PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

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Pediatrics International (2022) **64**, e15120 doi: 10.1111/ped.15120

Original Article

Rothmund-Thomson syndrome investigated by two nationwide surveys in Japan

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Abstract ***Background*:** Rothmund-Thomson syndrome (RTS) is an autosomal recessive genetic disorder characterized by poikiloderma of the face, small stature, sparse scalp hair, juvenile cataract, radial aplasia, and predisposition to cancers. Due to the rarity of RTS, the situation of patients with RTS in Japan has not been elucidated.

***Methods*:** In 2010 and 2020, following the results of a primary questionnaire survey, a secondary questionnaire survey on RTS was conducted nationwide to investigate the number of RTS cases and their associated skin lesions, bone lesions, other clinical features, and quality of life in Japan.

***Results*:** In 2010 and 2020, 10 and eight patients with RTS were recruited, respectively. Skin lesions such as poikiloderma, erythema, pigmentation, and abnormal scalp hair were observed in almost all cases. Bone lesions were observed in four cases in the 2010 and 2020 surveys, respectively. Two cases had mutations in the *RECQL4* gene in the 2020 survey.

***Conclusions*:** Two nationwide surveys have shown the actual situation of patients with RTS in Japan. Cutaneous and bone manifestations are important for the diagnosis of RTS. However, many patients have no *RECQL4* mutations. The novel causative gene of RTS should be further elucidated.

Key words nationwide survey, osteosarcoma, poikiloderma, RECQL4, Rothmund-Thomson syndrome.

There are five human RECQ-like proteins (RECQL1, BLM, WRN, RECQL4, and RECQL5), each having 3′ to 5′ DNA helicase activity but little sequence similarity outside their helicase motifs. Three of these helicases (BLM, WRN, and RECQL4) show genomic instability and cancer susceptibility, but each also has distinctive features. *RECQL4* is the causative gene for Rothmund-Thomson syndrome (RTS, OMIM 266280), which is characterized by poikiloderma and skeletal defects.[1–4] RECQL4 dysfunction leads to abnormal gene replication, increased sensitivity to oxidants, abnormal DNA repair, and causes the characteristic skin findings and osteosarcoma of RTS, as RECQL4 plays a particularly significant role in the replication and repair of bone and skin tissue.[5]

Because of the rarity of RTS, the condition of patients with the disease has not been elucidated. Therefore, we investigated the clinical features and quality of life (QOL) of patients with RTS in Japan by conducting two nationwide prospective surveys.

Methods

Following the administration of a primary questionnaire in 2010, a secondary questionnaire was formulated to investigate the number of patients with RTS and their associated skin lesions, bone lesions, other clinical features, and QOL. The formats of the 2010 and 2020 questionnaires had some

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Received 16 July 2021; revised 4 December 2021; accepted 27 December 2021.

differences; however, questions about skin lesions, bone lesions, and other clinical features were asked similarly in both surveys. In 2020, RTS severity was assessed using the modified Rankin scale. Further, we asked the doctors if they knew that RTS was a designated intractable disease in Japan and was covered by the medical expense subsidy system. In this study, RTS was clinically diagnosed after observation of characteristic skin lesions, such as poikiloderma and/or bone lesions, with or without a mutation in the *RECQL4* gene.

In the 2010 survey, 515, 500, and 377 questionnaires were sent, respectively, to the department of pediatrics at pediatric training hospitals, the department of dermatology at dermatologist training hospitals, and to hospitals with a cancer center (Fig. 1).

In the 2020 survey, 495 and 658 questionnaires were sent to the pediatrician training hospitals and the dermatologist training hospitals, respectively.

This study was approved by the ethics committee of the National Hospital Organization, Nagara Medical Center and Gifu Prefectural General Medical Center.

Results

In the 2010 survey, 427, 342, and 136 replies were obtained from the pediatric training hospitals, the dermatologist training hospitals, and hospitals with a cancer center, respectively (Fig. 1). In the 2020 survey, 370 and 317 replies were obtained from the pediatric training hospitals and the dermatologist training hospitals, respectively. In the 2020 survey, the primary questionnaire was not sent to hospitals with a cancer center because of the low response rate observed in 2010. Ten and eight patients with RTS were recruited after the 2010 and 2020 surveys, respectively. Since one patient recruited in 2010 was recruited again in 2020, who was classified as part of the 2020 survey, a total of 17 patients were recruited by the two surveys.

Table 1 presents the clinical features of the cases in each survey. The male:female ratio and average age of those who were alive at the time of the survey were similar in both surveys. One patient in the 2010 survey died of osteosarcoma, and two patients in the 2020 survey died. Except for one case in the 2020 survey that was not described in detail, skin lesions such as poikiloderma (Fig. 2), erythema, pigmentation,

Table 1 Clinical features of Rothmund-Thomson syndrome in the 2010 and 2020 surveys

	2010 survey (9 cases)	2020 survey (8 cases)
Male:female	7:2	5:3
Alive:dead	7:2	6:2
Present age of living patients	15 years (range, 1–37)	15 years (range, 5–24)
Age at death (cause)	8 years (lung metastasis of osteosarcoma)	14 years (lung metastasis of osteosarcoma)
	25 years (respiratory insufficiency)	18 years (multi-organ metastases of osteosarcoma)
Skin lesion	9 cases	7 cases
Bone lesion	4 cases	4 cases
Tooth dysplasia	0 case	4 cases
Osteosarcoma	1 case	2 cases
Eye lesion	1 case (cataract bilateral)	1 case (cataract), 1 case (amblyopia)
Intellectual disability	1 case	3 cases
RECQL4 analysis	3 cases (no mutations were detected)	7 cases (2 of 7 cases had mutations)

One case in 2020 survey did not answer most of the questions.

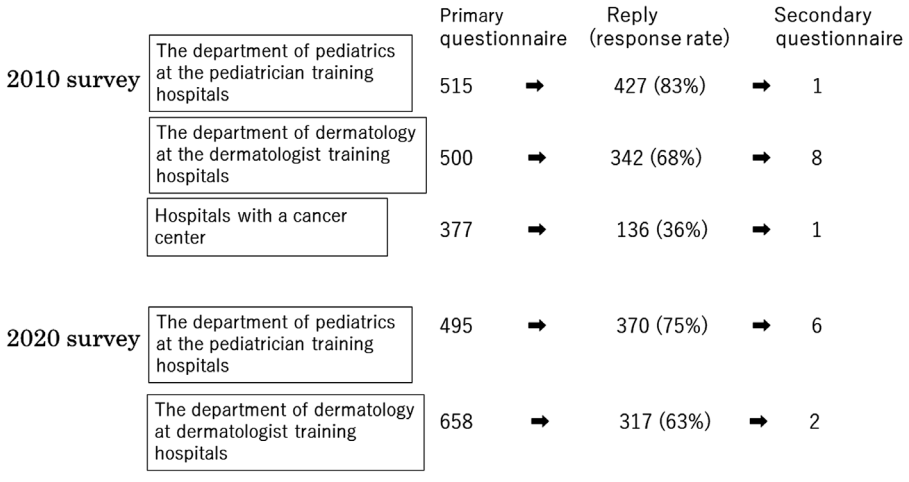

Fig. 1 Flowchart of the use of the primary and secondary questionnaires on Rothmund-Thomson syndrome (RTS). Ten and eight patients with RTS were recruited after the 2010 and 2020 surveys, respectively. Since one patient recruited in 2010 was recruited again in 2020, who was classified as part of the 2020 survey, total 17 patients were recruited by the two surveys.

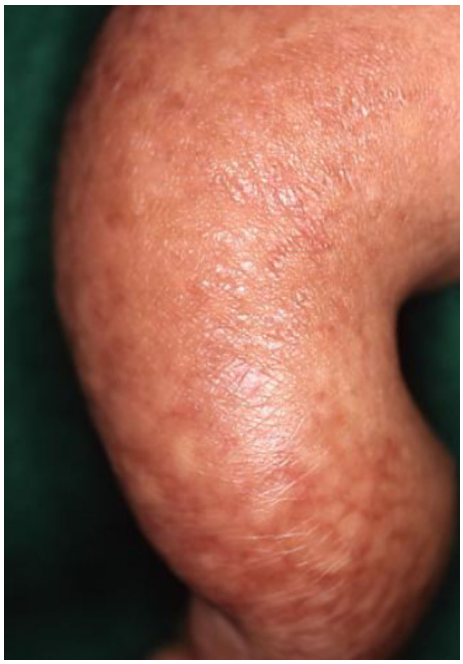

Fig. 2 Skin lesion with poikiloderma appeared in the right forearm of case 11 in the 2020 survey.

or abnormal scalp hair were observed in all cases (Table 2). Bone lesions were observed in four cases in the both the 2010 and 2020 surveys. With respect to bone lesions, there were two cases of syndactyly and three cases of radial dysplasia in both the 2010 and 2020 surveys. Cataracts were observed in one case in the 2010 and 2020 surveys, respectively. Additionally, intellectual disability was observed in one case in the 2010 survey and three cases in the 2020 survey.

The *RECQL4* gene was investigated in three patients recruited in the 2010 survey; however, no mutation was detected. In the 2020 survey, seven patients were investigated for the *RECQL4* gene, and two patients had pathogenic variants of the *RECQL4* gene. The two patients with *RECQL4* gene mutations had both poikiloderma and radial malformation.

In the 2020 survey, we asked the doctors if they knew that RTS was one of the designated intractable diseases in Japan and was covered by the medical expense subsidy system; six of the seven doctors were aware of this. In 2020, the severity of RTS was assessed using the modified Rankin scale. There was one patient each on scales 0 to 3 (Table 3).

Discussion

We conducted two national surveys of patients with RTS with a 10-year interval. These two surveys showed that there were 10 patients in 2010 and eight patients in 2020. The severity of RTS in Japan was variable. The presence of skin lesions, especially poikiloderma, and bone lesions is important in the diagnosis of RTS. Osteosarcoma was relatively common in RTS.

The specific symptoms or laboratory data encountered in RTS have not been adequately delineated. As such, many patients may not have been diagnosed with RTS. With advances in comprehensive gene analysis technology, patients with atypical clinical symptoms of RTS are more likely to have *RECQL4* gene mutations.[6] Poikiloderma is a pathognomonic symptom of RTS. In addition to patients with skin lesions, patients with skeletal abnormalities, such as syndactyly and radial dysplasia, small stature, and juvenile cataracts are suspected to have RTS. All patients with osteosarcoma should be investigated for RTS.

Although current diagnostic criteria require the presence of an *RECQL4* gene mutation in the diagnosis of RTS, in this study RTS was clinically diagnosed by characteristic skin lesions, such as poikiloderma, and/or bone lesions, with or without a mutation in the *RECQL4* gene; this is a limitation of the study. Because *RECQL4* gene mutations are not found in approximately 40% of patients with RTS,[7] the diagnosis should be based on clinical findings.

In the 2020 survey, three of eight patients had intellectual disability. Mild to moderate intellectual disability has been reported in a small number of RTS cases. Gelaw reported a patient with RTS with mild cerebral atrophy.[8] The pathogenesis of intellectual disability in RTS should be examined in future studies. Moreover, the assessment of QOL, focusing on patients with intellectual disability, should also be planned.

To the best of our knowledge, only one case of an *RECQL4* gene mutation has previously been reported in Japan.[9] The patient was reported to have Baller-Gerold syndrome, which has clinical features that overlap with those of RTS, caused by an *RECQL4* gene mutation. Baller-Gerold syndrome has the characteristic features of craniosynostosis and radial dysplasia. In this survey, *RECQL4* mutations were not detected in many cases. Recently, mutations in *ANAPC1* have been reported to cause RTS type 1.[10] When an *RECQL4* gene mutation is not detected in patients with suspected RTS, gene analysis that investigates genes other than *RECQL4* is required. A comprehensive gene search, such as next generation exome analysis, should be widely conducted for patients without an *RECQL4* gene mutation.

Only one patient was recruited from the pediatric departments in the 2010 survey while six were recruited in the 2020 survey. Although the exact reason for this difference remains unknown, it could be that the 2010 survey may have raised awareness of RTS among Japanese doctors, especially among pediatricians. To support this idea, in the 2020 survey, six of seven doctors knew that RTS was one of the designated intractable diseases in Japan and covered by the medical expense subsidy system. Patients with RTS require regular follow-up because of the risk of cancer. Life expectancy is not impaired in RTS patients if they do not develop cancer.[11] Specifically, the 5-year survival rates for patients with osteosarcoma associated with RTS and those with osteosarcoma without RTS are similar (60–70%).[12] Cataract and skeletal abnormalities are mainly treated with supportive measures.

Table 2 Clinical manifestations for 17 cases

	Case	Age	Sex	Skin lesion				Bone lesion				Eye lesion	Intellectual disability	Osteosarcoma	*RECQL4* mutation
				Poikiloderma	Erythema	Pigmentation	Abnormal scalp hair	Radial dysplasia	Syndactyly	Scoliosis	Others				
2010	1	1	M	+	+										
	2	5	F	+								Cataract			
	3	6	M	+											
	4	8	M	+		+								+	
	5	10	M		+	+			+						
	6	25	F	+		+	+			+					
	7	25	M			+							+		
	8	27	M	+							Micrognathia				
	9	37	M		+				+						
2020	10	14	M											+	
	11	18	F	+		+	+	+				Cataract		+	
	12	19	M	+		+	+								
	13	19	M	+		+	+						+		
	14	21	M	+		+	+								
	15	24	F				+			+			+		
2020	16	5	F	+		+		+$				Ambylopia	+		+
	17	7	M	+		+		+#							+

The formats of the 2010 and 2020 questionnaires had some differences of question items about each organ lesion. In the 2010 survey, we asked the question about the presence of erythema, including sun-sensitive erythema, but not in 2020 survey. In the 2020 survey, we asked whether the patients had abnormal scalp hair. In the 2010 survey, we asked about the presence of sparse hair. The case 7 patient in the 2010 survey is the younger brother of the case 9 patient. The case 10 patient in the 2020 survey was not described in detail. The case 12 patient in 2020 was recruited in both the 2010 and 2020 surveys. + denoted that the question item was present in the patients. $: radio-ulnar fusion, #: radio-ulnar malalignment, thumb hypoplasia. M: male, F: female

Table 3 Severity of the condition of patients with Rothmund-Thomson syndrome in the 2020 survey, according to the modified Rankin scale

	6 cases
0—No symptoms.	1 case
1—No significant disability. Able to carry out all usual activities, despite some symptoms.	1 case
2—Slight disability. Able to look after own affairs without assistance, but unable to carry out all previously performed activities.	1 case
3—Moderate disability. Requires some help, but able to walk unassisted.	1 case
4—Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.	0 case
5—Severe disability. Requires constant nursing care and attention, bedridden, incontinent.	0 case
6—Death	2 cases

More importantly, genetic counseling should be provided to patients and their families.

Conclusion

This survey clarified the actual state of patients with RTS in Japan. It is believed it will be useful in improving the QOL of patients with RTS.

Acknowledgments

We are grateful to the pediatricians and dermatologists who provided the data for all the cases in this study.

Funding information

This work was supported by the Ministry of Health, Labour, and Welfare (MHLW) of Japan (grant no. H30-nanchi-ippan-009 [Koutaro Yokote]).

Disclosure

The authors declare no conflict of interest.

Author contributions

H.K., M.T., K.I., R.K., S.M., A.T., M.M., M K., Y.M., and K.Y. designed the study. N.Y., C.N., and J.T. collected the data. H.K. and H.M. wrote the manuscript. All authors contributed to the intellectual content of this manuscript. All authors read and approved the final manuscript.

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