Telomere shortening by mutations in the RTEL1 helicase cause severe form of dyskeratosis congenita, Hoyeraall-Hreidarsson syndrome

Reference


Germline mutations of regulator of telomere elongation helicase 1, RTEL1, in Dyskeratosis congenital

Ballew et al. (2013)

Constitutional mutations in RTEL1 cause severe dyskeratosis congenita

Walne et al. (2013)

Dyskeratosis congenita (DC; MIM 305000) is a rare multi-systemic disorder caused by defective telomere biology and is characterized by the classical presentation of nail dystrophy, abnormal skin pigmentation and oral leukoplakia. In the phenotypically severe variant of DC, Hoyeraall-Hreidarsson syndrome (HHS; MIM 300240), affected individuals present additional features such as bone marrow failure, cerebral hypoplasia and intrauterine growth retardation resulting in an earlier onset of disease and a clinically poor prognosis. Mutations in eight genes (KDC1, TERC, TERT, TINF2, NOP10, NHP2, WRAP53, and CTC1) involved in telomere maintenance have been identified for the majority of classical DC cases. The genetic basis of HHS, however, is still largely unknown and poorly understood.

Recently, two separate studies have identified mutations in regulation of telomere elongation helicase 1 (RTEL1) as a cause for HHS, implicating a novel telomere biology gene in the etiology of DC. First, Ballew et al. examined two families affected by HHS but clinically tested and negative for mutations in the known DC genes. Using whole-exome sequencing, the authors identified novel nonsense (p.Arg1010X, p.Arg998X) and missense (p.Glu615Asp) mutations in RTEL1 in three affected patients from the two families. The first family demonstrated autosomal dominant inheritance of the p.Arg1010X mutation whereas the second family exhibited compound heterozygote autosomal recessive inheritance of the p.Arg998X and p.Glu615Asp mutations. The p.Arg1010X and p.Arg998X mutations introduce a pre-mature stop codon resulting in the loss of the pCNA-interacting protein (PIP) motif whereas the p.Glu615Asp substitution is located in a highly conserved residue of the helicase domain. Strikingly, nearly all individuals (8/9) harboring one of these mutations had significantly shorter telomeres than normal, suggesting the variants have a damaging effect on RTEL1 function and telomere maintenance. A subsequent larger study by Walne et al. reported autosomal recessive inheritance of biallelic RTEL1 mutations in 10 patients with HHS from seven independent families. Again, patients carrying RTEL1 variants were demonstrated to have significantly shorter telomere lengths. Of the 11 mutations identified in this study, only one missense mutation was previously described in the NHLBI Exome variant server, which contains exome sequence data from over 12,000 individuals. Furthermore, the RTEL1 variants were shown to be specific to individuals with the HHS phenotype as no biallelic variants were identified in 102 index cases with classical DC.

Additionally, Walne et al. illustrate a novel pathogenic mechanism in which telomere shortening occurs in the absence of a dysfunctional telomerase complex. In mice, RTEL1 is shown to be required for T-loop disassembly allowing telomere replication and efficient elongation by telomerase. (1) These T-loops are thought to have a functional role in protecting chromosome ends from degradation and aberrant DNA-repair activities, but are removed during DNA replication. Persistent T-loops are cleaved by the SLX4 complex to form T-circles, which effectively shortens the length of telomeres. (Fig. 1) Interestingly, the authors found significantly higher T-circle formation in HHS patients carrying the RTEL1 variants compared with controls, suggesting that these mutations affect the ability of RTEL1 to efficiently process T-loops and maintain telomere length. Aberrant T-circle formation is shown to be exclusive to HHS patients with RTEL1 mutations as no significant differences in T-circle levels were seen in HHS cases harboring the DKC1 gene.

The findings from these recent studies implicate a new gene and mechanism in the pathogenesis of a clinically severe form of DC. Furthermore, the role of helicases in telomere biology and its relevance in telomere-associated disorders provides a new target for potential therapeutic opportunities.

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