American Journal of Medical Genetics Part A

WILEY

AMERICAN JOURNAL OF medical genetics PART A

ORIGINAL ARTICLE OPEN ACCESS

Germline *RTEL1* Variants in Telomere Biology Disorders

Ashley S. Thompson[1] | Marena R. Niewisch[1,2] | Neelam Giri[1] | Lisa J. McReynolds[1] | Sharon A. Savage[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA | [2]Department of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany

Correspondence: Sharon A. Savage (savagesh@mail.nih.gov)

Received: 21 June 2024 | **Revised:** 22 August 2024 | **Accepted:** 2 September 2024

Funding: This work was supported by the intramural research program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute.

Keywords: dyskeratosis congenita | Hoyeraal-Hreidarsson syndrome | *RTEL1* | telomere | telomere biology disorder | variant curation

ABSTRACT

Rare germline variation in regulator of telomere elongation helicase 1 (RTEL1) is associated with telomere biology disorders (TBDs). Biallelic *RTEL1* variants result in childhood onset dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome whereas heterozygous individuals usually present later in life with pulmonary fibrosis or bone marrow failure. We compiled all TBD-associated *RTEL1* variants in the literature and assessed phenotypes and outcomes of 44 individuals from 14 families with mono- or biallelic *RTEL1* variants enrolled in clinical trial NCT00027274. Variants were classified by adapting ACMG-AMP guidelines using clinical information, telomere length, and variant allele frequency data. Compared with heterozygotes, individuals with bi-allelic *RTEL1* variants had an earlier age at diagnosis (median age 35.5 vs. 5.1 years, $p < 0.01$) and worse overall survival (median age 66.5 vs. 22.9 years, $p < 0.001$). There were 257 unique *RTEL1* variants reported in 47 publications, and 209 had a gnomAD minor allele frequency <1%. Only 38.3% (80/209) met pathogenic/likely pathogenic criteria. Notably, 8 of 209 reported disease-associated variants were benign or likely benign and the rest were variants of uncertain significance. Given the considerable differences in outcomes of TBDs associated with *RTEL1* germline variants and the extent of variation in the gene, systematic functional studies and standardization of variant curation are urgently needed to inform clinical management.

1 | Introduction

RTEL1 encodes regulator of telomere elongation helicase 1, a DNA helicase essential for DNA replication, telomere homeostasis, and recombination in mitotic and meiotic cells. Genome-wide association studies have identified common, noncoding germline *RTEL1* variants associated with risk of brain tumors (Shete et al. 2009; Wrensch et al. 2009; Jin et al. 2013; Melin et al. 2013; Delgado et al. 2018). Rare biallelic and monoallelic germline *RTEL1* variants have been reported across the spectrum of telomere biology disorders (TBDs), including dyskeratosis congenita (DC) and Hoyeraal-Hreidarsson syndrome (HH) (Walne et al. 2013; Le Guen et al. 2013; Ballew, Yeager, et al. 2013; Speckmann et al. 2017). A pathogenic germline founder variant in the Ashkenazi Jewish population (g.20:62326972G>A (hg19), p.R1264H) has also been reported in patients with HH (Ballew, Joseph, et al. 2013; Fedick et al. 2015).

DC, the prototypical TBD, is a rare inherited bone marrow failure (BMF) and cancer predisposition syndrome caused by germline pathogenic/likely pathogenic (P/LP) variants in telomere biology genes (Niewisch et al. 2022; Tummala, Walne, and Dokal 2022; Revy, Kannengiesser, and Bertuch 2023). Classically identified by the triad of abnormal skin pigmentation, oral leukoplakia, and dysplastic nails, DC phenotypes are progressive and exist on a clinical spectrum, including pulmonary fibrosis (PF), liver disease, immunodeficiency, and stenosis of the esophagus, lacrimal ducts, and/or urethra (Niewisch et al. 2022; Tummala, Walne, and Dokal 2022; Revy, Kannengiesser, and Bertuch 2023). HH is marked by intrauterine growth retardation,

cerebellar hypoplasia, microcephaly, developmental delay, and immunodeficiency (Niewisch et al. 2022; Tummala, Walne, and Dokal 2022; Revy, Kannengiesser, and Bertuch 2023; Glousker et al. 2015). Lymphocyte telomere length measured by flow cytometry with fluorescence in situ hybridization (flow FISH) less than the first percentile for age is diagnostic of DC and related TBDs (Alter et al. 2012).

A subset of patients with idiopathic PF, a chronic, progressive, irreversible, and lethal lung disease, have germline P/LP variants in telomere biology genes and telomeres less than the 10th percentile for age (Armanios 2009; King Jr., Pardo, and Selman 2011; Cogan et al. 2015). Often exhibiting incomplete penetrance, rare *RTEL1* variants account for approximately 3% of diagnosed cases of PF (Stuart et al. 2015; Kropski, Blackwell, and Loyd 2015). Detailed assessment of family history of those with PF may reveal features of a TBD including aplastic anemia and/or nonalcoholic/noninfectious liver disease.

The diagnosis of a TBD has major implications for the patient and their relatives due to the variable penetrance and expressivity of the phenotypes (Niewisch et al. 2022; Tummala, Walne, and Dokal 2022; Revy, Kannengiesser, and Bertuch 2023). Careful curation of germline variants is essential for understanding disease etiology and for appropriate tailoring of therapy and reproductive planning (Richards et al. 2008). In this study, we compiled, annotated, and classified all germline *RTEL1* variants in our cohort study of TBDs and in the literature to better understand the role of germline *RTEL1* variation in disease etiology.

2 | Methods

2.1 | Study Participants

Forty-four individuals from 14 families with mono- or biallelic rare *RTEL1* variants enrolled in the NCI's Institutional Review Board approved inherited BMF syndromes study between January 1, 2002 and May 31, 2019 and were included in this analysis (clinicaltrials.gov, Identifier: NCT00027274) (Alter et al. 2018). All participants or their legal guardian signed informed consent. Questionnaire data were collected, and medical records reviewed. Twenty affected individuals were evaluated at the National Institutes of Health Clinical Center. Severe BMF was defined as transfusion dependency, and/or androgen treatment, and/or abnormal blood counts; absolute neutrophil count <500/mm^3 and/or platelet count <20,000/mm^3 and/or hemoglobin <8.0 g/dL. All study participants had leukocyte telomere lengths measured by flow FISH at Repeat Diagnostics, Inc. (Vancouver, BC, Canada). Study participants underwent genetic testing and *RTEL1* variants were identified by clinical laboratories and/or research genetic testing at the NCI (Table S1).

2.2 | *RTEL1* Variant Identification and Curation

Disease-associated *RTEL1* variants were extracted from the following publicly available biomedical literature databases: The National Library of Medicine's PubMed database, Arizona State University's Telomerase Database, and the Human Gene Mutation Database (HGMD). The *RTEL1*-associated diseases assessed were "DC," "HH syndrome," "idiopathic pulmonary fibrosis," "PF," "aplastic anemia," "myelodysplastic syndrome," "liver fibrosis," and nonspecific "gastrointestinal enteropathy." Literature reviewed was published prior to May 31, 2023 (Table S2).

All genomic positions were converted to the GRCh37 (hg19) human genome build. Due to the presence of multiple *RTEL1* transcript isoforms, the transcript on which variants are reported was inconsistent. cDNA positions and resulting amino acids were converted to the longest *RTEL1* transcript (4615 base pairs, isoform 3, NM_001283009.2, ENST00000360203.11) using Mutalyzer (Leiden University Medical Center) and the ClinGen Allele Registry (https://reg.clinicalgenome.org). The first report of the variant was used as the primary report and additional reports were added to the dataset.

Disease-associated germline variants were annotated using ANNOVAR and those with a minor allele frequency (MAF) less than 1% were selected for further classification. Variant curation following the ACMG-AMP recommendations was adapted to *RTEL1* as detailed in the Supplementary Methods—Data S1 and previously described (Niewisch et al. 2022).

2.3 | Statistical Analyses

Fisher's exact test for categorical variable analyses while Mann–Whitney *U* test was used for continuous variables. Survival probabilities were calculated using Kaplan–Meier estimates. For comparison of survival probabilities between autosomal dominant (AD, heterozygous) and autosomal recessive (AR, biallelic) *RTEL1* associated TBD log-rank test was used. *p*-values less than 0.05 were considered significant. Statistical analyses were performed using R (version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Clinical Features of *RTEL1* Variants in the NCI Cohort

There were 29 individuals with heterozygous and 15 with biallelic *RTEL1* variants from 14 families in our cohort (Table 1). Eight of the 14 families had both heterozygous and biallelic genotypes present in affected individuals. Three patients had homozygous *RTEL1* variants. There were more females with heterozygous variants and slightly more males with biallelic variants (male:female ratios 0.71:1 and 1.14:1, respectively). Patients with biallelic variants were significantly younger at diagnosis than the heterozygotes (median age 5.08 years [range 0.78–16.93] vs. 35.52 [range 1.32–63.75], $p < 0.01$, excluding 6 patients with diagnosis established after death). Biallelic patients were also younger than heterozygotes at last follow-up (median age 16.2 years [range 2.16–26.33] vs. 37.68 [range 2.4–66.5], respectively, $p < 0.01$). Individuals with biallelic *RTEL1* variants were also more likely to have shorter telomeres than those with heterozygous *RTEL1* variants (Figure 1). Overall survival was significantly poorer for those with biallelic *RTEL1* variants

TABLE 1 | Comparison of clinical phenotypes of participants with *RTEL1* variants (grouped by genotype) in the NCI cohort. Twenty-four participants underwent detailed evaluation at the NIH Clinical Center. For the 20 not evaluated at the NIH, features not specifically reported in medical records were considered as absent.

	Total (%)	AD (%)	AR (%)
Number of individuals	44	29	15
Male:Female	0.83:1	0.71:1	1.14:1
Median age at diagnosis (range)	24.11 (0.78–63.75)	35.52 (1.32–63.75)	5.10 (0.78–16.93)
Median age at follow-up in years (range)	25.73 (2.15–66.50)	37.68 (2.40–66.50)	16.20 (2.16–26.33)
DC triad features present[a]	13/41 (31.7%)	0/26 (0%)	13/15 (86.7%)
• Abnormal skin pigmentation	6/41 (14.6%)	0/26 (0%)	6/15 (40%)
• Oral leukoplakia	13/41 (31.7%)	0/26 (0%)	13/15 (86.7%)
• Dysplastic nails	10/41 (24.4%)	0/26 (0%)	10/15 (66.7%)
Bone marrow failure			
• Non-severe	6/43 (13.9%)	5/28 (17.9%)	1/15 (6.67%)
• Severe[b]	17/43 (39.5%)	4/28 (14.3%)	13/15 (86.7%)
Pulmonary fibrosis			
• PF w/o HCT	2	1	1
• PF post HCT	3	0	3
Liver disease[c]	2/37 (5.41%)	0/26 (0%)	2/11 (18.2%)
Short stature	5/37 (13.5%)	1/26 (3.85%)	4/11 (36.4%)
CNS abnormalities			
• Structural	15/19 (78.9%)	2/5 (40%)	13/14 (92.9%)
• Developmental delay	14/36 (38.9%)	4/25 (16%)	10/11 (90.1%)
PAVM			
• Spontaneous	0	0	0
• PAVM post HCT	4	1	3
AVN			
• Spontaneous	3	1	2
• AVN after HCT	4	2	2
Gastrointestinal abnormalities	9/25 (36%)	1/14 (7.14%)	8/11 (72.7%)
Endocrine abnormalities	4/36 (11.1%)	3/25 (12%)	1/11 (9.10%)
Dental anomalies	6/21 (28.6%)	3/14 (21.4%)	3/7 (42.9%)

Abbreviations: AVN, avascular necrosis of femoral or humeral head; CNS, central nervous system; HCT, hematopoietic cell transplant; PAVM, pulmonary arteriovenous malformations.
[a]At least 2 out of 3 DC triad features present.
[b]Severe BMF: transfusion dependency, and/or androgen treatment, and/or abnormal blood counts; absolute neutrophile count <500/mm3 and/or platelet count <20,000/mm3 and/or hemoglobin <8.0 g/dL.
[c]Liver disease: portal hypertension and/or liver cirrhosis/fibrosis.

than heterozygous individuals (median survival 22.9 years vs. 66.5 years, $p < 0.001$, Figure 1).

The mucocutaneous triad was not present in patients with heterozygous *RTEL1* variants. At least two of three mucocutaneous triad features were present in 86.7% (13/15) participants with biallelic *RTEL1* variants. BMF occurred in approximately one third of heterozygous participants (9/28, 32.1%). Notably, 86.7% (13/15) of participants with biallelic *RTEL1* variants experienced severe BMF. PF was observed in one monoallelic and four biallelic patients with most diagnoses occurring after hematopoietic cell transplant (HCT) (3/5, 60%). Pulmonary arteriovenous malformations were another common complication post-HCT in the biallelic *RTEL1* setting (4/4, 100%). Avascular necrosis occurred similarly across all genotypes and did not seem to be impacted by HCT (3/7, 42.9% spontaneous AVN; 4/7, 57.1% post-HCT AVN).

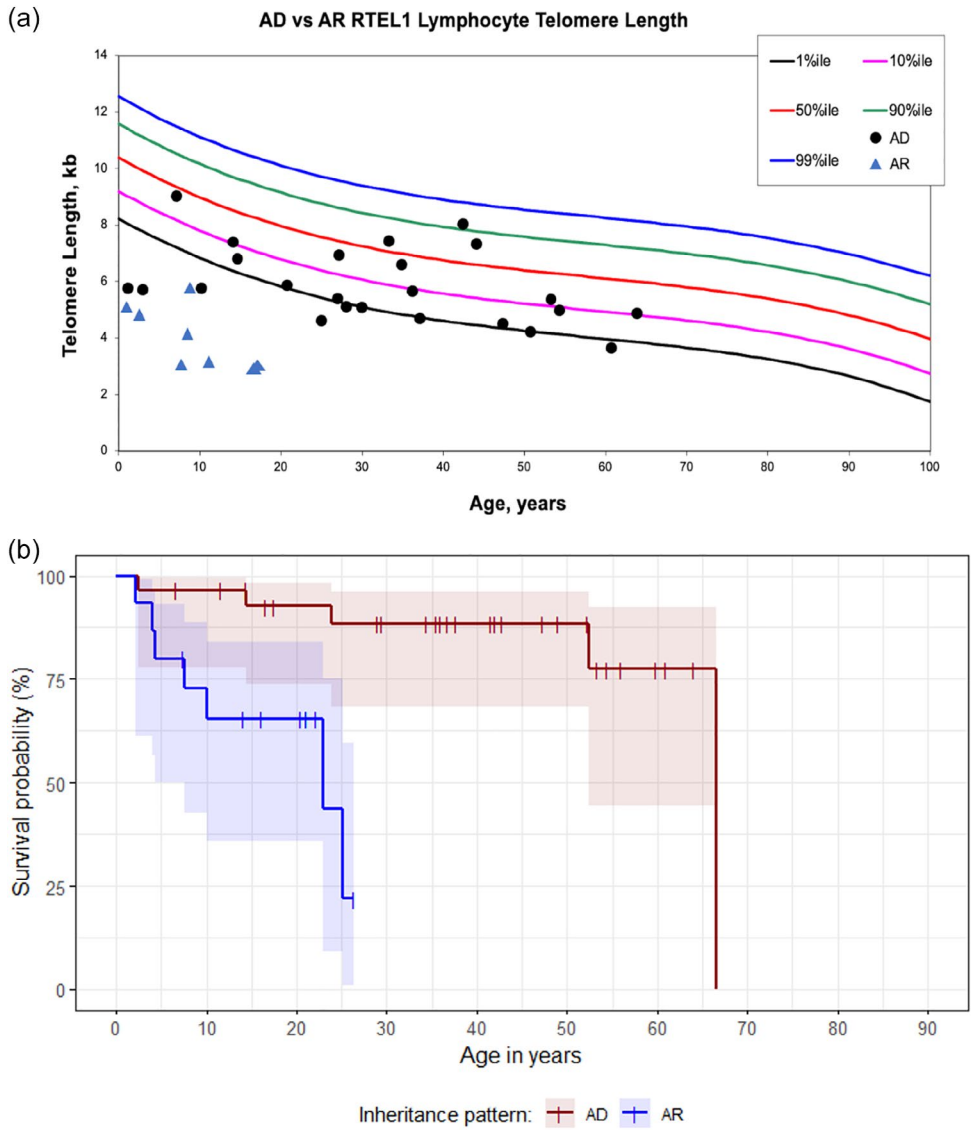

FIGURE 1 | Telomere lengths and overall survival of study participants with germline *RTEL1* variants. (A) Flow FISH telomere lengths in total lymphocytes are very short in all participants; (B) Kaplan–Meier estimates were compared between patients with heterozygous or biallelic *RTEL1* variants participating in the NCI IBMFS cohort. Patients with biallelic *RTEL1* variants showed significantly lower overall survival than those with heterozygous *RTEL1* variants ($p < 0.001$).

Liver disease, including portal hypertension and/or liver cirrhosis/fibrosis was identified only in those with biallelic genotypes (2/37, 5.41%). Other clinical findings observed more commonly in those with biallelic genotypes included short stature (4/11, 36.4%) and developmental delay (10/11, 90.1%), structural central nervous system abnormalities (13/14, 92.9%), gastrointestinal abnormalities, (8/11, 72.7%), and dental anomalies (3/7, 42.9%). Endocrine abnormalities including diabetes mellitus or thyroid disease, occurred at similar frequencies across the cohort (AD: 3/25, 12% vs. AR: 1/11, 9.10%).

3.2 | TBD-Associated *RTEL1* Variants in the Literature

Literature review identified 257 unique *RTEL1* variants in 47 publications associated with TBDs (Table S2). Two hundred nine of these were rare variants (absent in gnomAD or present at a MAF <1%) and further curated as shown in Figure S1. Only 38.3% (80/209) of the TBD-associated literature variants were classified as P/LP according to modified ACMG criteria. Notably, 3.8% (8/209) TBD-associated variants were classified as likely benign, and no variants were classified as benign. The remaining disease-associated variants (57.9%, 121/209) in the literature were classified as VUS due to MAF >1%, limited clinical data and functional studies, and/or insufficient bioinformatic predictions (Table S2). Figure 2 shows the location of nonsynonymous, nonsense, and frameshift *RTEL1* variants by protein domain.

4 | Discussion

Heterozygous and biallelic rare germline *RTEL1* variants are associated with a wide spectrum of TBD-related clinical manifestations, located throughout the protein, and few studies have been performed to understand their effect on protein function

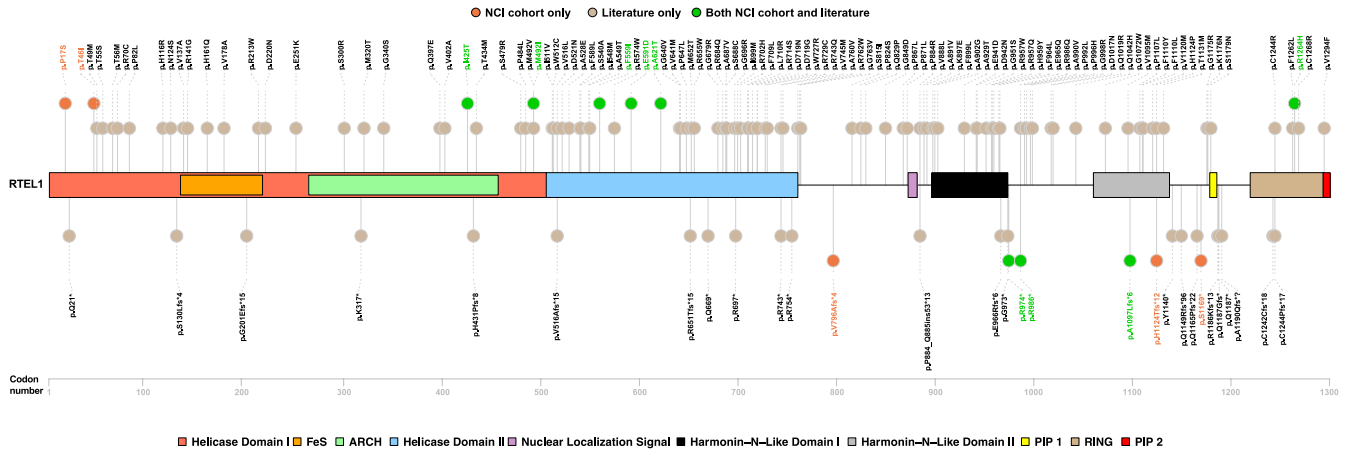

FIGURE 2 | Schematic of the RTEL1 protein with locations of germline variants. Nonsynonymous variants are pictured on the top of the schematic. Nonsense and frameshift variants are pictured at the bottom of the schematic. The previously unreported NCI cohort patients are denoted separately by orange circles. Tan circles denote literature variants and green denote both NCI and literature variants. Location of protein domains is based on PMID: 26847928 (Jullien et al. 2016).

(Niewisch et al. 2022; Revy, Kannengiesser, and Bertuch 2023; Glousker et al. 2015; Lansdorp, van Wietmarschen, and Helicases 2019; Hourvitz, Awad, and Tzfati 2024). In this study, we present survival data on patients with TBD due to biallelic or heterozygous *RTEL1* variants which shows shorter telomeres, earlier age at diagnosis, and worse survival for biallelic patients. We combined these data with a comprehensive literature review of germline *RTEL1* variants and associated phenotypes to inform our approach to variant classification.

Curation of *RTEL1* variants is complicated because it is a large gene with 35 exons over 4615 base pairs, contains numerous splice variants resulting in 21 transcripts (https://ensembl.org), and has thousands of variants reported in gnomAD (968 synonymous, 1940 missense, and 89 loss of function) (Hourvitz, Awad, and Tzfati 2024; Jullien et al. 2016). Inconsistencies in genomic nomenclature, including publications not reporting the genome build or transcript isoform used, added to the curation challenges. Incomplete clinical data, heterozygous and biallelic disease states, variable methods of telomere length measurement, and lack of comprehensive functional studies further complicated variant interpretation. Our comprehensively studied cohort of individuals with TBD due to *RTEL1* variation allowed us to use those variants as part of the curation criteria (Niewisch et al. 2022). We recognize that this strength is also a limitation because most of these variants lack functional data, other than telomere length, and the cohort participants are likely ascertained due to more severe phenotypes.

Less than half of the disease-associated variants in the literature met the adapted ACMG-AMP P/LP criteria (80/209, 38.3%). The remainder were VUS (121/209, 57.9%), or were likely benign (8/209, 3.8%). This finding is especially concerning because it adds considerable uncertainty in determining affected status of possible TBD patients and their family members. Patients with biallelic *RTEL1* TBDs generally present as young children with BMF, immunodeficiency, mucocutaneous features, and/or other complications. However, individuals harboring a heterozygous P/LP *RTEL1* variant may not develop disease until middle or late adulthood (Delgado et al. 2018; Speckmann et al. 2017; Tummala, Walne, and Dokal 2022). The challenges in *RTEL1* variant interpretation, complex and time dependent clinical manifestations, and genetic testing of affected and unaffected family members make genetic counseling in this situation exceedingly challenging and fraught with uncertainty.

Lymphocyte telomere length <1st percentile for age measured by flow FISH is diagnostic of DC/TBDs and has successfully been used in discovering their underlying genetic etiology (Alter et al. 2012; Savage et al. 2007). In this study, we used flow FISH telomere length as a component of variant classification to address, in part, challenges related to the incomplete penetrance and variable expressivity of *RTEL1*-associated TBDs. This was possible with variants in the NCI cohort but there were limited telomere length data linked to the literature variants which likely led to more of the latter being classified as VUS. Given the importance of variant classification in clinical management, assessment of telomere length in individuals being evaluated for TBDs is essential to provide appropriate counseling and medical management for affected and at-risk individuals.

RTEL1 encodes a helicase with important functions in genome integrity and telomere biology and is associated with complex phenotypes due to rare biallelic and heterozygous variants. This study illustrates the need for standardization of *RTEL1* variant classification, consistency in genomic nomenclature, telomere length measurement, robust functional studies, and additional clinical and family studies to improve understanding of the role of *RTEL1* variation in human disease.

Author Contributions

Ashley S. Thompson: data acquisition, data curation, formal analysis, writing – reviewing and editing. **Marena R. Niewisch:** data acquisition, data curation, formal analysis, writing – reviewing and editing. **Neelam Giri:** data acquisition, writing – reviewing and editing. **Lisa J. McReynolds:** data acquisition, writing – reviewing and editing. **Sharon A. Savage:** data acquisition, data curation, formal analysis, writing – reviewing and editing. All authors reviewed and approved the final manuscript.

Acknowledgments

The authors thank Dr. Kelvin de Andrade, NCI for assistance in creating Figure 2. We are especially grateful to all study participants for their valuable contributions to this work.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The literature data herein were derived from publicly available databases and are compiled in Table S2. There are restrictions to the availability of data from clinicaltrials.gov Identifier: NCT00027274 due to the importance of maintaining participant confidentiality. De-identified data from that study may be requested from the corresponding author, Dr. Sharon A. Savage, and will be made available to qualified scientists after completion of appropriate data transfer agreements and NIH Institutional Review Board approval.

References

Alter, B. P., N. Giri, S. A. Savage, and P. S. Rosenberg. 2018. "Cancer in the National Cancer Institute Inherited Bone Marrow Failure Syndrome Cohort After Fifteen Years of Follow-Up." *Haematologica* 103, no. 1: 30–39.

Alter, B. P., P. S. Rosenberg, N. Giri, G. M. Baerlocher, P. M. Lansdorp, and S. A. Savage. 2012. "Telomere Length Is Associated With Disease Severity and Declines With Age in Dyskeratosis Congenita." *Haematologica* 97, no. 3: 353–359.

Armanios, M. 2009. "Syndromes of Telomere Shortening." *Annual Review of Genomics and Human Genetics* 10: 45–61.

Ballew, B. J., V. Joseph, S. De, et al. 2013. "A Recessive Founder Mutation in Regulator of Telomere Elongation Helicase 1, RTEL1, Underlies Severe Immunodeficiency and Features of Hoyeraal Hreidarsson Syndrome." *PLoS Genetics* 9, no. 8: e1003695.

Ballew, B. J., M. Yeager, K. Jacobs, et al. 2013. "Germline Mutations of Regulator of Telomere Elongation Helicase 1, *RTEL1*, in Dyskeratosis Congenita." *Human Genetics* 132, no. 4: 473–480.

Cogan, J. D., J. A. Kropski, M. Zhao, et al. 2015. "Rare Variants in RTEL1 Are Associated With Familial Interstitial Pneumonia." *American Journal of Respiratory and Critical Care Medicine* 191, no. 6: 646–655.

Delgado, D. A., C. Zhang, L. S. Chen, et al. 2018. "Genome-Wide Association Study of Telomere Length Among South Asians Identifies a Second RTEL1 Association Signal." *Journal of Medical Genetics* 55, no. 1: 64–71.

Fedick, A. M., L. Shi, C. Jalas, et al. 2015. "Carrier Screening of RTEL1 Mutations in the Ashkenazi Jewish Population." *Clinical Genetics* 88, no. 2: 177–181.

Glousker, G., F. Touzot, P. Revy, Y. Tzfati, and S. A. Savage. 2015. "Unraveling the Pathogenesis of Hoyeraal-Hreidarsson Syndrome, a Complex Telomere Biology Disorder." *British Journal of Haematology* 170, no. 4: 457–471.

Hourvitz, N., A. Awad, and Y. Tzfati. 2024. "The Many Faces of the Helicase RTEL1 at Telomeres and Beyond." *Trends in Cell Biology* 34, no. 2: 109–121.

Jin, T. B., J. Y. Zhang, G. Li, et al. 2013. "RTEL1 and TERT Polymorphisms Are Associated With Astrocytoma Risk in the Chinese Han Population." *Tumour Biology* 34, no. 6: 3659–3666.

Jullien, L., C. Kannengiesser, L. Kermasson, et al. 2016. "Mutations of the RTEL1 Helicase in a Hoyeraal-Hreidarsson Syndrome Patient Highlight the Importance of the ARCH Domain." *Human Mutation* 37, no. 5: 469–472.

King, T. E., Jr., A. Pardo, and M. Selman. 2011. "Idiopathic Pulmonary Fibrosis." *Lancet* 378, no. 9807: 1949–1961.

Kropski, J. A., T. S. Blackwell, and J. E. Loyd. 2015. "The Genetic Basis of Idiopathic Pulmonary Fibrosis." *European Respiratory Journal* 45, no. 6: 1717–1727.

Lansdorp, P., N. van Wietmarschen, and F. A. N. C. J. Helicases. 2019. "RTEL1 and BLM Act on Guanine Quadruplex DNA In Vivo." *Genes (Basel)* 10, no. 11: 870.

Le Guen, T., L. Jullien, F. Touzot, et al. 2013. "Human RTEL1 Deficiency Causes Hoyeraal-Hreidarsson Syndrome With Short Telomeres and Genome Instability." *Human Molecular Genetics* 22, no. 16: 3239–3249.

Melin, B., A. M. Dahlin, U. Andersson, et al. 2013. "Known Glioma Risk Loci are Associated With Glioma With a Family History of Brain Tumours—a Case-Control Gene Association Study." *International Journal of Cancer* 132, no. 10: 2464–2468.

Niewisch, M. R., N. Giri, L. J. McReynolds, et al. 2022. "Disease Progression and Clinical Outcomes in Telomere Biology Disorders." *Blood* 139, no. 12: 1807–1819.

Revy, P., C. Kannengiesser, and A. A. Bertuch. 2023. "Genetics of Human Telomere Biology Disorders." *Nature Reviews. Genetics* 24, no. 2: 86–108.

Richards, C. S., S. Bale, D. B. Bellissimo, et al. 2008. "ACMG Recommendations for Standards for Interpretation and Reporting of Sequence Variations: Revisions 2007." *Genetics in Medicine* 10, no. 4: 294–300.

Savage, S. A., N. Giri, G. M. Baerlocher, N. Orr, P. M. Lansdorp, and B. P. Alter. 2007. "TINF2, a Component of the Shelterin Telomere Protection Complex, Is Mutated in Dyskeratosis Congenita." *Blood* 110, no. 11: 256A.

Shete, S., F. J. Hosking, L. B. Robertson, et al. 2009. "Genome-Wide Association Study Identifies Five Susceptibility Loci for Glioma." *Nature Genetics* 41, no. 8: 899–904.

Speckmann, C., S. S. Sahoo, M. Rizzi, et al. 2017. "Clinical and Molecular Heterogeneity of RTEL1 Deficiency." *Frontiers in Immunology* 8: 449.

Stuart, B. D., J. Choi, S. Zaidi, et al. 2015. "Exome Sequencing Links Mutations in PARN and RTEL1 With Familial Pulmonary Fibrosis and Telomere Shortening." *Nature Genetics* 47, no. 5: 512–517.

Tummala, H., A. Walne, and I. Dokal. 2022. "The Biology and Management of Dyskeratosis Congenita and Related Disorders of Telomeres." *Expert Review of Hematology* 15, no. 8: 685–696.

Walne, A. J., T. Vulliamy, M. Kirwan, V. Plagnol, and I. Dokal. 2013. "Constitutional Mutations in RTEL1 Cause Severe Dyskeratosis Congenita." *American Journal of Human Genetics* 92, no. 3: 448–453.

Wrensch, M., R. B. Jenkins, J. S. Chang, et al. 2009. "Variants in the CDKN2B and RTEL1 Regions Are Associated With High-Grade Glioma Susceptibility." *Nature Genetics* 41, no. 8: 905–908.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.