Rothmund-Thomson Syndrome
Type 1 vs. Type 2

Webinar Series, #3

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History of RTS

• 1868: Auguste Rothmund first described the characteristic rash and cataracts in brothers from an inbred Austrian families

• 1923: M. Sydney Thomson described the rash and skeletal anomalies in sisters in England; coined term “poikiloderma congenitale”
• 1957: William Taylor united the two disorders, proposed eponym “Rothmund-Thomson Syndrome”
## Summary of Clinical Findings in 41 RTS Subjects

**Baylor College of Medicine Study**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Occurrence</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>41/41</td>
<td>100%</td>
</tr>
<tr>
<td>Small stature</td>
<td>25/38</td>
<td>66%</td>
</tr>
<tr>
<td>Skeletal dysplasia</td>
<td>15/20</td>
<td>75%</td>
</tr>
<tr>
<td>Radial ray defect</td>
<td>8/40</td>
<td>20%</td>
</tr>
<tr>
<td>Sparse scalp hair</td>
<td>15/30</td>
<td>50%</td>
</tr>
<tr>
<td>Sparse brows/lashes</td>
<td>19/26</td>
<td>73%</td>
</tr>
<tr>
<td>GI disturbance</td>
<td>7/41</td>
<td>17%</td>
</tr>
<tr>
<td>Cataracts</td>
<td>2/32</td>
<td>6%</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>1/41</td>
<td>2%</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>13/41</td>
<td>32%</td>
</tr>
</tbody>
</table>

Characteristic rash of RTS. The *acute phase* of the rash starts on the cheeks during infancy (A) and spreads to buttocks (B) and extremities (C). The *chronic phase* persists as *poikilodermata*.
RTS rash-extremities
RTS rash-extremities
Radial Ray Defects in RTS
Radial Ray Defects in RTS
Nail abnormalities in RTS
RTS Hyperkeratosis
RTS Hyperkeratosis
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

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

  • Hearing loss, gastrointestinal problems, immune deficiency…

# Enrollment of RTS Families

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Probands</th>
<th>Type 2 Probands</th>
<th>Type 1 Family Members</th>
<th>Type 2 Family Members</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>21</td>
<td>33</td>
<td>50</td>
<td>83</td>
<td>187</td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>45</td>
<td>34</td>
<td>76</td>
<td>184</td>
</tr>
<tr>
<td>TOTAL</td>
<td><strong>50</strong></td>
<td><strong>78</strong></td>
<td><strong>84</strong></td>
<td><strong>159</strong></td>
<td><strong>371</strong></td>
</tr>
</tbody>
</table>

Baylor College of Medicine Study, November 2020
Kitao et al. (1999) Nature Genetics; 22: 82-84

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

Saori Kitao¹, Akira Shimamoto¹, Makoto Goto², Robert W. Miller³, William A. Smithson⁴, Noralane M. Lindor⁴ & Yasuhiro Furuichi¹

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 neoplasia¹⁻⁴. Cytogenetic studies indicate that cells from

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

The coding sequence of **RECQL4**, consisting of 3,627 bases and encoding a protein with 1,208 amino acids, has been published¹⁸; 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
**RECQL4**

- Genetic locus: *RECQL4* at 8q24.3
- Encodes member of RECQ DNA helicase family
- RECQ helicases: DNA unwinding enzymes involved in basic cellular functions (DNA replication, recombination, transcription, repair)
- Important for maintaining *genomic stability*
Cellular Roles of RECQL4

- Initiation of DNA replication
- DNA repair: double strand break and base excision repair
- Telomere maintenance
- Maintenance of mitochondrial integrity
- Response to oxidative stress
1st Question:

Does the presence of *RECQL4* mutations correspond to increased risk of osteosarcoma in RTS patients?
Sequence RECQL4 gene in RTS patients to determine mutation frequency

- Mutation testing done initially in the lab as part of research
- Now widely available as a clinical test
Association Between Osteosarcoma and Deleterious Mutations in the RECQL4 Gene in Rothmund-Thomson Syndrome

Lisa L. Wang, Anu Gannavarapu, Claudia A. Kozielnz, 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 (polioderma), small stature, and skeletal dysplasia. 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) \( (P = .037; \text{two-sided log-rank test}) \). 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]

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Presence of *RECQL4* mutations increases risk of OS in RTS

2nd Question:

Does the presence of \textit{RECQL4} mutations correspond to increased risk of \textit{skeletal defects} in RTS patients?
Type 2 RTS and skeletal defects

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

Amy R. Mehollin-Ray
Claudia A. Koziner
Alan E. Schlessinger
R. Paul Gullamer
Lisa L. Wang

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 nutritional 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 most common being abnormal metaphyseal trabeculation, brachymesophalangy, thumb aplasia or hypoplasia, osteopenia, dislocation of the radial head, radial aplasia or hypoplasia, and postural ossification defects. Three subjects had a history of destructive bone lesion (osteosarcoma). Genotype–phenotype analysis showed a significant correlation between RECQL4 mutation status and the presence of skeletal abnormalities (p < 0.0001).

CONCLUSION. Skeletal abnormalities are frequent in patients 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 characteristic physiologic alopecia, skin lesions, and growth retardation. However, skeletal abnormalities are also a hallmark of RTS.

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

DOI: 10.2114/A.J.07.1619

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

Supported by National Institutes of Health grants RO1 HD010421R, a Doris Duke Charitable Foundation Clinical Scientist Development Award, National Institutes of Health grant P50 HG003072 (GCRC, General Clinical Research Center), National Institutes of Health grant RO1HD30084 (BCOR, Mental Retardation Developmental Disabilities Research Center, Texas.

2008
Skeletal Findings in RTS

- 75% (21/28) had major skeletal abnormalities
- The most common findings were:
  - Abnormal metaphyseal trabeculation (64%)
  - Brachymesophalangy (64%)
  - 1st metacarpal or thumb agenesis/hypoplasia (43%)
  - Osteopenia (25%)
  - Radial agenesis/hypoplasia (21%)
  - Radioulnar synostosis (18%)
  - Ulnar hypoplasia (18%).
  - History of OS (11%)

RTS Classification

• **Type II RTS**
  – Poikiloderma
  – Mutations in \textit{RECQL4}
  – Increased risk for OS
  – Association with skeletal defects

• **Type I RTS**
  – Poikiloderma
  – No mutations in \textit{RECQL4}
  – Less risk of cancer

Type 1 RTS

- Cause unknown at the time
- Likely due to gene(s) other than *RECQL4*
- Classic poikiloderma and skin findings
- Less cancer risk
- More juvenile cataracts
- Exome sequencing project with Dr. Philippe Campeau (BCM-Montreal)
A cause for Type 1 RTS

• Mutations in ANAPC1 identified in 10/18 subjects (7/14 families) with Type 1 RTS
Causative genes in RTS

<table>
<thead>
<tr>
<th>RTS</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene defect</td>
<td>ANAPC1</td>
<td>Unknown</td>
</tr>
<tr>
<td># of individuals</td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>
# Type 1 and Type 2 RTS Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poikiloderma</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sparse hair/brows/lashes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bone defects</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Osteopenia/osteoporosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Cataracts</td>
<td>++(juvenile)</td>
<td>+</td>
</tr>
<tr>
<td>Squamous or basal cell skin cancer</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hearing problems</td>
<td>+</td>
<td>++</td>
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Thank you