Stronger Together: Teaming Up Against Cancer

Bloom Syndrome Association Family Conference

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August 6, 2022

Outline

- Cancer 101
- What's known about cancer and Bloom Syndrome
- What we'd like to know
- Lessons from Rothmund-Thomson Syndrome
- Questions to ask your oncologist, if you need one
- Proposed ways to get involved
  - Standard operating procedure when cancer is diagnosed

Cancer 101

- What is cancer?
  - Cancer vs benign tumor
- How is cancer usually diagnosed?
  - Radiologist
  - Surgeon
  - Pathologist
- What are the main categories of cancer treatment?
  - Surgery
  - Chemotherapy
  - Radiation
  - Other

What’s known

- Two primary sources
  - Bloom Syndrome Registry
  - Published literature, usually case studies
  - Plus anecdotes from the community
- Limitations
  - Outdated information
  - Publication bias
- By coming together, we can start to overcome these limitations

What's known - diagnoses

- Information from 290 participants in the BSR, 1960-2021
- 155 (53%) participants developed 251 cancers

- The most common cancer is leukemia/lymphoma
- The most common solid cancers are colorectal, breast, and oropharyngeal

- Cancer screening is challenging due to the different types of cancer
- Screening recommendations are based on the types of cancers that have been found in Bloom patients and the average ages that they have been found

What’s known- treatment

- Early reports from the Registry on 14 patients with acute leukemia diagnosed between 1950-1970s
  - 7 developed severe treatment reactions - some despite reduced doses of chemotherapy
  - Others had no unusual reactions, some had no data

What's known- treatment

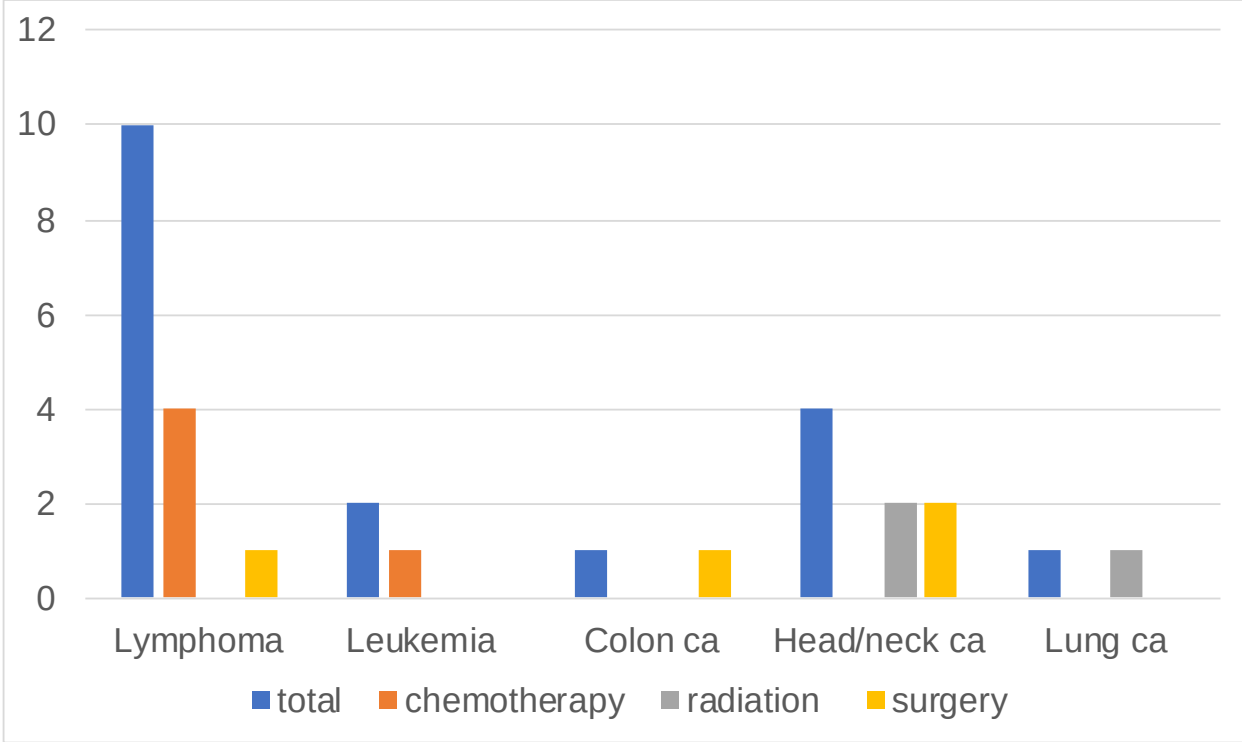
- Of 78 people who received chemotherapy, 23 (29.5%) confirmed receiving modified treatment
  - including lower doses or fewer cycles of chemotherapy

- 19 reported varying degrees of side effects, most commonly gastrointestinal complications (nausea, vomiting), liver toxicity
  - 2 cases of hyperglycemia and 3 cases of diabetes

- Of 28 participants known to have received radiation, 8 (28.6%) experienced toxicity, including 3 cases of esophageal stricture

What's known- treatment

- 18 published reports on cancer in patients with Bloom
  - 5 mention doses of chemotherapy
  - 3 mention doses of radiation
  - 4 mention surgery used
- Side effects
  - Prolonged bone marrow suppression
    - Fever, infection, bleeding
  - Gastrointestinal complications
    - Nausea, vomiting, mucositis, liver injury
  - Endocrine
    - High blood sugars
  - Strictures after radiation



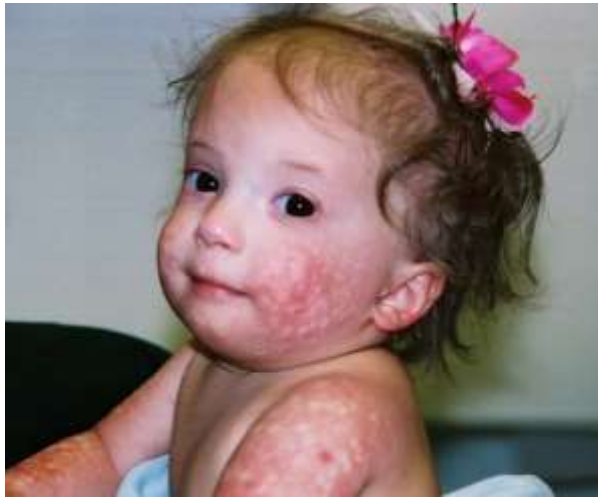
What we'd like to know

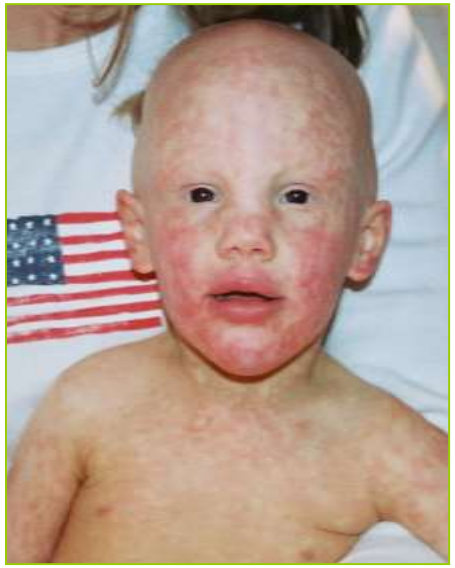
- Cancer diagnoses
  - Are cancers in patients with Bsyn the same or different from patients without Bsyn?
- Treatment
  - How does treating oncologist select the best regimen/modifications?
  - Would patients with Bsyn respond to immunotherapy?
- Surveillance
  - What are effective screening strategies?
  - Can we detect abnormalities in blood sampled over time that signals development of cancer?

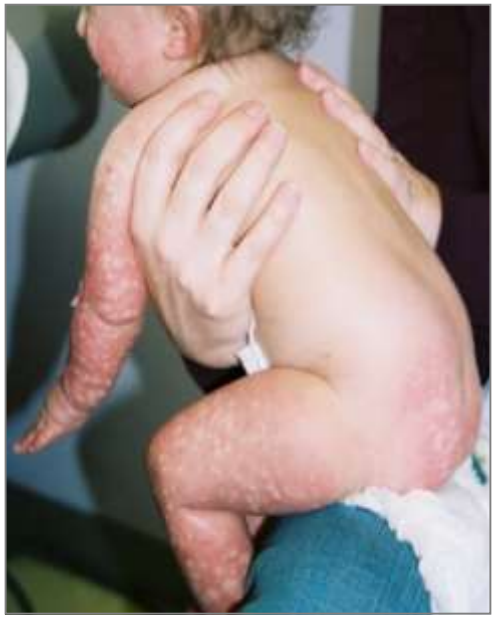
Example from Rothmund-Thomson Syndrome (RTS) Registry

Rothmund-Thomson Syndrome (RTS)

- Cancer predisposition syndrome
- RECQ helicase syndrome







Human RECQ Helicase Syndromes

Disease	Clinical features	Cancer Predisposition	Gene Location
Bloom	Small stature, photosensitive rash, immunodeficiency	Multiple tumor types, including leukemia, lymphoma, solid tumors	*BLM* 15q26.1
Werner	Premature aging, cataracts, diabetes, atherosclerosis	Soft tissue sarcomas, skin, thyroid cancers	*WRN* 8p11
Rothmund-Thomson	Poikiloderma, skeletal defects small stature, juvenile cataracts	*Osteosarcoma*, skin cancer	*RECQL4* 8q24.3

1st RTS Conference 2007

Texas Children's Hospital
Houston, TX

Texas Children's Cancer Center

BCM Baylor College of Medicine

RECQ2016

“Partnering for Progress”

3rd International Meeting on RECQ Helicases in Biology and Medicine

05/28/16 – 05/30/16
Fred Hutchinson Cancer Research Center
Seattle, WA

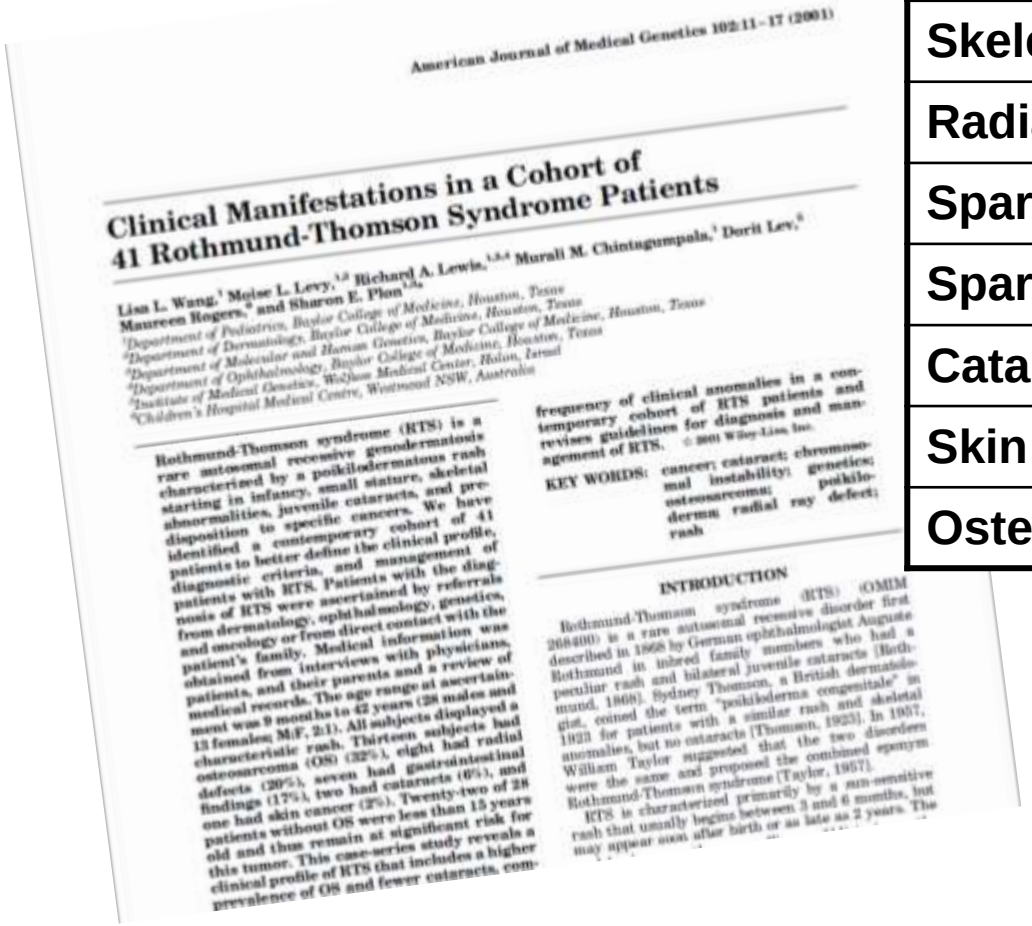
How we got started

- Patient diagnosed with osteosarcoma (OS)
- 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?**

1999

1: Defining the syndrome

- IRB protocol
- Identify RTS patients from around the world
- Collect clinical data



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

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

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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 propose a revised 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

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%**

- Established clinical diagnostic criteria for RTS
- Helpful for clinicians

2001

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

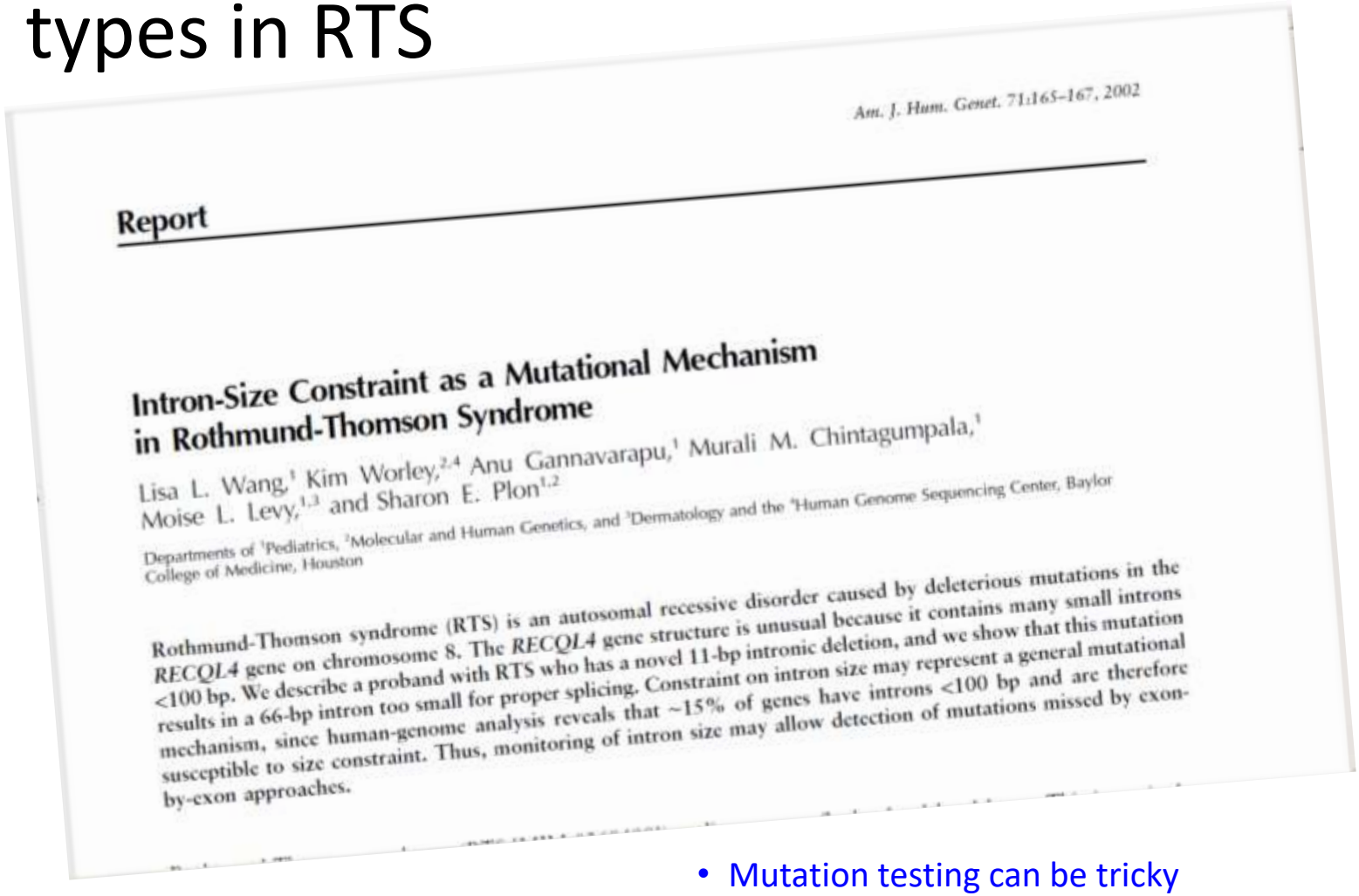
The coding sequence of *RECQL4*, consisting of 3,627 bases and encoding a protein with 1,208 amino acids, has been published[18]; exon and intron junctions have also recently been identified (unpublished data). We amplified all exon regions of *RECQL4* from patients by PCR and compared their sequences

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

3: Sequenced 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 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.

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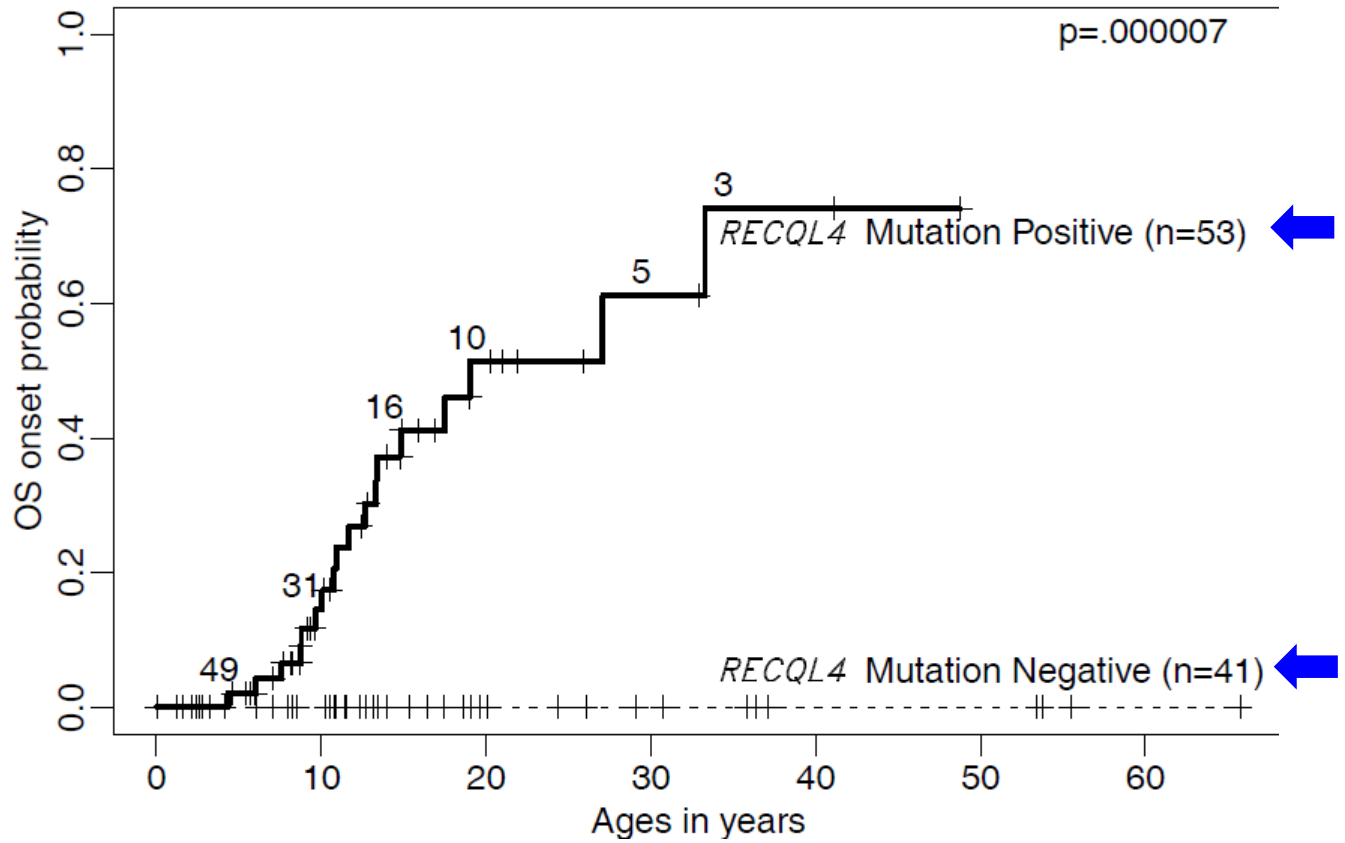
2003

RECQL4 mutation status and OS in RTS



Type 2 RTS:

RECQL4 mutations

Increased risk of OS compared to Type 1

Type 1 RTS:

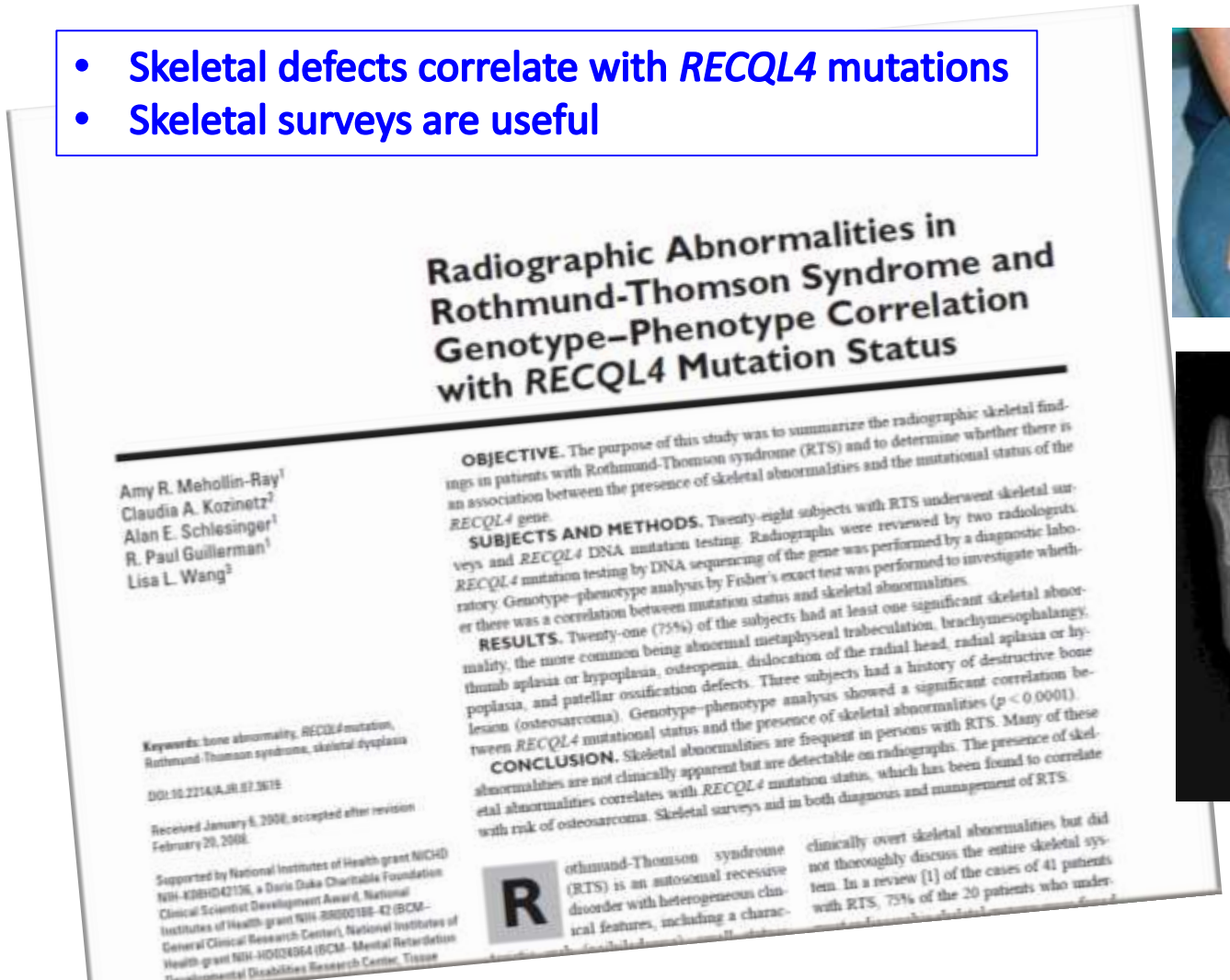
No *RECQL4* mutations

- Useful for doctors and genetic counselors

Lu, Adv Exp Med Biol 2014

4: Determining if *RECQL4* mutations correlate with other features of RTS: *Skeletal (bone) 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

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Claudia A. Kozinetz[2]
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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.

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

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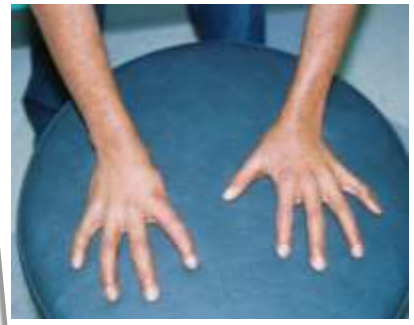
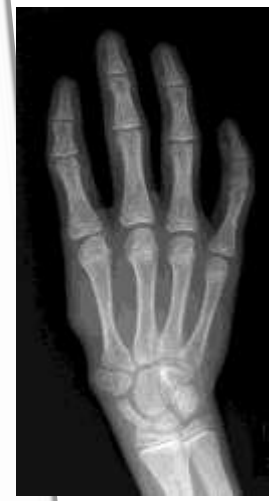
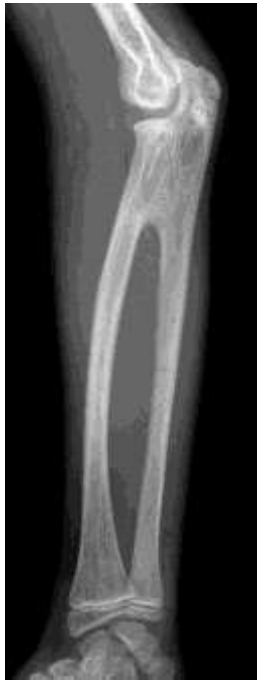
Supported by National Institutes of Health grant NICHD NIH-K08HD42136, a Doris Duke Charitable Foundation Clinical Scientist Development Award, National Institutes of Health grant NIH-RR00188-42 (BCM–General Clinical Research Center), National Institutes of Health grant NIH-HD024064 (BCM–Mental Retardation Developmental Disabilities Research Center, Tissue

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

VOLUME 25 · NUMBER 4 · FEBRUARY 1 2007

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.

Supported by NIH-NICHD K08HD42136, the Doris Duke Charitable Foundation Clinical Scientist Development Award, NIH-RR00188-42 (BCM-General Clinical Research Center), and NIH-HD024064 (BCM-Mental Retardation Developmental Disabilities Research Center, Tissue Culture Core).

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.

- 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.

2007

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

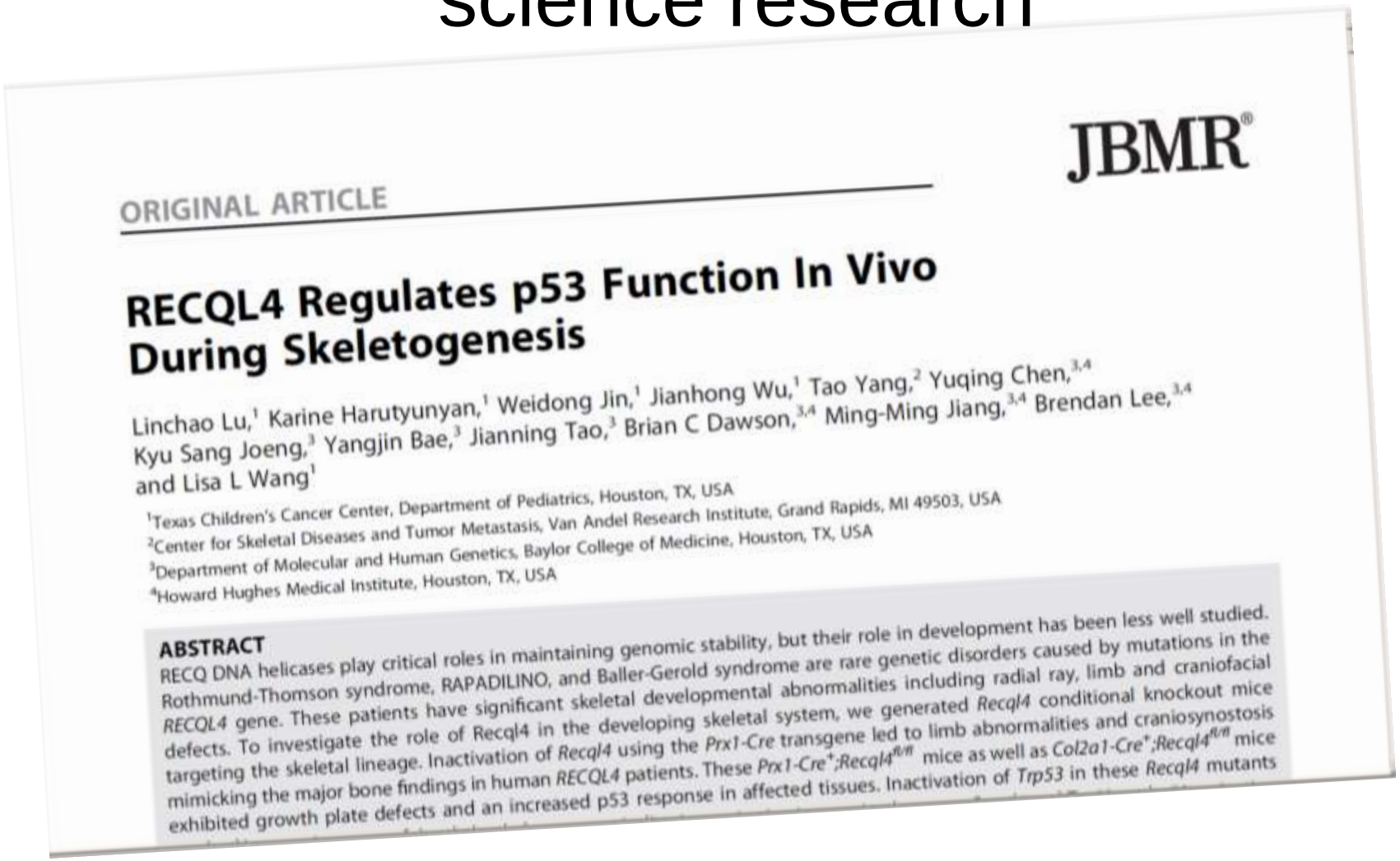
function of the RECQL4 protein. Our results show that primary fibroblasts from RTS patients carrying two deleterious *RECQL4* mutations, compared to wild type (WT) fibroblasts, have increased sensitivity to HU, CPT, and doxorubicin (DOX), modest sensitivity to other DNA damaging agents including ultraviolet (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: Modeling RTS in the lab for basic science research



ORIGINAL ARTICLE

JBMR®

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

8: Do RTS patients have altered bone metabolism?

Human Molecular Genetics, 2017, Vol. 0, No. 0 1–10
doi: 10.1093/hmg/ddx178
Advance Access Publication Date: 9 May 2017
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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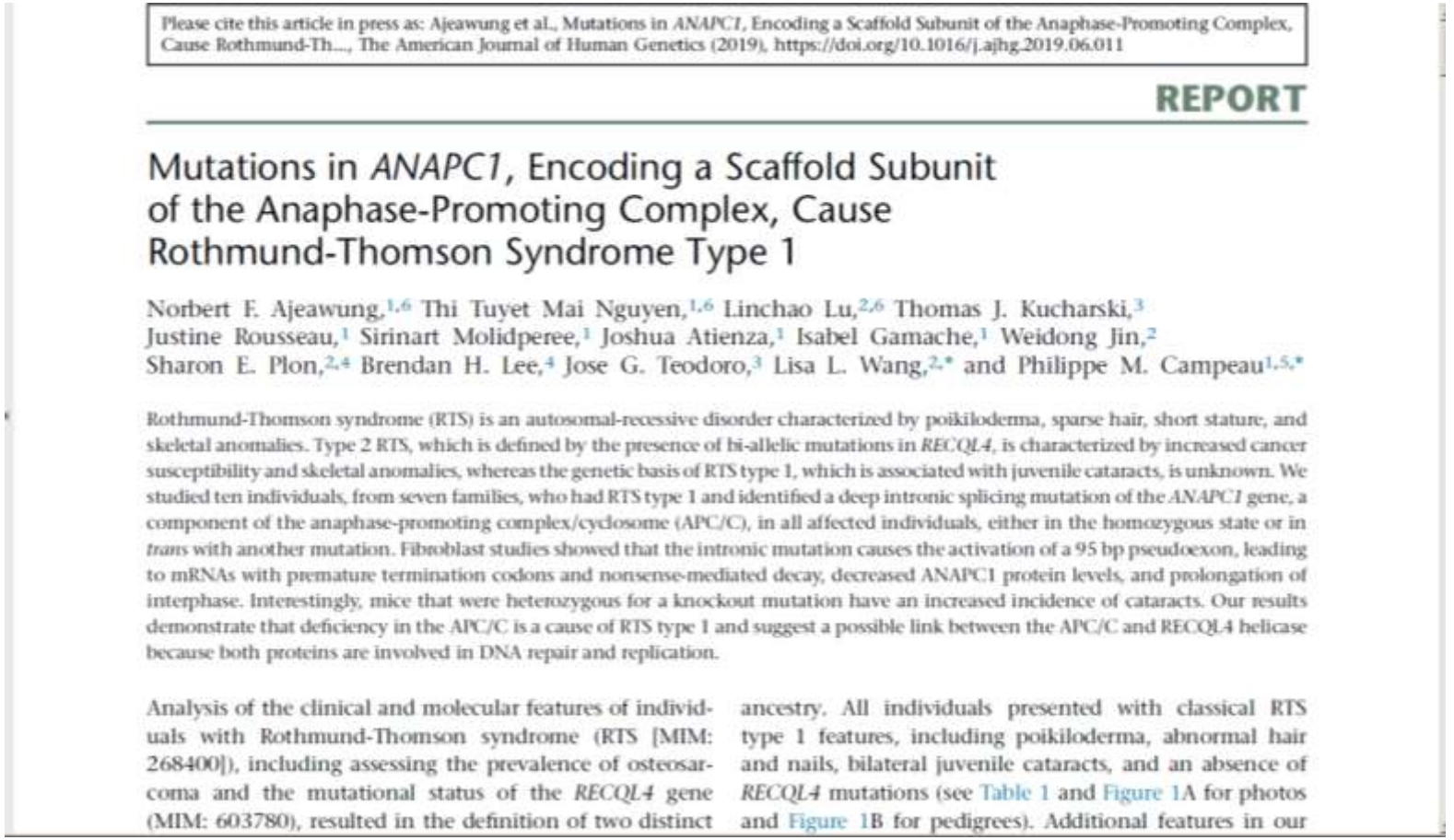
Abstract

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

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

2017

9: 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

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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

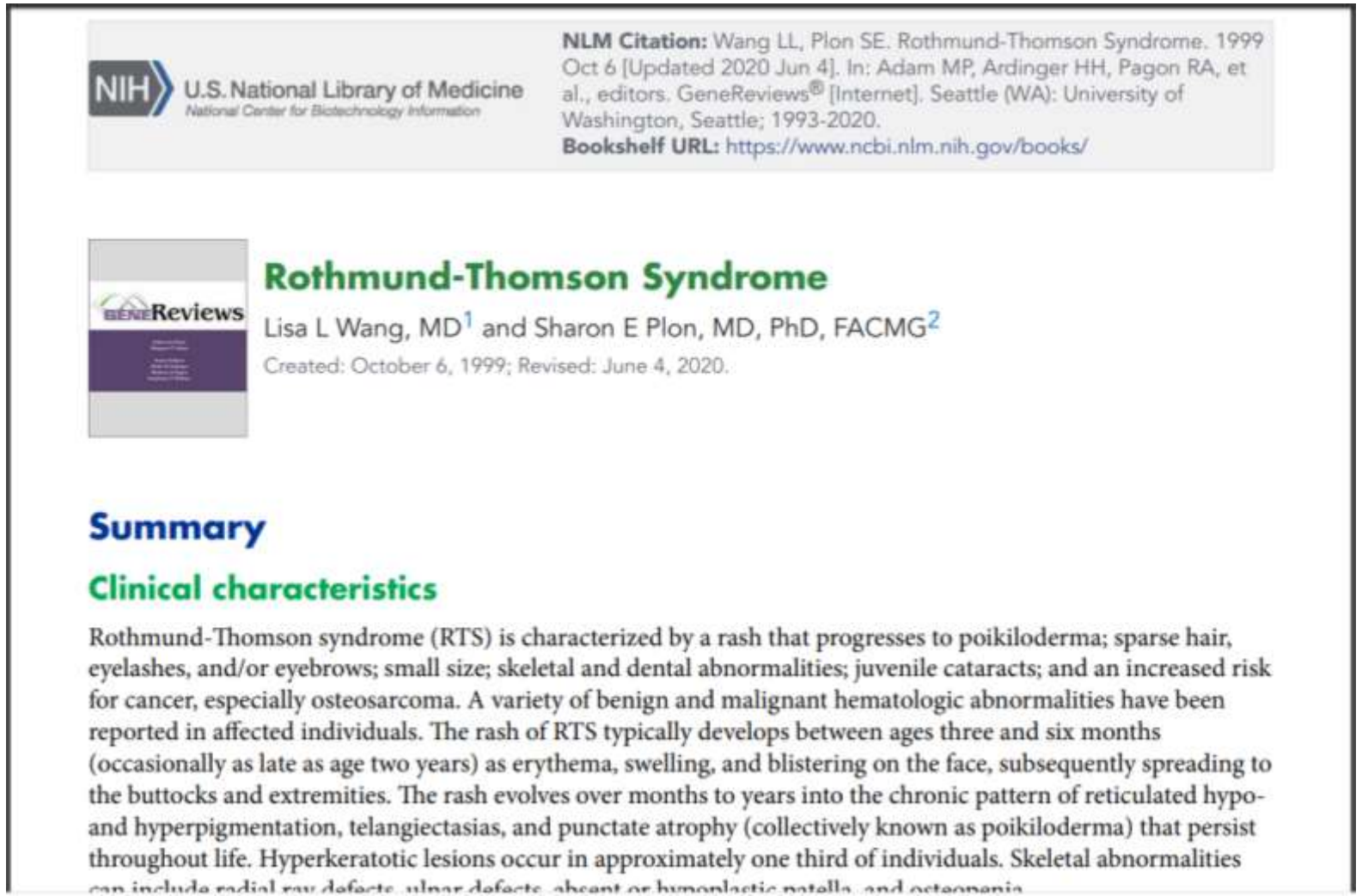
- Mutations in *ANAPC1* identified in 10/18 subjects (7/14 families) with Type 1 RTS
- Correlation with juvenile cataracts
- Helpful in diagnosing, managing and counseling patients

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/



NIH U.S. National Library of Medicine
National Center for Biotechnology Information

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

GeneReviews

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

RTS Registry

- Information entered into database
- Yearly recontact
- Allows researchers to
  - describe the natural history of RTS
  - understand the full clinical manifestations in RTS patients and their family members
  - Identify new areas of research study

Demographics of RTS Subjects

	White, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Black, not Hispanic Origin	Mixed Race	Unknown	TOTAL
Female	46 *(30.2%)*	12 *(7.8%)*	5 *(3.2%)*	*0*	*3 (1.9%)*	*1 (0.6%)*	***67 (44%)***
Male	54 *(35.5%)*	*22 (14.4%)*	*7 (4.6%)*	*2 (1.3%)*	*0*	0	***85 (55.9%)***
TOTAL	**100 *(65.7%)***	**34 *(22.3%)***	**12 *(7.8%)***	***2 (1.3%)***	***3 (1.9%)***	**1 *(0.6%)***	**152 *(100%)***

Texas Children's Cancer and Hematology Centers

Baylor College of Medicine Study, August 2022

Baylor College of Medicine

Enrollment of RTS Families

	RTS probands	Parents	Siblings	Other Relatives	TOTAL
Male	85	90	32	4	211
Female	67	104	40	11	222
TOTAL	152	194	72	15	**433**

Texas Children's Cancer and Hematology Centers

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Biologic Samples from RTS Families

Probands	DNA	LCLs	Fibroblasts
152	115	90	65
Relatives	DNA	LCLs	Fibroblasts
278	177	160	100

Texas Children's Cancer and Hematology Centers

Baylor College of Medicine Study, August 2022

Baylor College of Medicine

Key points

Why it is important to work together as a team

- Recognition of RTS as underlying genetic disorder
- Delivery of all therapy
- Recognition of the cancer risk – multiple primary cancers
- Modification of treatment according to specific situation (IE/MTX, XRT)
- Understanding of the biology to look for targeted therapies

Questions to ask your oncologist

- What type of cancer is it? (copy of pathology report)
- How much experience do you have treating this type of cancer? How much experience do you have treating cancer in a patient with Bsyn?
- Are there any targeted or personalized therapies available?
- Should I get a second opinion?
- What are the risks/benefits of each treatment option?
- How can I manage potential side effects?
- Contact BSR and BSA

How to get involved

- All new patients with Bloom Syndrome registered through the Registry
- Let the BSR know any health updates
  - Annual questionnaire
  - Samples
    - Serial blood samples
    - Tumor samples- contact Registry as early as possible
  - Treatment roadmaps
  - Documentation of side effects
  - Outcomes
- Ongoing research studies at UCLA focusing on blood cancers
  - Contact Vivian Y. Chang vchang@mednet.ucla.edu

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