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METABOLIC BONE DISEASE AND FRACTURE RISK IN ROTHMUND-THOMSON SYNDROME

Dr. Kapil Pawar[1], Dr. Anil Patel[2]

[1]Associate Professor Dept. of Orthopedics Govt. Medical College and Shri Vinoba Bhave Civil Hospital, Silvassa.

[2]Senior Consultant Dept. of Orthopedics Govt. Medical College and Shri Vinoba Bhave Civil Hospital, Silvassa.

ABSTRACT:

Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive genodermatosis disorder. It is characterized by poikiloderma, small stature, sparse hair, skeletal abnormalities, juvenile cataract, increased risk of osteosarcoma, decreased bone mass, and predisposition to certain cancers particularly certain types of skin and bone cancer in addition to associated with diminished bone mineral density. In childhood, the inflammation tends to affected skin area develops into a more chronic pattern of rash called as poikiloderma, characterized by telangiectases; small spots of atrophy; and abnormal skin areas pigmentation alternating between hyperpigmentation and hypopigmentation, giving a lacy, web-like, or mottled appearance. Skin manifestations that to be more prominent in adulthood is called hyperkeratosis, where certain areas of body like palms and soles, knees and around the fingers or toes, become thickened and overgrown and develop a rough, wart-like texture. In study we have reported that a majority of patients with RTS having some skeletal abnormalities like radial aplasia or hypoplasia, synostoses, abnormal metaphyseal trabeculation, brachymesophalangy, and patellar defects. In addition osteopenia, pathologic fractures, and delayed fracture healing have also been founded; it may lead to a more systemic skeletal involvement. ***Material and method:*** *The present study was conducted in the Dept. of Ortho at Govt. Medical College and Shri Vinoba Bhave Civil Hospital, Silvassa. Total 35 patients with RTS were included in this study (22 males, 13 females). The study includes children (23 mean ages was 5.94 ± 1.34) and adults (12 mean ages was 35.98 ± 6.87). Radiographs were reviewed by two radiologists. From the patients and their relative family history were taken and pedigree was constructed for each kindred. Peripheral blood samples and skin punch biopsy samples were obtained from each patient. Skin biopsy samples were transported in -modified Eagle medium (-MEM) with 10% fetal bovine serum (Invitrogen, Carlsbad, CA). Blood samples obtained in acid– citrate–dextrose collection tubes were used to establish Epstein– Barr virus-transformed lymphoblastoid cell lines (LCLs).* ***Result:*** *Total 35 patients were included in this study with RTS 24 males and 11 females. The study includes children (23 mean ages was 5.94 ± 1.34) and adults (12 mean ages was 35.98 ± 6.87). Twenty three had pathogenic variants in alleles of RECQL4 and twelve had no detectable pathogenic variants (Type 1 RTS: n = 12). The median age in this sub study (8 males, 5 females) was 10years (range 1–49 years). Eight patients who participated in calcium kinetic studies DXA scans were performed. The median whole body aBMD-for-age Z-score in these individuals was 1.3 (IQR 0.9 to 1.4) and median lumbar spine aBMD-for-age Z-score was 2.5 (IQR 0.2 to 3.1). EP and V0þ were found to be within the age-adjusted normal ranges for all patients.* ***Conclusion:*** *Rothmund-Thomson syndrome is a rare autosomal recessive disorder in most common which is characterized by particularly radial ray defects and imaging by dental and skeletal abnormalities. In RTS patients with mutations in RECQL4 gene skeletal abnormalities are very common and skeletal abnormalities are also increased risk for pathologic fragility fractures. Due to associated diminished bone mineral density there will be delayed fracture healing. Hence RTS patients with the RECQL4 gene mutation are also high risk of developing*

Corresponding author: Dr. Anil Patel

osteosarcoma which could be present as a pathologic fracture. Therefore attention should be made for underlying malignancy in all fractures occurring in RTS patients.
Keywords: *Rothmund-Thomson syndrome (RTS), Osteosarcoma, RECQL4, Poikiloderma.*

Introduction

Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive genodermatosis disorder. It is characterized by poikiloderma, small stature, sparse hair, skeletal abnormalities, juvenile cataract, increased risk of osteosarcoma, decreased bone mass, and predisposition to certain cancers particularly certain types of skin and bone cancer in addition to associated with diminished bone mineral density [1,2].

In childhood, the inflammation tends to affected skin area develops into a more chronic pattern of rash called as poikiloderma, characterized by telangiectases; small spots of atrophy; and abnormal skin areas pigmentation alternating between hyper pigmentation and hypo pigmentation, giving a lacy, web-like, or mottled appearance. Skin manifestations that to be more prominent in adulthood is called hyperkeratosis, where certain areas of body like palms and soles, knees and around the fingers or toes, become thickened and overgrown and develop a rough, wart-like texture [3].

A many individuals suffering from RTS have slow growth before and after birth and it leads to mild to moderate small stature. In child age, some children suffer from RTS may also develop sudden clouding of the lenses. These developed cataracts may result in severe visual impairment. Most of the patients with RTS have bone abnormalities sometimes they visible clinically or not be. One of the most important abnormalities is a radial ray defect, which is small, malformed or missing thumbs or shortened forearms and some of these bone findings can only be seen on x-rays. Patients may also have decreased bone density called as osteoporosis which in severe cases could lead to fractures. Some patients require feeding tubes to maintain nutritional intake [4,5].

Diagnosis of RTS is based on clinical findings and molecular analysis for RECQL4 mutations. The gene defect in two-thirds of cases is due to mutations in a gene called RECQL4 [6]. A fully informative test requires transcript analysis not to overlook intronic deletions causing misplacing. The diagnosis of RTS should be considered in all patients with osteosarcoma, particularly if associated with skin changes. Patients having signs of RTS during infancy, and the first feature of RTS is a rash that starts appearing on the cheeks and later it spreads to other parts of the body (arms and legs). The rash become chronic and persists for life. Other features may appear other areas of the body such as the eyes, bones, teeth, and hair, and patients may often be small in size compared to their peers. Lifespan is generally felt to be normal in the absence of death due to cancer [7].

In study we have reported that a majority of patients with RTS having some skeletal abnormalities like radial aplasia or hypoplasia, synostoses, abnormal metaphyseal trabeculation, brachymesophalangy, and patellar defects. In addition osteopenia, pathologic fractures, and delayed fracture healing have also been founded; it may lead to a more systemic skeletal involvement [8-11]. Low areal bone mineral density (aBMD) in individuals with RTS could be due a central role of RECQL4 in bone development, nutrient deficiencies, feeding issues, and exposure to sunlight. Low aBMD and its associated risk for pathologic fractures can add to the significant morbidity in this disorder. Here, we investigate 35 individuals of metabolic bone disease and fracture with RTS.

MATERIAL AND METHODS

The present study was conducted in the Dept. of Ortho at Govt. Medical College and Shri Vinoba Bhave Civil Hospital, Silvassa. Total 35 patients with RTS were included in this study (22 males, 13 females). The study includes children (23 mean ages was 5.94 ± 1.34) and adults (12 mean ages was 35.98 ± 6.87). Radiographs were reviewed by two radiologists.

Table 1: Distribution of RTS patients

	Children		Adults	
	Male	**Female**	**Male**	**Female**
	16	7	8	4
Total	23		12	

The patients were initially diagnosis of RTS and osteosarcoma then all the patients and from their relatives were counsel and written provided for consent to participate in our research protocol, which was approved by the Institutional committee of Seth GS Medical College and KEM Hospital Parel Mumbai. From the patients and their relative family history were taken and pedigree was constructed for each kindred. Peripheral blood samples and skin punch biopsy samples were obtained from each patient. Skin biopsy samples were transported in -modified Eagle medium (-MEM) with 10% fetal bovine serum (Invitrogen, Carlsbad, CA). Blood samples obtained in acid– citrate–dextrose collection tubes were used to establish Epstein– Barr virus-transformed lymphoblastic cell lines (LCLs)[12].

OBSERVATIONS & RESULTS

Total 35 patients were included in this study with RTS 24 males and 11 females. The study includes children (23 mean ages was 5.94 ± 1.34) and adults (12 mean ages was 35.98 ± 6.87). Twenty three had pathogenic variants in alleles of RECQL4 and twelve had no detectable pathogenic variants (Type 1 RTS: n = 12) as shown in table below (table no.1)

Table 2: Characteristics of RTS in patients

Subject	Age at Enrollment (Year, month)	Sex	Pathogenic Variants in RECQL4	Weight-for -age Z-score	Height-for-age Z-score	WB aBMD Z-score	LS aBMD Z-score	TH aBMD Z-score	FN aBMD Z-score	Fat mass/ Height^2 percentile	Lean mass/ Height^2 percentile	History of fractures	Number of fractures	Age in yrs at first fracture
1	1 Y, 0 m	F	c.1483 þ 27_1483 þ 37del	4.5	5.0	NA	NA	NA	NA	NA	NA	–	0	NA
2	1 Y, 9 m	F	ND	1.7	0.4	NA	2.4	NA	NA	NA	NA	–	0	NA
3	1 Y, 10 m	F	c.2269C>T/p.Gln757Ter	1.9	3.4	NA	NA	NA	NA	NA	NA	–	0	NA
4	3 Y, 5 m	F	c.1573del	4.2	3.0	NA	2.4	NA	NA	NA	NA	–	0	NA
5	4 Y, 1 m	M	c.2719C>T/p.Gln907Ter	7.3	5.0	NA	4.6	5.1	4	NA	NA	þ	1	1
6	4 Y, 5 m.	M	c.2269C>T/p.Gln757Ter	0.2	0.2	1.1	0.2	0.2	NA	NA	NA	-	0	NA
7	4 Y, 11 m	F	c.3284_3287dupAGCG	0.9	2.1	NA	NA	NA	NA	NA	NA	-	0	NA
8	5 Y, 7 m	M	c.118 þ 27_118 þ 51del	4.4	3.9	0.39	2.7	3.3	2.4	NA	NA	-	0	NA
9	5 Y, 9 m	F	c.2269C>T/p.Gln757Ter	0.7	0.6	NA	NA	NA	NA	NA	NA	þ	2	5
10	5 Y, 10 m.	F	c.2161C>T/p.Arg721Ter	1.1	1.4	1.18	2.8	0	0.1	NA	NA		1	5
11	5 Y, 11 m	F	ND	8.1	7.6	2.32	3.0	2.9	2.5	NA	NA	-	O	NA
12	6 Y, 6 m	M	c.1573del	1.6	3.1	1.33	2.4	2.6	2	NA	NA	Þ	2	3
13	8 Y, 1,	M	c.2269C>T/p.Gln757Ter	4.9	4.1	NA	NA	NA	NA	NA	NA	-	0	NA
14	8 Y, 5 m	F	ND	3.6	3.4	1.31	1.2	1.3	0.7	14	5	Þ	2	1
15	8 Y, 8 m	F	c.2269C>T/p.Gln757Ter	3.4	3.0	NA	NA	NA	NA	NA	NA	-	0	NA
16	8 Y, 11 m	M	c.2269C>T/p.Gln757Ter	2.8	2.3	NA	NA	NA	NA	NA	NA	Þ	1	3
17	9 Y, 1 m	M	ND[#]	0.2	0.5	0.4	0.2	1.0	0.2	29	30	Þ	1	9
18	9 Y, 9 m	M	ND	2.6	3.2	1.4	2.1	2.4	1.7	35	7	þ	1	7
19	9 Y, 9 m	M	ND	2.0	2.7	1.4	3.1	2.1	1.5	32	8	–	0	NA
20	15 Y, 0 m	F	ND	3.0	1.2	2.2	2.6	4.4	4.6	4	1	þ	3	6
21	24 Y, 7 m	F	c.3283_3284insGAGC[#]	2.8	3.8	0.5	1.2	1.5	0.7	36	16	þ	4	10

22	30 Y, 0 m	F	c.2492_2493del [#]	0.9	1.6	1.2	1.3	1.4	1.3	38	18	þ	9	2
23	33 Y, 0 m	M	c.1391-1G>A [#]	2.4	3.7	2.1	2.3	2.0	2.2	53	13	þ	11	15
24	34 Y, 3 m.	M	c.1573del	1.5	2.7	1.1	0	0.8	1.0	46	3	Þ	2	5
25	36 Y, 3 m	F	c.2555_2560del	1.0	0.5	1.1	0.2	0.1	0	55	57	þ	5	8
26	36 Y, 6 m	M	c.2207_2208insC	2.0	3.6	0.9	1.3	0.6	0.6	24	19	-	0	NA
27	38Y, 4 m	M	c.2492_2493del	3.6	3.7	1.2	2.2	1.3	1.7	16	1	Þ	12	5
28	39 Y, 2 m	F	ND	0.3	1.1	1.6	1.0	0.4	0.2	21	19	–	0	NA
29	40 Y, 11 m	F	5446delAG	1	2.1	0.6	0.2	0.7	0.8	73	68	–	0	5
30	42 Y, 4 m	M	c.2492_2493del	1.6	3.2	1.4	2.1	2.5	1.7	35	7	þ	1	7
31	43 Y, 2 m	F	ND	2.0	2.7	1.4	3.1	2.1	1.5	32	8	–	0	NA
32	46 Y, 11 m	F	ND	3.0	1.2	2.2	2.6	4.5	4.6	4	1	þ	3	7
33	47 Y, 7 m	M	4644delAT	0.9	2.1	NA	NA	NA	NA	NA	NA	-	0	NA
34	49 Y	F	ND	4.4	4.0	0.3	2.7	3.2	2.4	NA	1	-	1	1
35	50 Y	F	ND	1.7	0.6	0.4	NA	1.6	NA	NA	NA	þ	2	3

M - male; F- female; ND – mutation not detected; þ and – denote presence and absence of fracture history, respectively; NA - not applicable. [#]Sequencing results performed by a research laboratory at Baylor College of Medicine (L.L.W.); WB – whole body; LS – lumbar spine; TH – total hip; FN – femoral neck; [a]Number of reported fractures at time of enrollment.Further for the determination of abnormalities in calcium metabolism in RTS which can be contribute to the low aBMD, particularly with respect to deposition in the bone. 13 individuals underwent calcium kinetic studies [13, 14]. The parameters evaluate the calcium kinetic studies included the rate of calcium deposition in bone (V0þ) and the size of the exchangeable calcium pool in bone (EP)[13]. The median age in this sub study (8 males, 5 females) was 10years (range 1–49 years). eight patients who participated in calcium kinetic studies DXA scans were performed. The median whole body aBMD-for-age Z-score in these individuals was 1.3 (IQR 0.9 to 1.4) and median lumbar spine aBMD-for-age Z-score was 2.5 (IQR 0.2 to 3.1). EP and V0þ were found to be within the age-adjusted normal ranges for all patients as shown in table below (table no. 2)[15-18].

Table 3: Calcium kinetic parameters in RTS patients

Subject	Exchangeable pool of bone EP (g)	Bone calcium deposition Vo þ (g/d)	Rate constant Ko þ (d^{1})
1	2.2	1.5	0.4
5	2.6	1.0	0.4
7	5.7	2.5	0.3
9	7.8	1.5	0.2
10	6.4	2.9	0.4
12	5.0	1.5	0.3
15	3.7	1.5	0.3
17	6.2	1.1	0.2
18	10.8	3.7	0.4
19	6.1	2.9	0.3
20	5.5	1.6	0.3
31	4.3	0.6	0.1
32	4.6	0.7	0.2
Reference: Prepubertal	2.2–6.7	0.9–2.7	0.2–0.7
Reference: Healthy adult (age 20–40 years)	2.9–7.7	0.3–1.5	0.1–0.5

Besides this radiographic of the different site of the facture were done from the patients which shows different mild to severe deformity were observed.

Fig. 1: radiographic showing patients of young adult male with history of Rothmund-Thomson syndrome which was diagnosed at 2 years of age. In the findings there is no bridging bone formation occurred at the two-month follow-up radiograph of the olecranon fracture. Technique: lateral radiograph kVp = 60, mAs = 2.

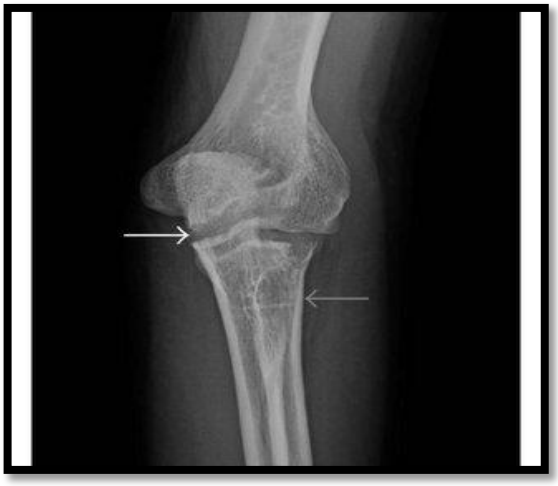

Fig. 3: radiographic showing patients of young adult male with history of Rothmund-Thomson syndrome diagnosed at 2 years of age.
In the findings: (a) mildly displaced fracture was observed through the olecranon (white arrow). It was also observed that congenital fusion of radial head and proximal ulna (grey arrow).
(b) The mild displaced olecranon is better observed on the lateral radiograph. There is osteolysis and cortication along the fracture margins (oval) and raised the concern for underlying lytic bone lesion. Congenital fusion of the radial head and ulna is again observed (grey arrow). Technique: (a) AP radiograph kVp = 65, mAs = 4, and (b) Lateral radiograph kVp = 65, mAs = 4.

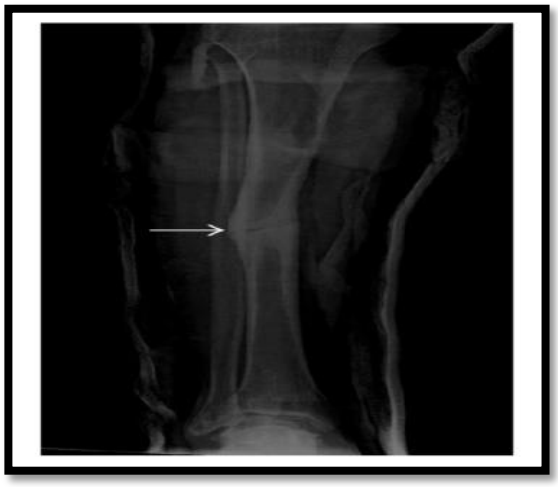

Fig. 2: radiographic showing patients of young adult male with history of Rothmund-Thomson syndrome diagnosed at 2 years of age. In findings it was observed that satisfactory alignment of the minimally displaced mid tibia diaphyseal fracture (arrow) on the AP projection after casting and lateral view also shows satisfactory alignment of the tibia diaphyseal fracture (arrow) after casting. Technique: (a) AP radiograph kVp = 60, mAs = 3, and (b) lateral radiograph kVp = 60, mAs = 4.

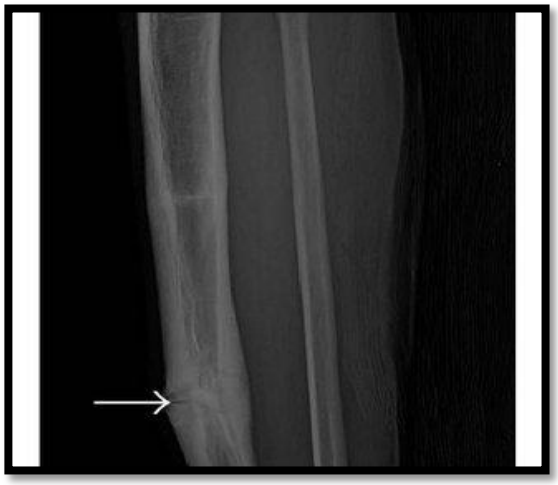

Fig: radiographic showing patients of young adult male with history of Rothmund-Thomson

syndrome diagnosed at 2 years of age. It was observed that recurrent mildly displaced mid tibia diaphyseal fracture through the area of tibia fracture 9 years earlier (arrow) and mildly displaced fracture of the mid tibia diaphysis again seen. This shows that there is increased cortical thickening of the mid tibia diaphysis (arrow). Technique: (a) AP radiograph kVp = 57, mAs = 3, and (b) lateral radiograph kVp = 57, mAs = 3.

DISCUSSION

In 1868 Auguste Rothmund was first to described Rothmund-Thomson syndrome (RTS) in inbred family members with an unusual rash and juvenile cataracts [19]. In 1923 Sydney Thomson described a condition in patients with a similar rash and skeletal anomalies but no cataracts, which he called "poikiloderma congenitale"[20]. RTS is a rare genetic disorder with only a few hundred cases reported in research. RTS typically presents with a poikilodermatous rash, skeletal, gastrointestinal in infancy in conjunction with a wide array of other derma. While RTS is associated with diminished bone mineral density generating potential risk for pathologic and stress related fractures that occurrence of fractures in RTS patients. This study shows the risk of stress and acute insufficiency fractures in a patient with diffusely demineralized bones related to RTS. RTS is a rare autosomal recessive disorder which is caused by deficiency of RECQL4 and DNA helicase belonging to the family of RecQ helicases[21,22]. About three-fourths of individuals with RTS have developmental skeletal abnormalities that my include absent or malformed bones, synostoses and radial ray defects , whereas about a fourth have osteopenia were detected on skeletal in a surveys and history of childhood fractures[23]. In this study detailed clinical investigation of the bone phenotype in 35 patients with RTS were taken. The strengths of the study are largest study to date evaluating metabolic bone disease in individuals with RTS. The evaluation DXA and calcium kinetic studies were performed in a single institution using validated methods. It was also observed the human phenotypes and concordant with the mechanistic studies performed in the genetic mouse model. The studies of Ng and colleagues also have shown RECQL4 is required for osteoblast expansion [24]. Other study also demonstrated that RECQL4 deficiency led to increased p53 activity [25]. Although human experience has not revealed evident association between teriparatide and osteosarcoma which give significantly elevated risk of osteosarcoma in RTS in which this medication would be best avoided [26]. Osteogenesis imperfecta (OI) describes group of heredity disorders of connective tissues which is characterized by decreased bone mineral density and increased bone fragility. Pediatric osteoporosis (OI) is the most common cause with a prevalence of approximately 1 in 12,000 to 15,000 childre[27]. Therefore the results in this study have important suggestion for follow-up and management of low bone mass in RTS. This study recommends a baseline DXA at time of diagnosis in order to establish baseline measurement of aBMD and screening for pathogenic variants in RECQL4 for any potential new patient. RECQL4 status can be correlated with more severe disease phenotype. Supplementation with vitamin D or calcium beyond the recommended daily intake is not warranted. Detailed history of fractures should be taken. Bisphosphonates should be considered for the treatment with history of multiple fractures particularly involving long bones or vertebral fractures.

CONCLUSIONS

Rothmund-Thomson syndrome is a rare autosomal recessive disorder in most common which is characterized by particularly radial ray defects and imaging by dental and skeletal abnormalities. In RTS patients with mutations in RECQL4 gene skeletal abnormalities are very common and skeletal abnormalities are also increased risk for pathologic fragility fractures. Due to associated diminished bone mineral density there will be delayed fracture healing. Hence RTS patients with the RECQL4 gene mutation are also high risk of developing osteosarcoma which could be present as a pathologic fracture. Therefore attention should be made for underlying malignancy in all fractures occurring in RTS patients.

REFERENCES

1. Wang, L.L., Levy, M.L., Lewis, R.A., Chintagumpala, M.M., Lev, D., Rogers, M. and Plon, S.E. Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. Am. J. Med. Genet., 2001;102, 11–17.
2. Larizza, L., Roversi, G. and Volpi, L. Rothmund-Thomson syndrome. Orphanet J. Rare Dis., 2010; 5, 2.
3. Hicks MJ, Roth J, Kozinetz CA, Wang LL. Clinicopathologic Features of Osteosarcoma in Patients with Rothmund-Thomson Syndrome. J Clin Oncol. 2007;25:370-375.
4. Vennos EM, et al. Rothmund-Thomson syndrome. Dermatol Clin. 1995;13:143-50.
5. Vennos EM, et al. Rothmund-Thomson syndrome: review of the world literature. J Am Acad Dermatol. 1992;27:750-62.
6. Kitao, S., Shimamoto, A., Goto, M., Miller, R.W., Smithson, W.A., Lindor, N.M. and Furuichi, Y. Mutations in RECQL4 cause a subset of cases of Rothmund-Thomson syndrome. Nat. Genet., 1999; 22, 82–84.
7. Cao, F., Lu, L., Abrams, S.A., Hawthorne, K.M., Tam, A., Jin, W., Dawson, B., Shypailo, R., Liu, H., Lee, B., Nagamani, S.C.S., Wang, L.L. 2017. Generalized metabolic bone disease and fracture risk in Rothmund-Thomson syndrome. Human Molecular Genetics. 2017; 5 (3).
8. Mehollin-Ray, A.R., Kozinetz, C.A., Schlesinger, A.E., Guillerman, R.P. and Wang, L.L. Radiographic abnormalities in Rothmund-Thomson syndrome and genotype phenotype correlation with RECQL4 mutation status. Am. J. Roentgenol., 2008; 191, W62–W66.
9. Carlson, A.M., Thomas, K.B., Kirmani, S. and Lindor, N.M. Chronic tibial nonunion in a Rothmund-Thomson syndrome patient. Am. J. Med. Genet. A, 2012;158A, 2250–2253.
10. Beckmann, N. Multiple low energy long bone fractures in the setting of Rothmund-Thomson syndrome. Case Rep. Med., 2015, 495164.
11. Barisonek, K.L., Protzman, N.M., Wobst, G.M. and Brigido, S.A. Delayed union of a Jones fracture in a patient with Rothmund-Thomson syndrome, A Case Report and Review of the Literature. J. Foot Ankle Surg., 2014;55, 291–293.
12. Neitzel H. A routine method for the establishment of permanent growing lymphoblastoid cell lines. Hum Genet 1986;73:320–6.
13. Abrams, S.A. (1999) Using stable isotopes to assess mineral absorption and utilization by children. Am. J. Clin. Nutr., 70, 955–964.
14. Abrams, S.A. (1993) Pubertal changes in calcium kinetics in girls assessed using 42Ca. Pediatr. Res., 34, 455–459
15. Abrams, S.A. (1993) Pubertal changes in calcium kinetics in girls assessed using 42Ca. Pediatr. Res., 34, 455–459
16. Abrams, S.A., O'Brien, K.O. and Stuff, J.E. (1996) Changes in calcium kinetics associated with menarche. J. Clin. Endocrinol. Metab., 81, 2017–2020.
17. Abrams, S.A., O'Brien, K.O., Liang, L.K. and Stuff, J.E. (1995) Differences in calcium absorption and kinetics between black and white girls aged 5–16 years. J. Bone. Miner. Res., 10, 829–833
18. Abrams, S.A., Copeland, K.C., Gunn, S.K., Gundberg, C.M., Klein, K.O. and Ellis, K.J. (2000) Calcium absorption, bone mass accumulation, and kinetics increase during early pubertal development in girls. J. Clin. Endocrinol. Metab., 85, 1805–1809.
19. A. Rothmund, "Ueber cataracten in verbindung mit einer eigenthum lichen hautdegeneration," Archiv fur Opthalmologie ¨ , vol. 14, no. 1, pp. 159–182, 1868.
20. M. S. Thomson, "An hitherto undescribed familial disease," British Journal of Dermatology, vol. 35, no. 12, pp. 455–462, 1923.
21. van Brabant, A.J., Stan, R. and Ellis, N.A. (2000) DNA helicases, genomic instability, and human genetic disease. Annu. Rev. Genomics Hum. Genet., 1, 409–459
22. Chakraverty, R.K. and Hickson, I.D. (1999) Defending genome integrity during DNA

replication, a proposed role for RecQ family helicases. Bioessays, 21, 286–294.

23. Mehollin-Ray, A.R., Kozinetz, C.A., Schlesinger, A.E., Guillerman, R.P. and Wang, L.L. (2008) Radiographic abnormalities in Rothmund-Thomson syndrome and genotypephenotype correlation with RECQL4 mutation status. Am. J. Roentgenol., 191, W62–W66.

24. Ng, A.J., Walia, M.K., Smeets, M.F., Mutsaers, A.J., Sims, N.A., Purton, L.E., Walsh, N.C., Martin, T.J. and Walkley, C.R. (2015) The DNA helicase recql4 is required for normal osteoblast expansion and osteosarcoma formation. PLoS Genet., 11, e1005160.

25. Lu, L., Harutyunyan, K., Jin, W., Wu, J., Yang, T., Chen, Y., Joeng, K.S., Bae, Y., Tao, J., Dawson, B.C. et al. (2015) RECQL4 regulates p53 function in vivo during skeletogenesis. J. Bone Miner. Res., 30, 1077–1089.

26. Andrews, E.B., Gilsenan, A.W., Midkiff, K., Sherrill, B., Wu, Y., Mann, B.H. and Masica, D. (2012) The US postmarketing surveillance study of adult osteosarcoma and teriparatide, study design and findings from the first 7 years. J. Bone Miner. Res., 27, 2429–2437

27. J. Harrington, E. Sochett, and A. Howard, "Update on the evaluation and treatment of osteogenesis imperfect," Pediatric Clinics of North America, vol. 61, no. 6, pp. 1243–1257, 2014.