Clinical and Experimental Dermatology and Therapies

OPEN ACCESS

Lang C, et al. Clin Exp Dermatol Ther 11: 248.

www.doi.org/10.29011/2575-8268.100248

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Case Report

A Rare Case of Coexisting Rothmund-Thomson Syndrome and *CHEK2*-Related Hereditary Cancer Predisposition Syndrome in A Patient With Multiple Malignancies

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Citation: Lang C, Sindrilaru MA, Dittrich T, Moawia A, Siebert R, et al. (2026) Department of Dermatology and Allergology, University Hospital Ulm, 89081 Ulm, Germany. Clin Exp Dermatol Ther 11: 248. DOI: https://doi.org/10.29011/2575-8268.100248

Received Date: 03 August, 2026; **Accepted Date:** 17 August, 2026; **Published Date:** 20 August, 2026

Genetic tumour syndromes are rare, yet clinically critical particularly in some early-onset malignancies. The exceptionally rare Rothmund-Thomson syndrome (RTS) and *CHEK2*-related hereditary (breast) cancer predisposition syndrome mechanistically both are characterized by defects in DNA repair but involve distinct molecular pathways. RTS is an autosomal recessive disorder genetically related to mutations in the *RECQL4* or *ANAPC1* genes affecting helicase function [1,2,6]. RTS-patients show marked phenotypic variability, including poikiloderma, skeletal abnormalities, premature aging and a heightened risk of malignancies [1,2]. Only about 400 genetically proven cases of RTS have been reported so far [1]. *CHEK2*-related hereditary (breast) cancer predisposition is an autosomal dominant syndrome caused by pathogenic germline variants in the tumour suppressor gene *CHEK2* encoding a checkpoint kinase involved in DNA damage response. Affected individuals have increased risk for breast cancer, sarcomas, brain tumours and hematologic malignancies [3,5].

Here we report a patient with a unique constellation of both RTS and *CHEK2*-related cancer predisposition underlying early-onset malignancies including multiple cutaneous carcinomas, breast cancer and osteosarcoma. To our knowledge, this is the first reported coexistence of RTS and *CHEK2*-related cancer predisposition highlighting the complexity of genetic tumour predisposition.

The propositus had a history of melanoma *in situ*, multiple Bowen's carcinomas, osteosarcoma at age 14 years, and breast cancer at 40 years, all surgically treated, the latter two also with radiotherapy and chemotherapy. Notably, her skin showed marked poikiloderma of the face and extremities, sparse eyelashes and eyebrows and brittle scalp hair (Figure 1a). With regard to family history, the patient's maternal grandmother reportedly also lacked eyebrows and eyelashes and had multiple skin tumours. No other family history of malignancy was noted.

The clinical diagnosis of RTS was established based on suggestive findings as described by Wang et al. (2020) [8]. The patient's early childhood cheek erythema, subsequent poikiloderma, sparse scalp and eyebrow hair and cutaneous tumours are highly characteristic and considered pathognomonic for RTS. Differential diagnoses with childhood poikiloderma, progeria, and/or early-onset malignancies were considered (Kindler's syndrome, acrokeratotic poikiloderma, dyskeratosis congenita, Cockayne's syndrome, Xeroderma Pigmentosum, Fanconi's anaemia and Bloom syndrome), many were excluded based on clinical features.

Genetic testing was performed using whole-exome (WES)-based virtual panel sequencing targeting pathogenic variants associated with RTS and other genetic tumour syndromes. Next generation sequencing analysis identified two heterozygous variants in the *RECQL4* gene on chromosome 8, namely NM_004260.4:c.2492_2493del; p.(His831Argfs*52) in exon 18 and NM_004260.4:c.3237-20T>G in intron 8, which were verified by targeted Sanger sequencing (Figure 1b). The NM_004260.4:c.2492_2493del; p.(His831Argfs*52) has been repeatedly reported as pathogenic for RTS in clinical databases and is classified as class 5 (pathogenic) under ACMG guidelines [4]. The identified two-nucleotide deletion is predicted to result in a frameshift leading to premature termination of protein synthesis and/or early mRNA degradation via nonsense-mediated mRNA decay. The second, intronic variant c.3237-20T>G likely causes splice acceptor loss as indicated by the moderate probability score of 0.45 using Splice AI. The patient's father carried the variant NM_004260.4:c.2492_2493del; p.(His831Argfs*52) heterozygously, but not the second *RECQL4* variant. Despite unavailable maternal testing, the clinical phenotype suggests the patient carries both variants in trans (compound heterozygous).

Additionally, the analyses of further 281 genes related to cancer predisposition and verification by Sanger sequencing detected a heterozygous nonsense variant in the *CHEK2* gene (NM_007194.4:c.1283C>T; p.(Ser428Phe) (Figure 1b), classified as likely pathogenic (class 4) under ACMG guidelines. It causes CHEK2 loss-of-function, increasing susceptibility to brain tumours and, in particular, breast cancer, making it a plausible contributor to the patient's complex phenotype (Figure 1b).

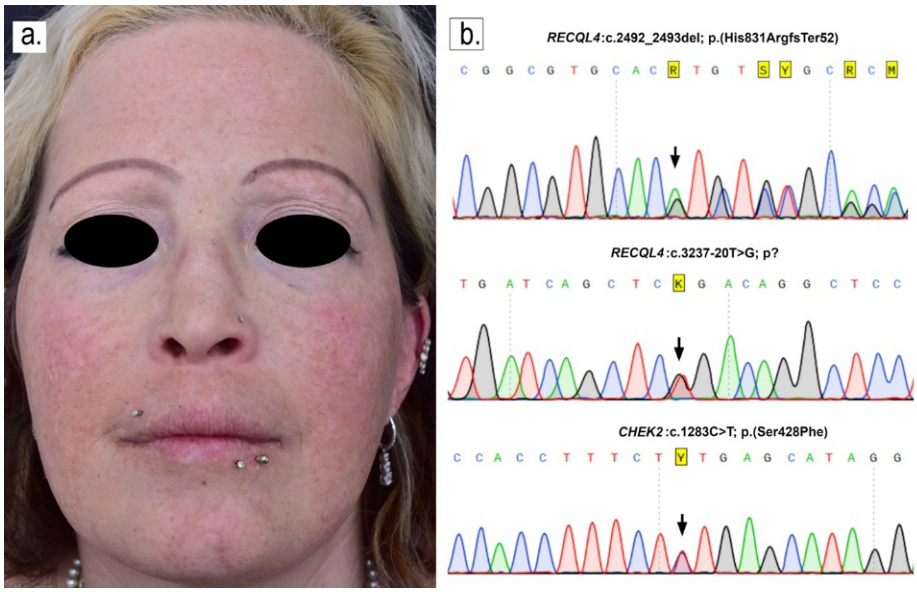


Figure 1: (a): Poikiloderma, sparse eyelashes and eyebrows, brittle scalp hair; **(b)** Electropherograms from Sanger sequencing validating the variants in the *RECQL* and *CHEK2* in the patient. The coloured peaks indicate the different DNA bases which are given above the respective electropherogram as letter code. Arrows indicate the positions of the variants where the colour signals of two bases overlay, also indicated by the yellow boxed letter (Y indicates pyrimidine, i.e. C or T; K indicates G or T; R indicates A or G). Top panel: Variant NM_004260.4:c.2492_2493del; p.(His831Argfs*52); Middle panel: Variant NM_004260.4:c.3237-20T>G and lower panel: NM_007194.4:c.1283C>T; p.(Ser428Phe). Notice that the deletion in the first panel leads to overlay of the same sequence with a 2bp spacing as indicated by the overlay 3' (right) of the arrow).

Based on clinical and genetic findings, we consider the patient to be affected by RTS and additionally *CHEK2*-related hereditary (breast) cancer predisposition syndrome. This dual genetic finding reflects the complex phenotype, combining characteristic type 2 RTS features caused by *RECQL4*-mutations (poikiloderma, scant hair, non-melanoma skin cancer and osteosarcoma) with *CHEK2*-related cancer predisposition, impacting oncologic management, tumour prevention, and follow-up. Given that the patient carries pathogenic variants in both *RECQL4* and *CHEK2*, her tumour predisposition is likely influenced by two independent but mechanistically related pathways of DNA damage repair. While *RECQL4* deficiency impairs DNA helicase activity and genome stability [6], *CHEK2* deficiency compromises cell-cycle checkpoint activation in response to DNA double-strand breaks [7]. It is therefore plausible that the coexistence of both defects may have additive or even synergistic effects on tumorigenesis. Clinically, this warrants interdisciplinary management with intensified surveillance for osteosarcoma, cutaneous malignancies, and breast cancer, involving close collaboration among dermatologists, oncologists, gynaecologists, and orthopaedists.

Genetic tumour syndromes should be considered in patients presenting with multiple early-onset malignancies. RTS should be strongly suspected in patients presenting with osteosarcoma, particularly when accompanied by poikiloderma, a hallmark dermatological finding in this condition.

References

1. Suter O, Kjellin H, Hertz JM, Ahmed M, Ashraf T, et al. (2016) Rothmund–Thomson Syndrome: novel pathogenic mutations and expanded clinical spectrum. Mol Genet Genomic Med 4: 620-635.
2. Siitonen HA, Kopra O, Kaariainen H, Benmansour A, Capri Y, et al. (2009) Mutation spectrum in RECQL4 diseases. Eur J Hum Genet 17:151-158.
3. Cybulski C, Górski B, Huzarski T, Masojć B, Mierzejewski M, et al. (2004) CHEK2 is a multiorgan cancer susceptibility gene. Am J Hum Genet 75:1131-1135.
4. Richards S, Aziz N, Bale S, Bick D, Das S, et al. (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation. Genet Med 17: 405-424.
5. Roeb W, Higgins JP, King MC (2012) Response to DNA damage of CHEK2 missense mutations in familial breast cancer. Hum Mol Genet 21: 2738-2744.
6. Lu H, Shamanna RA, Keijzers G, Anand R, Rasmussen LJ, et al. (2016) RECQL4 Promotes DNA End Resection in Repair of DNA Double-Strand Breaks. Cell Rep 16: 161-173.
7. Zannini L, Delia D, Buscemi G (2014) CHK2 kinase in the DNA damage response and beyond. J Mol Cell Biol 6: 442-57.
8. Wang L, Plon S (2020) Rothmund-Thomson Syndrome. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2025.