Now widely available in the U.S.



# Characterizing different *RECQL4* mutation types in RTS

Am. J. Hum. Genet. 71:165–167, 2002

Report

## Intron-Size Constraint as a Mutational Mechanism in Rothmund-Thomson Syndrome

Lisa L. Wang,[1] Kim Worley,[2,4] Anu Gannavarapu,[1] Murali M. Chintagumpala,[1] Moise L. Levy,[1,3] and Sharon E. Plon[1,2]

Departments of [1]Pediatrics, [2]Molecular and Human Genetics, and [3]Dermatology and the [4]Human Genome Sequencing Center, Baylor College of Medicine, Houston

Rothmund-Thomson syndrome (RTS) is an autosomal recessive disorder caused by deleterious mutations in the *RECQL4* gene on chromosome 8. The *RECQL4* gene structure is unusual because it contains many small introns <100 bp. We describe a proband with RTS who has a novel 11-bp intronic deletion, and we show that this mutation results in a 66-bp intron too small for proper splicing. Constraint on intron size may represent a general mutational mechanism, since human-genome analysis reveals that ~15% of genes have introns <100 bp and are therefore susceptible to size constraint. Thus, monitoring of intron size may allow detection of mutations missed by exon-by-exon approaches.

- Mutation testing can be tricky
- Need to examine intronic regions
- Make sure proper test is performed

2002

# 4: Determining if *RECQL4* mutations correlate with other features of RTS: *Osteosarcoma*

## Association Between Osteosarcoma and Deleterious Mutations in the RECQL4 Gene in Rothmund–Thomson Syndrome

*Lisa L. Wang, Anu Gannavarapu, Claudia A. Kozinetz, Moise L. Levy, Richard A. Lewis, Murali M. Chintagumpala, Ramon Ruiz-Maldanado, Jose Contreras-Ruiz, Christopher Cunniff, Robert P. Erickson, Dorit Lev, Maureen Rogers, Elaine H. Zackai, Sharon E. Plon*

***Background:*** **Rothmund–Thomson syndrome (RTS) is an autosomal recessive disorder associated with an increased predisposition to osteosarcoma. Children with RTS typically present with a characteristic skin rash (poikiloderma), small stature, and skeletal dysplasias. Mutations in the RECQL4 gene, which encodes a RecQ DNA helicase, have been reported in a few RTS patients. We examined whether a predisposition to developing osteosarcoma among an international cohort of RTS patients was associated with a distinctive pattern of mutations in the RECQL4 gene.** ***Methods:*** **We obtained clinical information about and biologic samples from 33 RTS patients (age range = 1–30 years). Eleven patients were diagnosed with osteosarcoma. All 21 exons and 13 short introns of the RECQL4 gene were sequenced from the genomic DNA of all subjects. Kaplan–Meier survival analysis was used to estimate the incidence of osteosarcoma among patients with and without mutations predicted to produce a truncated RECQL4 protein.** ***Results:*** **Twenty-three RTS patients, including all 11 osteosarcoma patients, carried at least one of 19 truncating mutations in their RECQL4 genes. The incidence of osteosarcoma was 0.00 per year in truncating mutation-negative patients (100 person-years of observation) and 0.05 per year in truncating mutation-positive patients (230 person-years of observation) ($P$ = .037; two-sided log-rank test).** ***Conclusions:*** **Mutations predicted to result in the loss of RECQL4 protein function occurred in approximately two-thirds of RTS patients and are associated with risk of osteosarcoma. Molecular diagnosis has the potential to identify those children with RTS who are at high risk of this cancer. [J Natl Cancer Inst 2003;95: 669–74]**

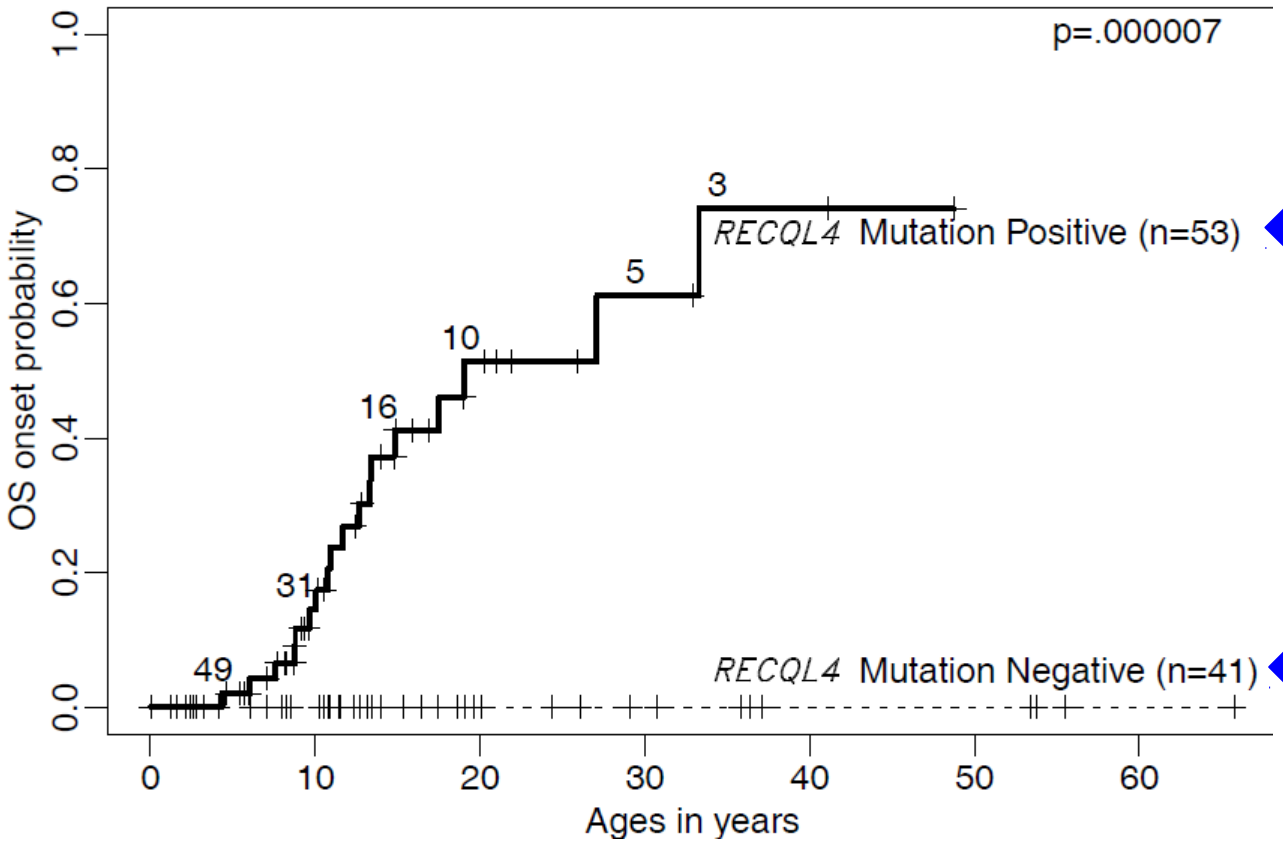
eral juvenile cataracts. However, evaluation of an international cohort of 41 RTS probands revealed a different clinical profile, which included a prevalence of osteosarcoma at approximately 0.30 *(2)*. Currently no clinical or molecular marker predicts which RTS patients will develop osteosarcoma, a malignancy that carries a substantial mortality rate despite available surgery and chemotherapy *(5)*.

In 1999, Kitao et al. *(6)* used a pure candidate gene approach to show that mutations in the RECQL4 gene, which is located on human chromosome 8q24.3, occurred in two of the six RTS kindreds they examined. The RECQL4 protein belongs to the RecQ family of DNA helicases, which includes proteins encoded by genes that are disrupted in Bloom syndrome and Werner syndrome, two clinically related cancer predisposition syndromes *(7)*. DNA helicases are enzymes that unwind DNA and are involved in many basic cellular processes; interruption of their functions may reduce genomic stability and thus contribute to tumorigenesis *(8,9)*. No complementation or linkage studies have been reported that might indicate whether mutations in more than one gene (termed genetic heterogeneity) are responsible for RTS, and no studies of RECQL4 gene mutations in sporadic osteosarcoma have been reported. We performed comprehensive DNA sequence analysis of the RECQL4 gene from 33 RTS patients to examine the spectrum of RECQL4 mutations in RTS and to assess whether RTS patients with osteosarcoma have a distinctive pattern of mutation.

*Affiliations of authors:* L. L. Wang, A. Gannavarapu, M. M. Chintagumpala (Texas Children's Cancer Center and Department of Pediatrics), C. A. Kozinetz (Department of Pediatrics), M. L. Levy (Departments of Pediatrics and Dermatology), R. A. Lewis (Departments of Pediatrics, Ophthalmology, and Molecular and Human Genetics), Baylor College of Medicine, Houston, TX; R. R. Maldanado, Department of Dermatology, National University of Mexico, Mexico

2003

# *RECQL4* mutation status and OS in RTS




**Type 2 RTS:**

*RECQL4* mutations

Increased risk of OS compared to Type 1

**Type 1 RTS:**

No *RECQL4* mutations

*Lu, Adv Exp Med Biol 2014*

# 4: Determining if *RECQL4* mutations correlate with other features of RTS: *Skeletal defects*

- Skeletal defects correlate with *RECQL4* mutations
- Skeletal surveys are useful

## Radiographic Abnormalities in Rothmund-Thomson Syndrome and Genotype–Phenotype Correlation with *RECQL4* Mutation Status

Amy R. Mehollin-Ray[1]
Claudia A. Kozinetz[2]
Alan E. Schlesinger[1]
R. Paul Guillerman[1]
Lisa L. Wang[3]

**Keywords:** bone abnormality, *RECQL4* mutation, Rothmund-Thomson syndrome, skeletal dysplasia

DOI:10.2214/AJR.07.3619

Received January 6, 2008; accepted after revision February 20, 2008.

Supported by National Institutes of Health grant NICHD NIH-K08HD42136, a Doris Duke Charitable Foundation Clinical Scientist Development Award, National Institutes of Health grant NIH-RR000188-42 (BCM–General Clinical Research Center), National Institutes of Health grant NIH-HD024064 (BCM–Mental Retardation Developmental Disabilities Research Center, Tissue

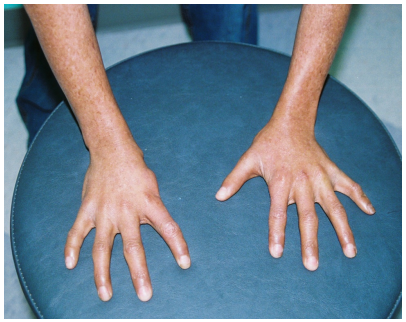
**OBJECTIVE.** The purpose of this study was to summarize the radiographic skeletal findings in patients with Rothmund-Thomson syndrome (RTS) and to determine whether there is an association between the presence of skeletal abnormalities and the mutational status of the *RECQL4* gene.

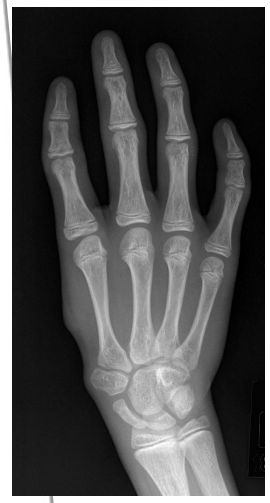
**SUBJECTS AND METHODS.** Twenty-eight subjects with RTS underwent skeletal surveys and *RECQL4* DNA mutation testing. Radiographs were reviewed by two radiologists. *RECQL4* mutation testing by DNA sequencing of the gene was performed by a diagnostic laboratory. Genotype–phenotype analysis by Fisher's exact test was performed to investigate whether there was a correlation between mutation status and skeletal abnormalities.

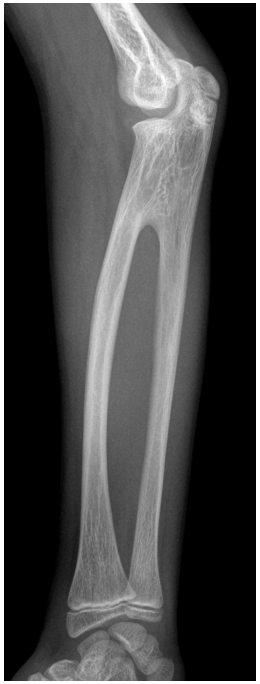
**RESULTS.** Twenty-one (75%) of the subjects had at least one significant skeletal abnormality, the more common being abnormal metaphyseal trabeculation, brachymesophalangy, thumb aplasia or hypoplasia, osteopenia, dislocation of the radial head, radial aplasia or hypoplasia, and patellar ossification defects. Three subjects had a history of destructive bone lesion (osteosarcoma). Genotype–phenotype analysis showed a significant correlation between *RECQL4* mutational status and the presence of skeletal abnormalities ($p < 0.0001$).

**CONCLUSION.** Skeletal abnormalities are frequent in persons with RTS. Many of these abnormalities are not clinically apparent but are detectable on radiographs. The presence of skeletal abnormalities correlates with *RECQL4* mutation status, which has been found to correlate with risk of osteosarcoma. Skeletal surveys aid in both diagnosis and management of RTS.

Rothmund-Thomson syndrome (RTS) is an autosomal recessive disorder with heterogeneous clinical features, including a characclinically overt skeletal abnormalities but did not thoroughly discuss the entire skeletal system. In a review [1] of the cases of 41 patients with RTS, 75% of the 20 patients who under-

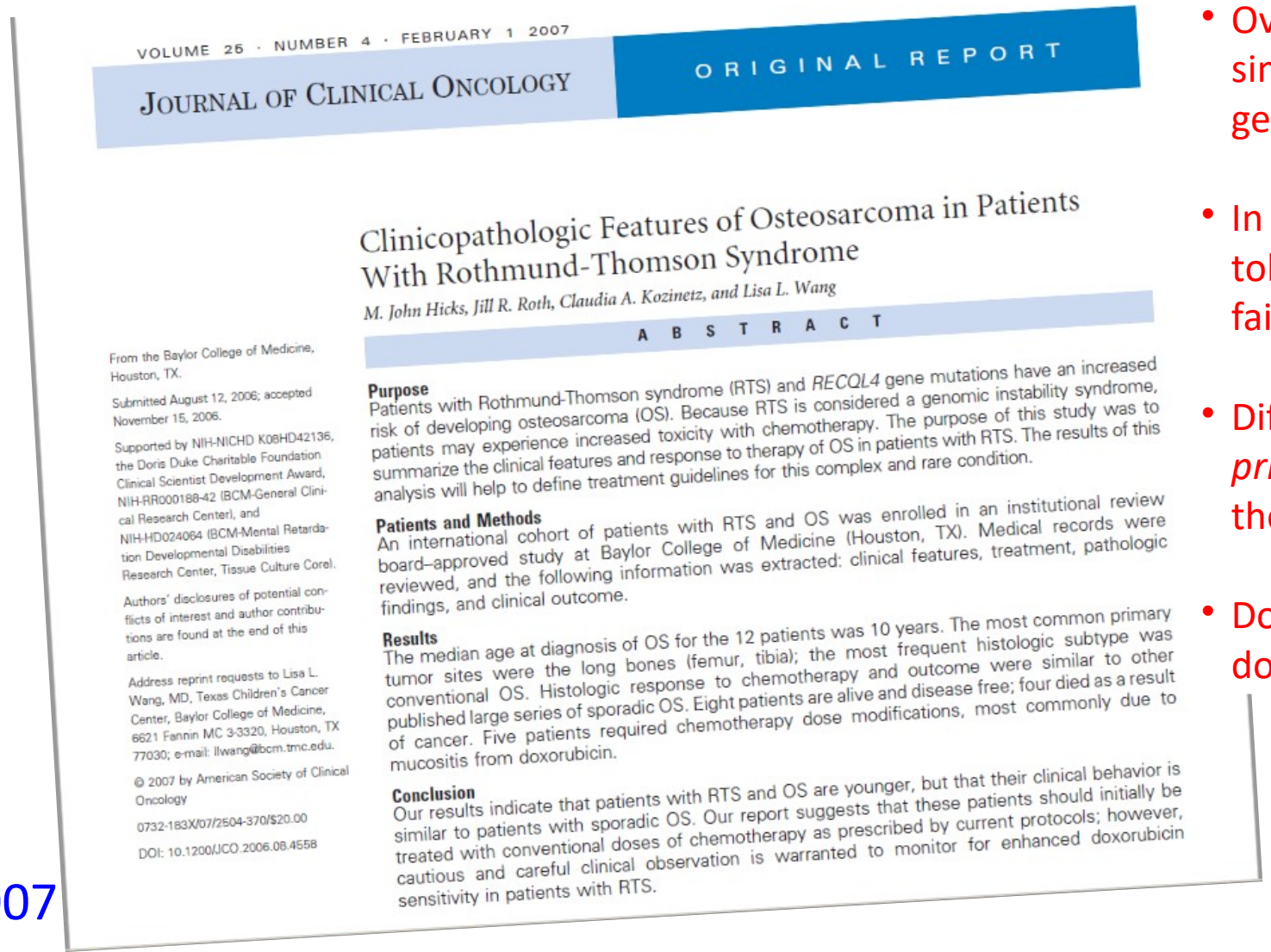






2008

# 5: Managing osteosarcoma in RTS patients



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Clinicopathologic Features of Osteosarcoma in Patients With Rothmund-Thomson Syndrome

*M. John Hicks, Jill R. Roth, Claudia A. Kozinetz, and Lisa L. Wang*

From the Baylor College of Medicine, Houston, TX.

Submitted August 12, 2006; accepted November 15, 2006.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2504-370/$20.00

DOI: 10.1200/JCO.2006.08.4558

A B S T R A C T

**Purpose**
Patients with Rothmund-Thomson syndrome (RTS) and *RECQL4* gene mutations have an increased risk of developing osteosarcoma (OS). Because RTS is considered a genomic instability syndrome, patients may experience increased toxicity with chemotherapy. The purpose of this study was to summarize the clinical features and response to therapy of OS in patients with RTS. The results of this analysis will help to define treatment guidelines for this complex and rare condition.

**Patients and Methods**
An international cohort of patients with RTS and OS was enrolled in an institutional review board–approved study at Baylor College of Medicine (Houston, TX). Medical records were reviewed, and the following information was extracted: clinical features, treatment, pathologic findings, and clinical outcome.

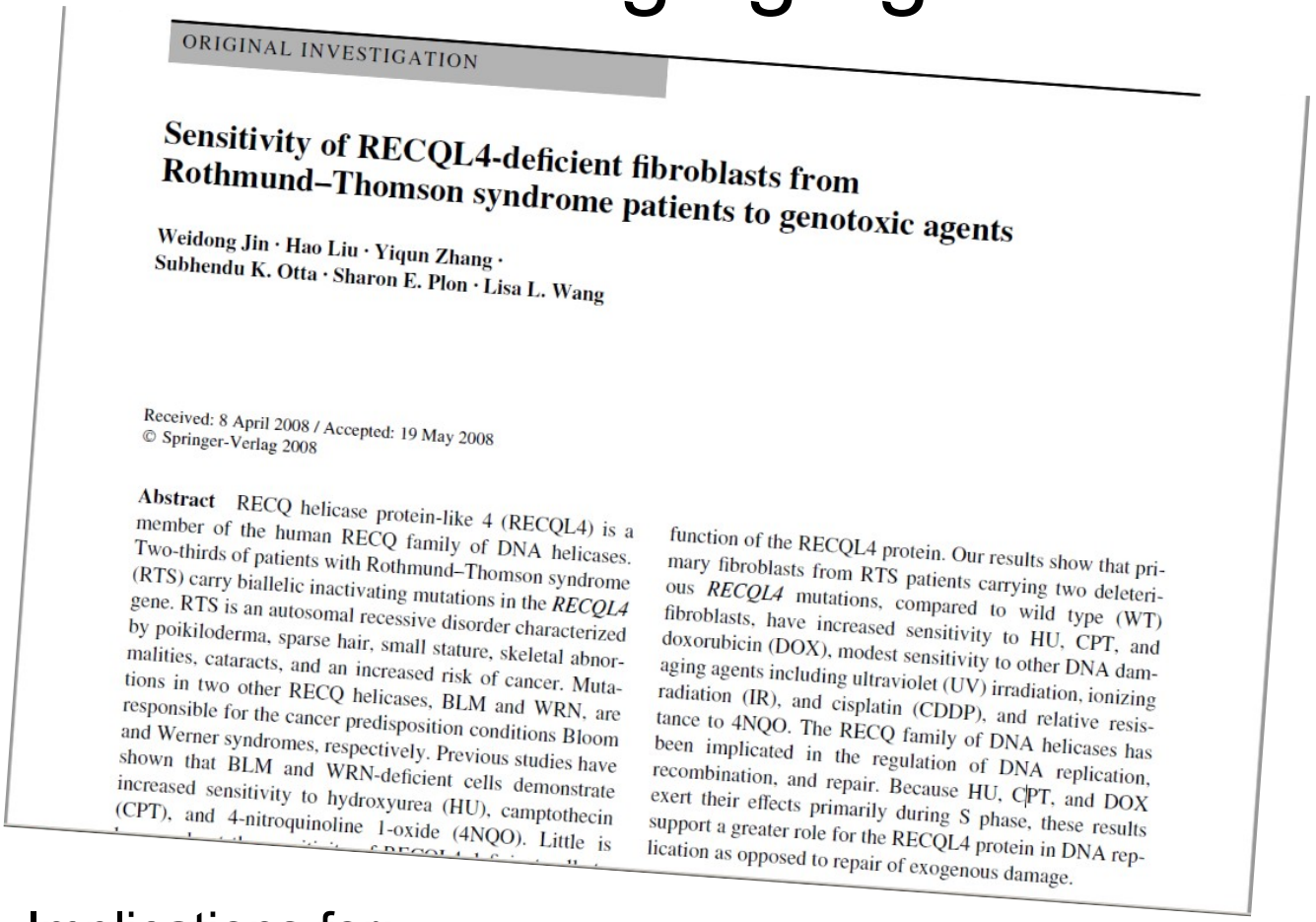
**Results**
The median age at diagnosis of OS for the 12 patients was 10 years. The most common primary tumor sites were the long bones (femur, tibia); the most frequent histologic subtype was conventional OS. Histologic response to chemotherapy and outcome were similar to other published large series of sporadic OS. Eight patients are alive and disease free; four died as a result of cancer. Five patients required chemotherapy dose modifications, most commonly due to mucositis from doxorubicin.

**Conclusion**
Our results indicate that patients with RTS and OS are younger, but that their clinical behavior is similar to patients with sporadic OS. Our report suggests that these patients should initially be treated with conventional doses of chemotherapy as prescribed by current protocols; however, cautious and careful clinical observation is warranted to monitor for enhanced doxorubicin sensitivity in patients with RTS.

2007

- Overall, OS in RTS is similar to OS in general population.
- In general, patients tolerate treatment fairly well.
- Difficult to predict *a priori* response to therapy
- Do not decrease doses up front.

# 6: Are RTS patients more sensitive to DNA-damaging agents?



ORIGINAL INVESTIGATION

**Sensitivity of RECQL4-deficient fibroblasts from Rothmund–Thomson syndrome patients to genotoxic agents**

Weidong Jin · Hao Liu · Yiqun Zhang · Subhendu K. Otta · Sharon E. Plon · Lisa L. Wang

Received: 8 April 2008 / Accepted: 19 May 2008

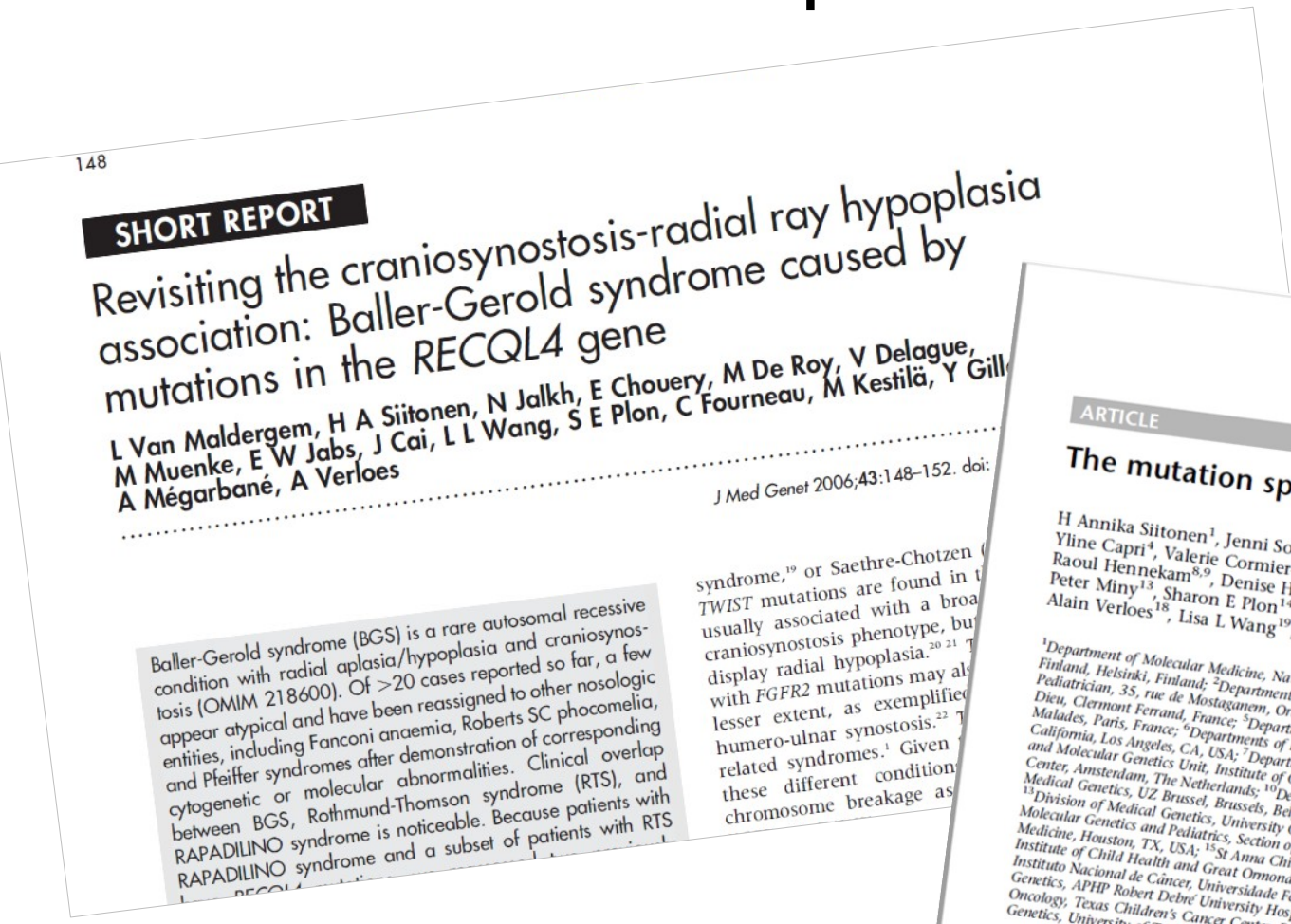

**Abstract** RECQ helicase protein-like 4 (RECQL4) is a member of the human RECQ family of DNA helicases. Two-thirds of patients with Rothmund–Thomson syndrome (RTS) carry biallelic inactivating mutations in the *RECQL4* gene. RTS is an autosomal recessive disorder characterized by poikiloderma, sparse hair, small stature, skeletal abnormalities, cataracts, and an increased risk of cancer. Mutations in two other RECQ helicases, BLM and WRN, are responsible for the cancer predisposition conditions Bloom and Werner syndromes, respectively. Previous studies have shown that BLM and WRN-deficient cells demonstrate increased sensitivity to hydroxyurea (HU), camptothecin (CPT), and 4-nitroquinoline 1-oxide (4NQO). Little is function of the RECQL4 protein. Our results show that primary fibroblasts from RTS patients carrying two deleterious *RECQL4* mutations, compared to wild type (WT) fibroblasts, have increased sensitivity to HU, CPT, and doxorubicin (DOX), modest sensitivity to other DNA damaging agents including ultraviolet (UV) irradiation, ionizing radiation (IR), and cisplatin (CDDP), and relative resistance to 4NQO. The RECQ family of DNA helicases has been implicated in the regulation of DNA replication, recombination, and repair. Because HU, CPT, and DOX exert their effects primarily during S phase, these results support a greater role for the RECQL4 protein in DNA replication as opposed to repair of exogenous damage.

Implications for:

- Sun protection (UV)
- Radiology tests, screening for cancer
- Prediction of side effects from cancer treatment

2008

# 7: RECQL4 Spectrum of Disorders



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SHORT REPORT

## Revisiting the craniosynostosis-radial ray hypoplasia association: Baller-Gerold syndrome caused by mutations in the *RECQL4* gene

L Van Maldergem, H A Siitonen, N Jalkh, E Chouery, M De Roy, V Delague, M Muenke, E W Jabs, J Cai, L L Wang, S E Plon, C Fourneau, M Kestilä, Y Gill A Mégarbané, A Verloes

J Med Genet 2006;43:148–152. doi:

Baller-Gerold syndrome (BGS) is a rare autosomal recessive condition with radial aplasia/hypoplasia and craniosynostosis (OMIM 218600). Of >20 cases reported so far, a few appear atypical and have been reassigned to other nosologic entities, including Fanconi anaemia, Roberts SC phocomelia, and Pfeiffer syndromes after demonstration of corresponding cytogenetic or molecular abnormalities. Clinical overlap between BGS, Rothmund-Thomson syndrome (RTS), and RAPADILINO syndrome is noticeable. Because patients with RAPADILINO syndrome and a subset of patients with RTS

syndrome,[19] or Saethre-Chotzen
*TWIST* mutations are found in t
usually associated with a broa
craniosynostosis phenotype, bu
display radial hypoplasia.[20 21]
with *FGFR2* mutations may al
lesser extent, as exemplifie
humero-ulnar synostosis.[22]
related syndromes.[1] Given
these different condition
chromosome breakage as

European Journal of Human Genetics (2008), 1–8

www.nature.com/ejhg

ARTICLE

## The mutation spectrum in *RECQL4* diseases

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Mutations in the *RECQL4* gene can lead to three clinical phenotypes with overlapping features. All these syndromes, Rothmund–Thomson (RTS), RAPADILINO and Baller–Gerold (BGS), are characterized by growth retardation and radial defects, but RAPADILINO syndrome lacks the main dermal manifestation, poikiloderma that is a hallmark feature in both RTS and BGS. It has been previously shown that RTS patients with *RECQL4* mutations are at increased risk of osteosarcoma, but the precise incidence of cancer in RAPADILINO and BGS has not been determined. Here, we report that RAPADILINO patients identified as carriers of the c.1390 + 2delT mutation (p.Ala420_Ala463del) are at increased risk to develop lymphoma or osteosarcoma (6 out of 15 patients). We also summarize all the published *RECQL4* mutations and their associated cancer cases and provide an update of 14 novel *RECQL4* mutations with accompanying clinical data.

European Journal of Human Genetics advance online publication, 20 August 2008; doi:10.1038/ejhg.2008.154

1. RTS
2. Baller-Gerold Syndrome (BGS)
3. RAPADILINO

2006, 2008

# *RECQL4* Spectrum of Disorders

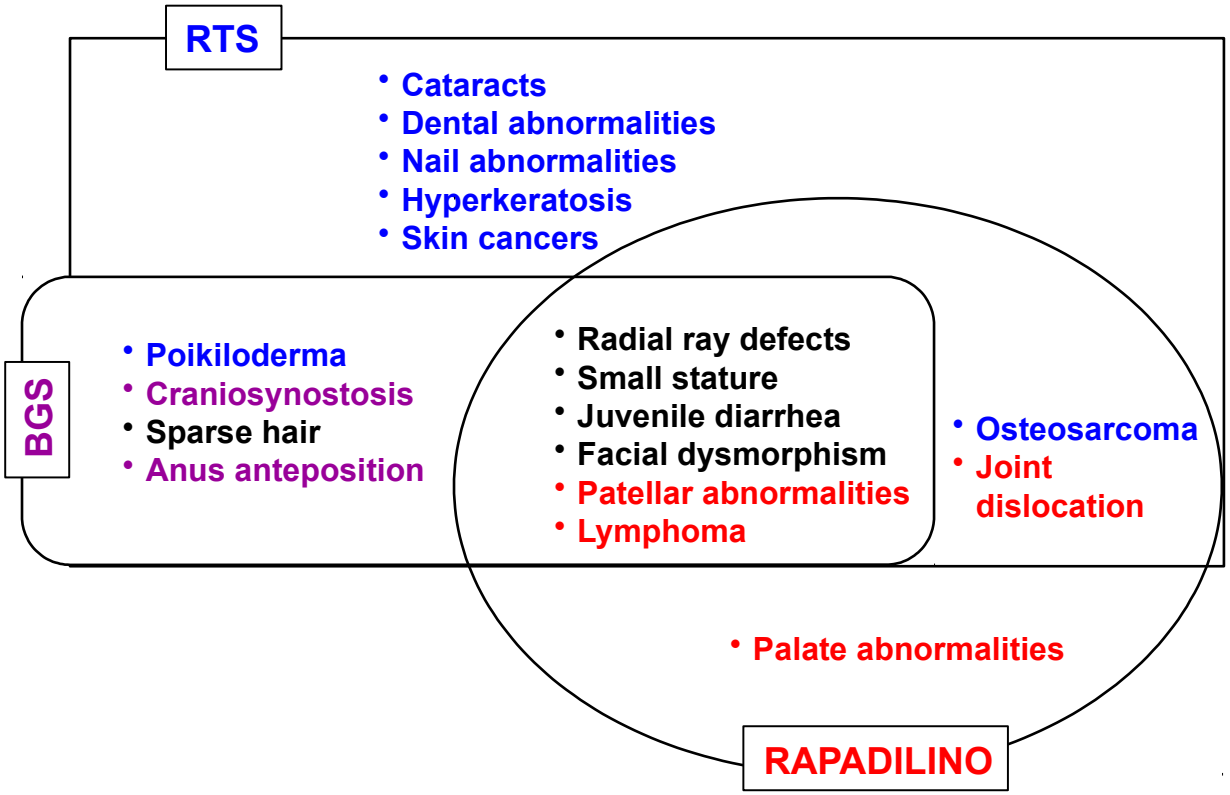
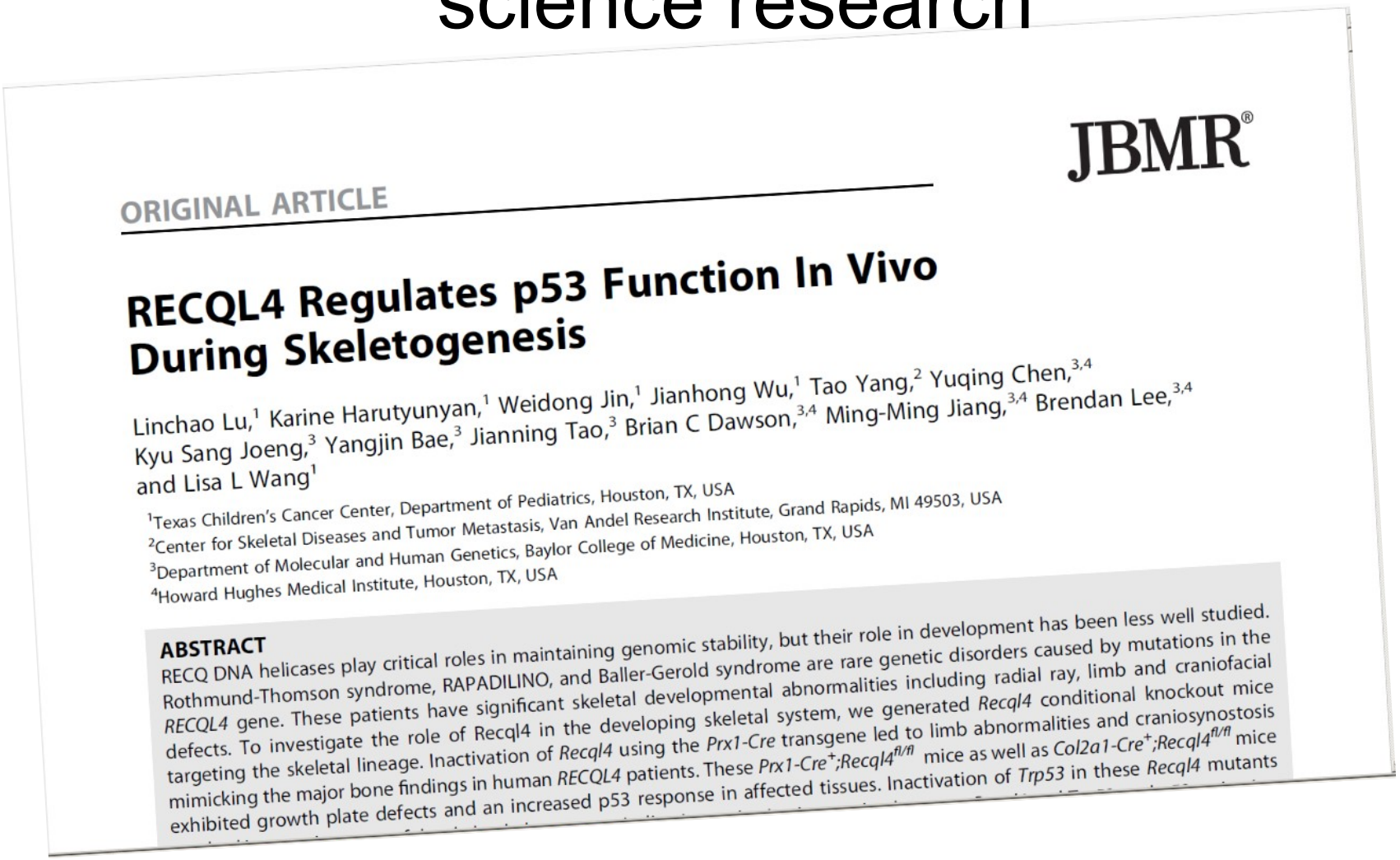



Diagram showing overlapping and unique clinical features of the *RECQL4* –associated disorders. Osteosarcomas and lymphomas have been described in both RTS and RAPADILINO, but osteosarcomas predominate in RTS, while lymphomas are more common in RAPADILINO. There has been only one case of lymphoma reported in a patient with BGS.

# History of BCM RTS Study

- **Third IRB Protocol** approved 10/11/2007
  - H-21708: "The Molecular Basis of Rothmund-Thomson Syndrome and Osteosarcoma"—current open protocol
- **Clinical Research Center (CRC) Study** approved 11/2010
  - "Evaluation of Calcium Absorption and Kinetics in Patients with Rothmund-Thomson Syndrome"
  - First subject enrolled in 2010
  - 29 subjects enrolled

# 8: Modeling RTS in the lab for basic science research



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ORIGINAL ARTICLE

## RECQL4 Regulates p53 Function In Vivo During Skeletogenesis

Linchao Lu,[1] Karine Harutyunyan,[1] Weidong Jin,[1] Jianhong Wu,[1] Tao Yang,[2] Yuqing Chen,[3,4] Kyu Sang Joeng,[3] Yangjin Bae,[3] Jianning Tao,[3] Brian C Dawson,[3,4] Ming-Ming Jiang,[3,4] Brendan Lee,[3,4] and Lisa L Wang[1]

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**ABSTRACT**

RECQ DNA helicases play critical roles in maintaining genomic stability, but their role in development has been less well studied. Rothmund-Thomson syndrome, RAPADILINO, and Baller-Gerold syndrome are rare genetic disorders caused by mutations in the *RECQL4* gene. These patients have significant skeletal developmental abnormalities including radial ray, limb and craniofacial defects. To investigate the role of Recql4 in the developing skeletal system, we generated *Recql4* conditional knockout mice targeting the skeletal lineage. Inactivation of *Recql4* using the *Prx1-Cre* transgene led to limb abnormalities and craniosynostosis mimicking the major bone findings in human *RECQL4* patients. These *Prx1-Cre*$^{+}$;*Recql4*$^{fl/fl}$ mice as well as *Col2a1-Cre*$^{+}$;*Recql4*$^{fl/fl}$ mice exhibited growth plate defects and an increased p53 response in affected tissues. Inactivation of *Trp53* in these *Recql4* mutants

These mice with *Recql4* mutations had skeletal features similar to RTS patients; however, they did not develop osteosarcoma unless crossed with p53 deficient mice

2015

# 9: Do RTS patients have altered bone metabolism?

OXFORD

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Original Article

ORIGINAL ARTICLE

## Generalized metabolic bone disease and fracture risk in Rothmund-Thomson syndrome

Felicia Cao[1,2,†], Linchao Lu[3,†], Steven A. Abrams[4], Keli M. Hawthorne[4], Allison Tam[5], Weidong Jin[3], Brian Dawson[5], Roman Shypailo[6], Hao Liu[7], Brendan Lee[5], Sandesh C.S. Nagamani[5,8,‡] and Lisa L. Wang[3,8,*,‡]

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**Abstract**

Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive disorder characterized by poikiloderma, small stature, sparse hair, skeletal abnormalities, increased risk of osteosarcoma, and decreased bone mass. To date, there has not been a comprehensive evaluation of the prevalence and extent of metabolic bone disease in RTS. Furthermore, the mechanisms that

Some RTS patients have decreased bone mineral density (osteoporosis) and may need monitoring (DXA scans).

2017

# 10: Finding a cause for Type 1 RTS

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REPORT

## Mutations in *ANAPC1*, Encoding a Scaffold Subunit of the Anaphase-Promoting Complex, Cause Rothmund-Thomson Syndrome Type 1

Norbert F. Ajeawung,[1,6] Thi Tuyet Mai Nguyen,[1,6] Linchao Lu,[2,6] Thomas J. Kucharski,[3] Justine Rousseau,[1] Sirinart Molidperee,[1] Joshua Atienza,[1] Isabel Gamache,[1] Weidong Jin,[2] Sharon E. Plon,[2,4] Brendan H. Lee,[4] Jose G. Teodoro,[3] Lisa L. Wang,[2,*] and Philippe M. Campeau[1,5,*]

Rothmund-Thomson syndrome (RTS) is an autosomal-recessive disorder characterized by poikiloderma, sparse hair, short stature, and skeletal anomalies. Type 2 RTS, which is defined by the presence of bi-allelic mutations in *RECQL4*, is characterized by increased cancer susceptibility and skeletal anomalies, whereas the genetic basis of RTS type 1, which is associated with juvenile cataracts, is unknown. We studied ten individuals, from seven families, who had RTS type 1 and identified a deep intronic splicing mutation of the *ANAPC1* gene, a component of the anaphase-promoting complex/cyclosome (APC/C), in all affected individuals, either in the homozygous state or in *trans* with another mutation. Fibroblast studies showed that the intronic mutation causes the activation of a 95 bp pseudoexon, leading to mRNAs with premature termination codons and nonsense-mediated decay, decreased ANAPC1 protein levels, and prolongation of interphase. Interestingly, mice that were heterozygous for a knockout mutation have an increased incidence of cataracts. Our results demonstrate that deficiency in the APC/C is a cause of RTS type 1 and suggest a possible link between the APC/C and RECQL4 helicase because both proteins are involved in DNA repair and replication.

Analysis of the clinical and molecular features of individuals with Rothmund-Thomson syndrome (RTS [MIM: 268400]), including assessing the prevalence of osteosarcoma and the mutational status of the *RECQL4* gene (MIM: 603780), resulted in the definition of two distinct ancestry. All individuals presented with classical RTS type 1 features, including poikiloderma, abnormal hair and nails, bilateral juvenile cataracts, and an absence of *RECQL4* mutations (see Table 1 and Figure 1A for photos and Figure 1B for pedigrees). Additional features in our

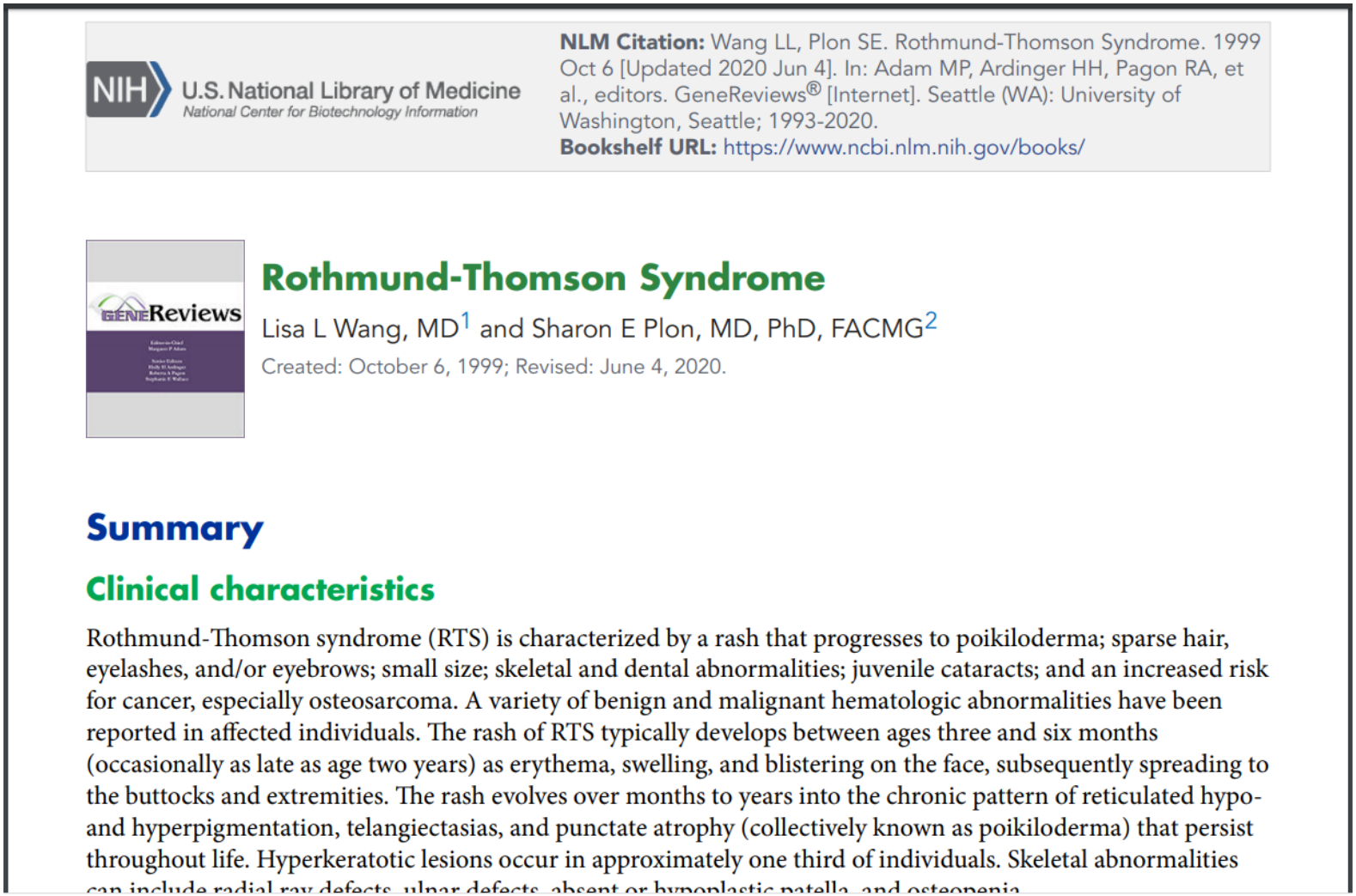
- Mutations in *ANAPC1* identified in 10/18 subjects (7/14 families) with Type 1 RTS

2019

**GeneReviews®**

Margaret P Adam, Editor-in-Chief; Senior Editors: Holly H Ardinger, Roberta A Pagon, and Stephanie E Wallace. Molecular Genetics: Lora JH Bean and Karen Stephens. Anne Amemiya, Genetic Counseling. Seattle (WA): University of Washington, Seattle; 1993-2020.ISSN: 2372-0697

https://www.ncbi.nlm.nih.gov/books/NBK1116/



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**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/

# Rothmund-Thomson Syndrome

Lisa L Wang, MD[1] and Sharon E Plon, MD, PhD, FACMG[2]

Created: October 6, 1999; Revised: June 4, 2020.

## 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

# What is on the horizon for RTS research?

# What is Needed to Continue Research on RTS?

- Researchers
  - Basic science research
  - Clinical & translational research
  - Infrastructure
- Patients and Families
  - Registry - clinical database; yearly questionnaires
  - Biologic material for laboratory studies
- Funding
  - Major funding – e.g., National Institutes of Health (NIH)
  - Foundation grants

# RESEARCHERS

Academic medicine -Physician scientist

- 80% research effort – grants
- 20% clinical effort - see patients

Grants must pay for:

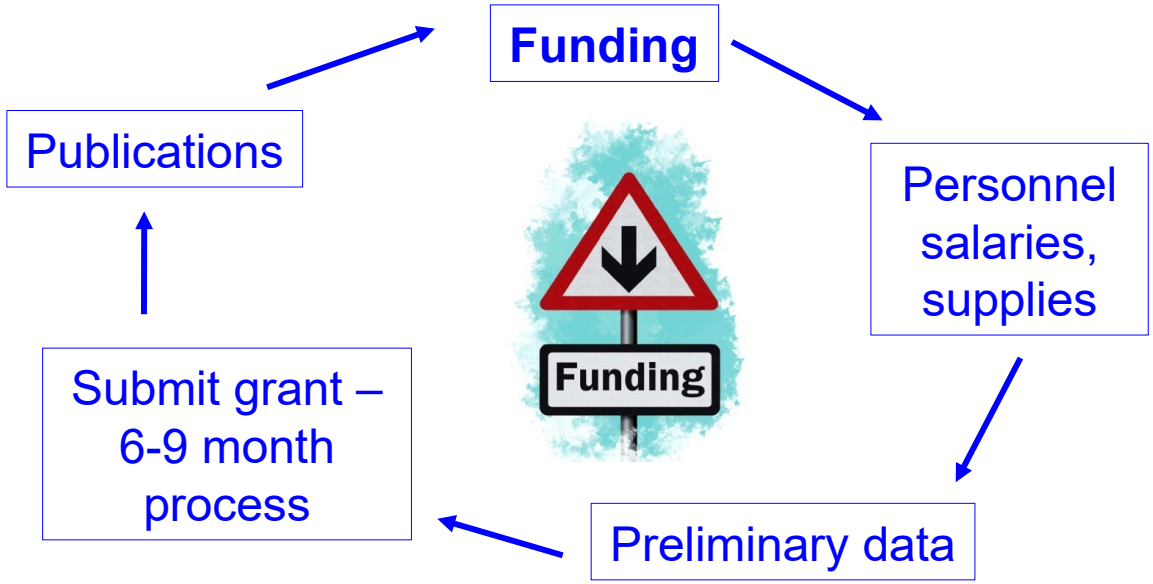
- Personnel – salaries including own
- Supplies
- Animal costs
- Maintenance of lab (liquid nitrogen, CO2, glasswashing, etc.)

# RTS Registry

- Information entered into database
- Yearly recontact
- This will allow us to
  - describe the natural history of RTS
  - understand the full clinical manifestations in RTS patients and their relatives
  - Identify areas of research study

# Roadblocks to Federal Funding

- Limited resources – diminishing payline; Covid-19 impact
- Fierce competition – more common diseases, larger labs, PhD scientists
- <u>The vicious cycle</u>:



# How Can We Sustain Research on RTS?

- Researchers
- Patients and Families
- Funding

- Continue to submit grants and conduct research

- Play an active role in research!
- Fill out questionnaires and provide clinical information
- Provide biologic samples when possible

- Local fundraisers to support RTSF and RTS research
- Facebook fundraisers
- Workplace, company support

# Challenges

- Raising money to support clinical research
  - Research is expensive
  - Research dollars are limited and competitive, especially for rare diseases
  - The Foundation needs to increase fundraising
- Building the patient registry and increasing the number of families involved in clinical trials
  - There have been tremendous advances, but there is much more to be done
- Fresh ideas, energetic members, renewed commitment

Baylor College of Medicine

ROTHMUND THOMSON SYNDROME FOUNDATION

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# 2020 Webinar Series #1