A Patient With Rothmund-Thomson Syndrome and All Features of RAPADILINO

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**Background:** Mutations of the human helicase gene RECQL4 have been identified in a subset of patients with Rothmund-Thomson syndrome (RTS) and in children with the diagnosis of RAPADILINO syndrome (RAdial hypoplasia/aplasia, PAtellar hypoplasia/aplasia, cleft or highly arched PAlate, Diarrhea and Dislocated joints, Little size [≥2 SDs below the mean in height] and LImb malformation, and slender NOse and NOrmal intelligence). While many features of the 2 genetic disorders overlap, poikiloderma—a hallmark of RTS—has been described as generally absent in RAPADILINO syndrome.

**Observations:** We report herein a patient with RTS who carries a truncating mutation and a newly identified missense mutation of RECQL4. The proband uniquely developed all criteria of RAPADILINO in addition to his prominent skin findings.

**Conclusions:** Patients with RTS may possess all features of RAPADILINO. Consequently, a genetic approach to RTS and RAPADILINO could be beneficial. This approach may provide a better understanding of the wide variety of related phenotypic findings and improve prognostics.

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RAPADILINO syndrome (OMIM 266280). The acronym stands for the specific features of this autosomal recessive disorder: RDial hypoplasia/aplasia, PAtellar hypoplasia/aplasia, cleft or highly arched PAlate, Diarrhea and DIstorted joints, Little size (>2 SDs below the mean in height) and Limb malformation, and slender NOse and NOrmal intelligence. This entity is most prevalent in Finland, where in all observed cases a specific splice site mutation of the RECQL4 intron 7 was found in either homozygous or compound heterozygous form. Although several hallmarks of RAPADILINO have been reported in RTS cases, their collective appearance and the peculiar absence of ectodermal symptoms (poikilodermatous, sparse scalp hair, and sparse brows and lashes) that are present in RAPADILINO syndrome have distinguished it as a separate disorder. The prevalence of osteosarcoma for patients with RAPADILINO (7%) is apparently lower than for a cohort of patients with RTS and RECQL4 mutations. However, no study has clearly documented the risk of osteosarcoma over time in patients with RAPADILINO.

Patients with RTS have also been reported to develop cutaneous squamous cell carcinoma, noncutaneous malignancies, and myelodysplasia on rare occasions. Patients with RTS have also been reported to develop cutaneous squamous cell carcinoma, noncutaneous malignancies, and myelodysplasia on rare occasions. In addition, there are more females than male patients with RAPADILINO syndrome, and they seem to be more severely affected, while patients with RTS are more commonly male. However, a non-Finnish patient with RAPADILINO syndrome has been described who developed poikilodermatous features, but the case was later revisited and reclassified as either a severe form of RTS or a new syndrome. Indeed, despite the differences, there are significant phenotypic overlaps between RTS and RAPADILINO. Consequently, the possibility that these diseases are subtypes of a single disorder has been considered.

**METHODS**

Verbal and written informed consent was obtained from the parents, who also authorized the scientific presentation of the data. RECQL4 polymerase chain reaction and direct sequencing were performed according to Siitonen et al. All of the exons of RECQL4 were sequenced. In addition, each intron except intron 12 was fully sequenced. However, exon-intron boundaries of intron 12 were analyzed. No splice site mutations or intronic deletions were found in the RECQL4 gene. Primers for mutation detection were ex7-9-F GTGGCCAGTGGTTCTTG and ex7-19-R TTAOOGGACACAGCAGTT for exons 7 through 9 and ex17-19-F GTGGGAGCAGGGTTGGAAGA and ex17-19-R CACTGCATCCACAGAGCAAG for exons 17 through 19.

The NetGene2 program (http://www.cbs.dtu.dk/services/NetGene2/) was used to predict creation of a possible new splice site by the R1021W amino acid change. The score for this motif was 5.322 in the wild-type (5’TGTGCAGCC3’) and the threshold for the high-score motif being 2.676. As a consequence of the mutation, the score was 3.770 (5’TGTGCGC3’) for the same area. These results suggest the mutation does not have an effect on the splicing.

**REPORT OF A CASE**

The male patient was born at 37 weeks’ gestation from the second pregnancy of a mother with multiple sclerosis. His birth weight was 1550 g (<third percentile); length, 38 cm (<third percentile); and head circumference, 31 cm (third to tenth percentile). Bilateral radial aplasia and absence of the thumbs was noted immediately after birth along with hypoplasias, bilateral inguinal hernia, prominent anterior fontanelle, slender nose, and micrognathia. At age 10 weeks, findings from his cardiac, ophthalmologic, and spinal radiographs and head ultrasound evaluations were negative. This workup was prompted by failure to thrive, which was accompanied by loose voluminous stools. His loose stools and poor growth persisted. At age 2 to 3 months, he developed a progressive, light-sensitive skin rash.

At age 22 months (length, 67 cm (<third percentile); weight, 5620 g (<third percentile)), he was hospitalized for failure to thrive and persistent diarrhea. His extensive workup revealed bilateral absence of the patellae, subluxation of the femoral heads, and prominent osteoporosis in addition to the earlier radiographic findings. An abdominal ultrasound showed the spleen to be localized at the upper pole of the left kidney in a circumferential position. Both lactose intolerance and fat malabsorption were detected. Through a genetic evaluation, he was diagnosed as having RAPADILINO syndrome, and the dermatologist’s opinion was that the patient had xeroderma pigmentosum. His chromosomal evaluation revealed a normal 46,XY karyotype with no signs of instability.

The patient’s diarrhea resolved by age 4 years. He underwent corrective surgical procedures to correct the deformities of his upper forelimbs, hypoplasias, and inguinal hernias. During a repeated dermatology evaluation, he was found to have poikilodermatous features, not xeroderma pigmentosum, and he was rediagnosed as having RTS.

On a follow-up genetic examination at age 9 years, the patient was a bright little boy who attended fourth grade with no difficulties and had a mildly hoarse voice. He was proportionately small: weight, 13 kg (<third percentile); height, 106 cm (<third percentile); and head circumference, 46.5 cm (>2 SDs below the mean). He had sparse hair with areas of alopecia, sparse eyebrows, a prominent forehead, slender nose, highly arched palate, and micrognathia. A striking upper limb abnormality was noted, as described herein. A prominent, diffuse dermatitis affected all parts of the body, characterized by variegated cutaneous pigmentation, atrophy, and telangiectasia. The dermatosis appeared more erythematous on sun-exposed areas such as the face, and the parents reported extreme sun sensitivity.

**RECQL4 sequencing revealed 3 mutations** (g.2881G→C; g.2886delT; and g.5435C→T) in the patient’s DNA. The evaluation of the mutations from the parental DNA showed that 2 mutations (g.2881G→C and
g.2886delT) segregated maternally and 1 (g.5435C→T) paternally. The mutations in the maternal allele have been found previously in 2 different RTS probands.12,19 The g.2886delT mutation causes a frameshift resulting in an early stop codon 97 codons downstream, while the g.2881G→C transversion is likely an associated single-nucleotide polymorphism being part of the founder haplotype. The paternal allele carries the g.5435C→T transversion, which leads to a R1021W missense mutation.

This defect of RECQL4 has not been described previously, to our knowledge. A missense mutation affecting the same triplet but leading to another amino acid substitution (R1021Q) has been found in a patient with RTS who carried only 1 allelic mutation of RECQL4.15 This mutation does not affect a conserved amino acid or the helicase domain of RECQL4. Computer-assisted analysis of the mutation suggested that it does not affect splicing mechanisms either. However, it leads to the loss of the positively charged arginine, which is substituted by a negatively charged aspartate. This alteration results in a net loss of a positive charge at the same location (arginine to glutamine) of the polypeptide. This alteration could potentially affect the normal folding of the helicase or lead to the destruction of the misfolded protein and/or mislocalization of the protein in the cell. Unfortunately, a functional assay to determine the RECQL4 activity is not yet available.15

**COMMENT**

Despite significant phenotypic overlaps between RAPADILINO and RTS, distinct findings have separated the 2 disorders. The present case is unusual in that all criteria of RAPADILINO developed in addition to the ectodermal symptoms (Table). This observation shows that patients with RTS may develop significant extracutaneous findings that may lead to a diagnostic dilemma between RTS and RAPADILINO. The presence of poikiloderma, alopecia, and sparse eyebrows, which are characteristic of RTS, may be useful to distinguish the 2 disorders. Patients whose rash or its onset has been atypical have been considered to represent RTS cases if they have additional features such as radial ray defects, loss of hair, cataracts, osteosarcoma, or skeletal dysplasia.5 However, based on our findings and those of others,23,24 we believe that genetic evaluation is important in probands who phenotypically possess features of RAPADILINO and/or RTS.

A recent cohort showed that all patients with RTS who developed osteosarcoma had at least 1 truncating RECQL4 mutation.13 On the contrary, patients with RAPADILINO have been shown to carry the IVS7+2delT mutation leading to inframe skipping of exon 7, either in a homozygous or compound heterozygous form. This defect possibly leaves the helicase domain of the polypeptide intact and might only partially affect RECQL4 function. The preserved helicase activity may lead to the phenotypic differences and to the lower tumor prevalence than is found in RTS.16 Consequently, designating these disorders as RECQL4 diseases should prompt a careful molecu-