DNA Repair Disorders

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Preface

Xeroderma pigmentosum (XP) is an autosomal recessive hereditary photosensitive disease, in which patients display extreme hypersensitivity to ultraviolet radiation (UVR) because of the deficiency in the ability to repair the UVR-induced DNA lesions. Although the existence of the disease had been known since the first case report on XP by a dermatologist, Kaposi, in 1883, the cause of XP was at length discovered in 1968, 85 years after the first case report. This year marks the 50th anniversary of the discovery of the cause of XP, a deficiency in nucleotide excision repair (NER), by James E. Cleaver. NER is an indispensable DNA repair mechanism for all living things on earth to remove various forms of DNA lesions from their genomic DNA, including UVR-induced DNA lesions, such as cyclobutane pyrimidine dimers and (6-4)photoproducts. In this sense, NER involves in an essential mechanism for living things and recently it has been shown that NER is closely involved in the biologically fundamental role such as transcription and replication. Therefore the deficiency in NER results in a disastrous condition. In this book we focused on the clinical aspects of DNA repair disorders. We would like to delineate the outcome of the deficiency of DNA repair so that we will come to know the essence of the DNA repair mechanisms. The authors are experts in this subject, and the publication of this book is timely because a Nobel Prize was given to the scientists who discovered the mechanisms of the NER, and the readers may be interested in what will become of individuals who are deficient in DNA repair.

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Chapter 11
Rothmund–Thomson Syndrome

Hideo Kaneko

Abstract Rothmund–Thomson syndrome is an autosomal recessive genetic disorder which is characterized by poikiloderma of the face, small stature, sparse scalp hair, juvenile cataracts, radial aplasia, and predisposition to cancers. Facial redness is particularly characteristic of this syndrome with redness gradually spreading over the four limbs. The redness appears within a year of birth and then progresses to poikiloderma. The causative gene for Rothmund–Thomson syndrome is *RECQL4*, which is essential for genetic replication and repair. *RECQL4* mutations are found in approximately 60% of all patients with Rothmund–Thomson syndrome. Some researchers classify Rothmund–Thomson syndrome with *RECQL4* mutations as type II and that without *RECQL4* mutations type I. Rothmund–Thomson type I is characterized by poikiloderma, ectodermal malformation, and juvenile cataracts, whereas Rothmund–Thomson type II is characterized by poikiloderma, congenital bone defects, the complication of osteosarcoma in infancy, and the complication of skin cancer with aging.

Keywords Rothmund–Thomson syndrome · RAPADILINO syndrome · Baller–Gerold syndrome · RECQL4 · Poikiloderma · Osteosarcoma

11.1 Introduction

There are five human RecQ-like proteins (RECQL1, BLM, WRN, RECQL4, and RECQ5), each having 3′ to 5′ DNA helicase activity but little sequence similarity outside the helicase motifs. Three of these helicases (BLM, WRN, and Rothmund–Thomson) show genomic instability and cancer susceptibility, but each also has distinctive features. RECQL4 is the causative gene for Rothmund–Thomson

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syndrome (OMIM 266280) characterized by poikiloderma and skeletal defects [1, 2]. Homozygous or compound heterozygous mutations of RECQL4 gene causes Rothmund–Thomson syndrome [3].

11.2 Epidemiology

Approximately 300 patients are reported to have Rothmund–Thomson syndrome worldwide [4]. On the basis of a questionnaire survey conducted by the departments of pediatrics and dermatology, and core hospitals for cancer, as part of the Research on Measures for Intractable Diseases supported by the Ministry of Health, Labour and Welfare in Japan, ten patients were identified to have Rothmund–Thomson syndrome in Japan [5]. Of these ten, eight were males, among whom seven had small stature (Table 11.1). The birth weights of two patients were low. Eight patients had poikiloderma, which was the basis for the diagnosis in many of them. Regarding cancer development, two patients had osteosarcoma. Four of the ten patients had undergone *RECQL4* screening, but none were found to carry *RECQL4* mutations.

11.3 Cause of Disease

Rothmund–Thomson type II is caused by mutations of the RECQL4 protein, which belongs to the RecQ helicase family (Fig. 11.1) [6]. Other proteins that also belong to the RecQ helicase family are WRN and BLM, mutations of which cause Werner syndrome and Bloom syndrome, respectively. Werner, Bloom, and Rothmund–Thomson syndromes have chromosomal instability and predisposition to cancers as their common characteristics. *RECQL4* is located on chromosome 8q24.3 and encodes a protein with 1208 amino acids and a molecular weight of 133 kDa. Helicase is a protein that unwinds the double-stranded DNA into single strands and plays an important role in genetic replication and repair. Rothmund–Thomson type I comprises a variety of pathological conditions. The pathogenesis of Rothmund–Thomson type I has not yet been clarified despite intensive research efforts. There are two diseases that are related to Rothmund–Thomson syndrome, namely, RAPADILINO syndrome and Baller–Gerold syndrome. The name RAPADILINO is an acronym for the following features commonly observed in affected patients: radial hypoplasia/aplasia, patella hypoplasia, palate hypoplasia/cleft palate, diarrhea, dislocated joints, little size, limb malformation, nose slender, and normal intelligence. Poikiloderma is not observed in patients with RAPADILINO syndrome [7, 8]. Baller–Gerold syndrome is characterized by brachycephaly due to the premature fusion of coronal sutures, prominent forehead, bulging eyes, low-set ears,

Table 11.1 Clinical feature of Rothmund–Thomson in Japan

No	Sex	Present (age)	Height (age)	Body weight (age)	Skin lesion (age)	Malignancy (age)	Others (age)
1	M	8 (death)	103 cm (7)	14 kg (7)	Poikiloderma (10 M) Pigmentation (10 M)	Osteosarcoma (7)	Death caused by lung metastasis of osteosarcoma (8)
2	M	10 (alive)	135 cm (10)	33 kg (10)	Sun-sensitive erythema (7) Pigmentation (2)	None	Syndactyly
3	M	10 (alive)	84 cm (3)	2126 g (at birth)	Sun-sensitive erythema (6 M) Poikiloderma (6 M) Sparse hair (6 M)	None	Tooth dysplasia (6) Pulmonary valve stenosis ventricular aneurysm cretinism (supplementation of thyroid hormone)
			130 cm (10)	26 kg (10)			
4	F	25 (alive)	150 cm (18)	34 kg (18)	Poikiloderma telangiectasia pigmentation sparse hair (5 M) Decreased sweating (14)	Osteosarcoma (20)	Scoliosis (14) Atrophic gastritis (16) Insufficiency of pancreatic function (fatty degeneration) (16)
5	M	37 (alive)	168 cm (37)	55 kg (37)	Erythema nodosum (34)	None	Syndactyly
6	M	25 (death) Younger brother of case 5	150 cm (25)	31 kg (25)	Recurrent skin ulcer and infectious granuloma	None	Acute glomerulonephritis, renal insufficiency, respiratory insufficiency (25), psychomotor retardation
7	M	6 (alive)	100 cm (6)	2000 g (at birth) 13 kg (6)	Reticulated pigmentation on the face and lower limbs and poikiloderma (1)	None	
8	M	27 (alive)	144.7 cm (20)	43 kg (20)	Poikiloderma (13)	None	Micrognathia
9	M	1 (alive)	72 cm (14 M)	7600 g (14 M)	Poikiloderma, reticulated erythema, and blister	None	
10	F	5 (alive)	106.4 cm (5)	19.5 kg (5)	Poikiloderma and reticulated depigmentation	None	Hearing loss and bilateral cataract

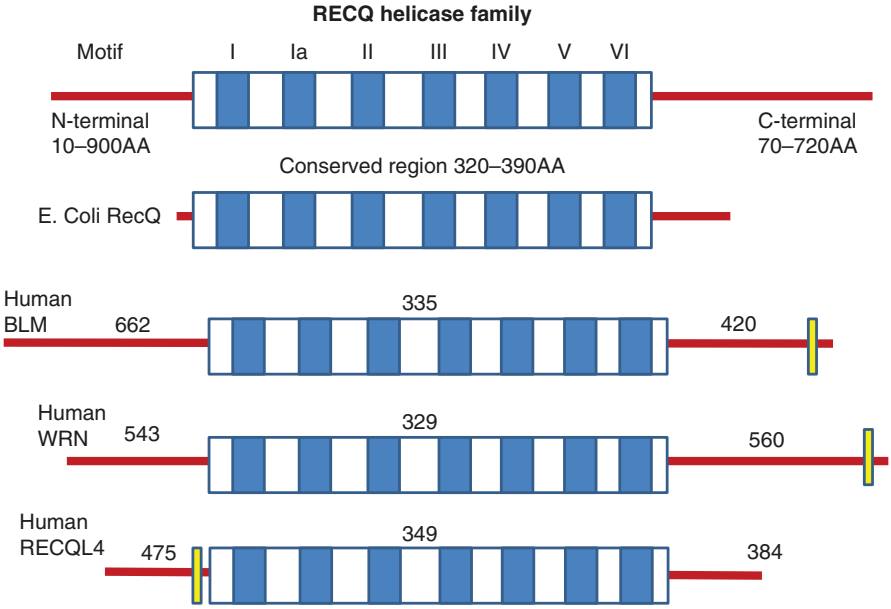

Fig. 11.1 Features of RECQ helicase family proteins and functional motif [6]. I–VI are helicase motif. AA: amino acids. Yellow boxes indicated nuclear localization signal. The number indicated the number of amino acids for N-terminal, C-terminal, and helicase motif, respectively

radial aplasia (Fig. 11.2), absence of a thumb, poikiloderma, and the complications of osteosarcoma, skin cancer, and malignant lymphoma. Cataracts are characteristic of Rothmund–Thomson syndrome, whereas dislocated joints and patella hypoplasia are characteristic of RAPADILINO syndrome. Moreover, craniostenosis is characteristic of Baller–Gerold syndrome.

To understand Baller- Gerold syndrome patients in Japan, a nationwide survey was conducted, which identified two families and three patients affected by the syndrome [9]. All the three patients showed radial defects and craniosynostosis. In one patient who showed a dislocated joint of the hip and flexion contracture of both the elbow joints and wrists at birth, a homozygous large deletion in the RECQL4 gene was identified (Fig. 11.3).

Because these diseases often exhibit common phenotypic features, in the future it would be more beneficial to diagnose these syndromes differently on the basis of causative genes, classifying them into those with *RECQL4* mutations and those without *RECQL4* mutations [10].

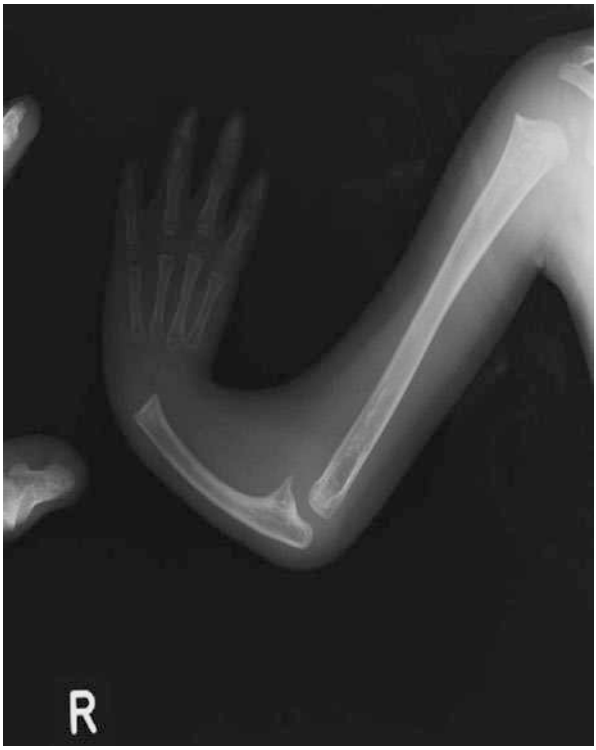

Fig. 11.2 Radial ray defects of Baller–Gerold syndrome revealed by X-ray examination

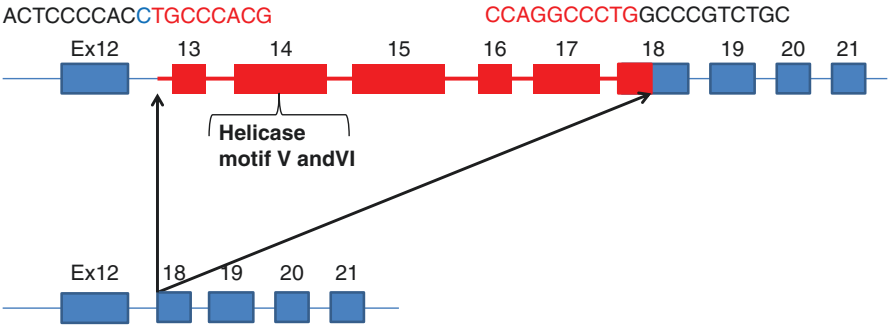

Fig. 11.3 Japanese Baller–Gerold syndrome detected homozygous deletion of the RECQL4 gene from intron 12 to the former part of exon 18, resulting in the deletion of amino acids after 687th. Red boxes indicated the deleted exons. Exon 14 encodes the helicase motif V and VI

11.4 Pathological Conditions

RECQL4 dysfunction leads to abnormal gene replication, increased sensitivity to oxidants, and abnormal DNA repair. It is considered that *RECQL4* dysfunction causes the characteristic skin findings and osteosarcoma, because RECQL4 plays a particularly significant role in the replication and repair of bone and skin tissue.

11.5 Diagnosis and Differential Diagnosis

Poikiloderma is a pathognomonic symptom for the diagnosis of Rothmund–Thomson syndrome. In addition Rothmund–Thomson syndrome is suspected when patients have small stature, skeletal abnormalities (dental hypoplasia and reduced bone density), sparse scalp hair, juvenile cataracts, intractable diarrhea in infancy, and nail abnormalities (Fig. 11.4). All patients with osteosarcoma should be examined for Rothmund–Thomson syndrome. Those patients with a family history of Rothmund–Thomson syndrome should undergo *RECQL4* screening; and those who found to carry *RECQL4* mutations should be diagnosed as having Rothmund–Thomson syndrome. Because *RECQL4* mutations are not found in approximately

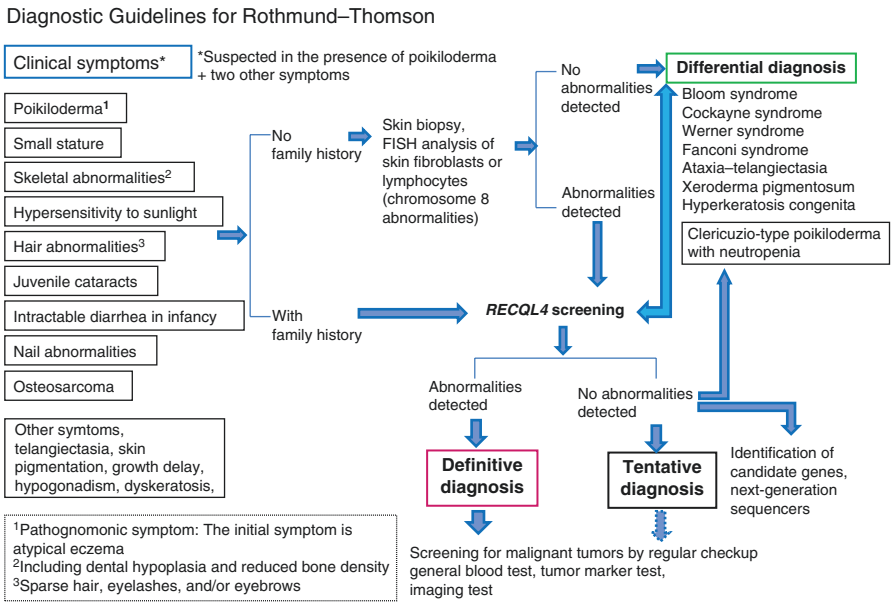

Fig. 11.4 Diagnostic guidelines for Rothmund–Thomson syndrome

40% of patients with Rothmund–Thomson syndrome, the diagnosis should be tentative, and at some time later, these patients should be screened for candidate genes using next-generation sequencers. When chromosome 8 abnormalities are detected by fluorescence in situ hybridization (FISH) analysis in patients without a family history of Rothmund–Thomson syndrome, they should undergo *RECQL4* screening. Skeletal abnormalities are frequent in persons with Rothmund-Thomson syndrome with *RECQL4* mutations compared with persons without *RECQL4* mutations. If they do not have *RECQL4* mutations, a diagnosis which differentiates from other diseases is required. The suspected diseases are discussed below.

The components of the causative genes for Bloom syndrome and Werner syndrome are helicases, which are the same as that for Rothmund–Thomson syndrome. Bloom syndrome and Werner syndrome show similar phenotypic features to Rothmund–Thomson syndrome [11]. Bloom syndrome is characterized by small stature, redness of the skin due to hypersensitivity to sunlight, and immune deficiency. In a chromosome test, the frequency of sister chromatid exchamges is high in patients with Bloom syndrome. Werner syndrome is typically associated with premature aging that is characterized by cataracts in both eyes, premature graying of the hair, and the calcification of subcutaneous tissue. Ataxia-telangiectasia is characterized by telangiectasia of the eyes, progressive ataxia, and immune deficiency. Xeroderma pigmentosum is characterized by hypersensitivity to sunlight from early postnatal life. The incidence of skin cancer is high in patients with xeroderma pigmentosum. Hyperkeratosis congenita is characterized by abnormal skin pigmentation, nail abnormalities, and leukoplakia and is associated with abnormal myeloid differentiation. Clericuzio-type poikiloderma with neutropenia, which is caused by the mutation of USB1 gene, is often diagnosed as Rothmund-Thomson syndrome.

11.6 Treatment and Prognosis

Patients with Rothmund–Thomson syndrome require regular follow-ups owing to the risk of cancer development. The life expectancy of those patients who do not have cancers is not poor. The 5-year survival rate for patients with osteosarcoma that developed as a complication of Rothmund–Thomson syndrome and that for patients with osteosarcoma that is not a complication of Rothmund–Thomson syndrome is similar (60–70%). Cataract and skeletal abnormalities are treated mainly by supportive measures. Genetic counseling should be provided to patients and their families.

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