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ORIGINAL PAPER

Understanding the evolving phenotype of vascular complications in telomere biology disorders

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Abstract
Vascular complications such as bleeding due to gastrointestinal telangiectatic anomalies, pulmonary arteriovenous malformations, hepatopulmonary syndrome, and retinal vessel abnormalities are being reported in patients with telomere biology disorders (TBDs) more frequently than previously described. The international clinical care consortium of telomere-associated ailments and family support group Dyskeratosis Congenita Outreach, Inc. held a workshop on vascular abnormalities in the TBDs at the National Cancer Institute in October 2017. Clinicians and basic scientists reviewed current data on vascular complications, hypotheses for the underlying biology and developed new collaborations to address the etiology and clinical management of vascular complications in TBDs.

Keywords Telomere · Dyskeratosis congenita · Consortium · Vascular biology

Background

The telomere biology disorders (TBDs) manifest with a wide array of complex medical complications and are caused by germline pathogenic variants in telomere biology genes [1–4]. These disorders have also been termed short telomere syndromes [3]. Patients with dyskeratosis congenita (DC), the prototypic TBD, are often clinically characterized by the triad of lacy reticular skin pigmentation, oral leukoplakia, and dysplastic nails. They are at high risk of developing bone marrow failure, pulmonary fibrosis, avascular necrosis of the hips or shoulders, esophageal stenosis, and other medical problems including a high lifetime risk of specific cancers [5, 6]. The discovery of germline pathogenic variants in *DKC1* (encoding dyskerin) as the cause of X-linked recessive DC showed, for the first time, that aberrations in telomere biology resulting in very short telomeres could cause clinically significant human phenotypes [7, 8]. Since then, 13 additional genes have been associated with DC and related TBDs with de novo, autosomal dominant, and autosomal recessive inheritance patterns (Fig. 1) [1, 9–11].

The clinical spectrum of TBDs has expanded as discoveries of the genetic causes have grown (Table 1). Some patients, primarily those with predominantly autosomal dominant disease due to *TERT, TERC, PARN*, or *RTEL1* mutations, may develop just one feature of DC in adulthood in the absence of the mucocutaneous triad [1–3, 12–16]. Other patients, including those with *DKC1* mutations, de novo *TINF2* mutations, or autosomal recessive disease may present at an earlier age. Those with Hoyeraal–Hreidarsson syndrome, a variant of DC that has features of immunodeficiency and cerebellar hypoplasia, or

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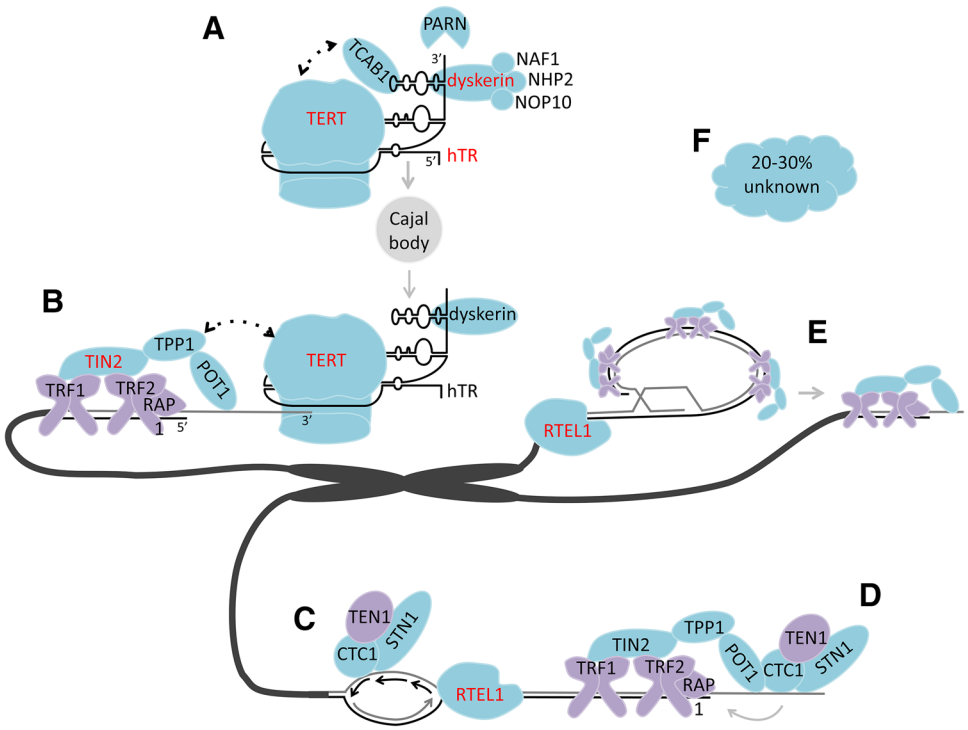

Fig. 1 Factors and pathways impacted by mutations found in patients with TBDs. *a* Telomerase biogenesis and activation. *b* Telomerase recruitment. *c* Duplex telomeric DNA replication. *d* Terminal DNA end structure. *e* Resolution of t loop structure. *f* Approximate number of classic DC patients without detected mutation in one of the known genes. Subunits in blue shade and hTR have been found mutated in patients with DC. Those with red font are the most commonly mutated

Table 1 Clinical features of TBDs

Disorder	Key clinical features
DC	Mucocutaneous triad of nail dysplasia, abnormal skin pigmentation (hyper/hypopigmented, lacy, reticular pigmentation), and oral leukoplakia. BMF, PF, PAVM, liver disease, hepatopulmonary syndrome, avascular necrosis of hips and/or shoulders, urethral stenosis, lacrimal duct stenosis, esophageal stenosis, HNSCC, MDS, AML, developmental delay. Traditional diagnosis of DC: classic triad or one of the triad, BMF, and two other findings [1]
Revesz syndrome	Features of DC plus bilateral exudative retinopathy. Intracranial calcifications and developmental delay also reported
Hoyeraal–Hreidarsson syndrome	Features of DC plus cerebellar hypoplasia. Immunodeficiency has been reported as presenting problem
Coats plus	Bilateral retinopathy, intracranial calcifications, leukodystrophy, anemia, osteopenia, poor bone healing
DC-like	BMF, AA, MDS, or PF occurring in the presence of at least one other DC-associated feature or family history suspicious of DC
Aplastic anemia	Progressive multi-lineage cytopenias. May occur in the absence of DC-associated features
Myelodysplastic syndrome	Cytopenias with morphologic dysplasia and/or clonal chromosomal abnormalities. May occur in the absence of DC-associated features
Acute myeloid leukemia	May progress from MDS or aplastic anemia. May occur in the absence of DC-associated features
Pulmonary fibrosis	May occur in the absence of DC-associated features
Liver fibrosis	Non-alcoholic, non-infectious liver fibrosis. May occur in the absence of DC-associated features

BMF bone marrow failure, *PF* pulmonary fibrosis, *PAVM* pulmonary arteriovenous malformations, *HNSCC* head and neck squamous cell carcinoma, *MDS* myelodysplastic syndrome, *AML* acute myeloid leukemia, *DC* dyskeratosis congenita, *AA* aplastic anemia

Revesz syndrome that encompasses features of DC with exudative retinopathy and intracranial complications [1, 6, 17], may present in infancy. Coats plus, a rare autosomal recessive disease, typically includes intracranial calcifications with associated brain cysts, gastrointestinal (GI) bleeding due to telangiectasias, retinal vascular abnormalities, and abnormal bone healing [18, 19]. Coats plus was linked with TBD when patients with DC were also found to have mutations in *CTC1* [20, 21].

New clinical presentations are now being recognized in patients with TBDs, likely due to improvements in supportive care and survival into adulthood allowing for the progression of disease. For example, hepatopulmonary syndrome, pulmonary shunting, and development of pulmonary

arteriovenous malformations (PAVM) have recently been recognized as a part of the phenotype [22, 23]. Life-threatening GI bleeding, similar to that reported in Coats plus [24, 25], has been reported by clinicians as a major cause of morbidity in DC/TBD.

The expanding vascular phenotype of DC/TBD prompted the international Clinical Care Consortium of Telomere-associated Ailments (CCCTAA) to hold a workshop on this topic at the National Cancer Institute in Rockville, MD, USA on October 24 and 25, 2017. The 48 attendees consisted of clinicians with expertise in pediatric and adult hematology, oncology, hematopoietic stem cell transplantation (HCT), gastroenterology, hepatology, ophthalmology, pulmonology, vascular anomalies, and genetics, as well as representatives from the family support group Dyskeratosis Congenita Outreach, Inc. (DCO; http://teamtelomere.org). Vascular complications in patients with DC/TBD were discussed with goals for developing new studies aimed at addressing these challenging medical problems.

Are vascular complications more frequent than previously appreciated?

Bleeding due to vascular telangiectatic anomalies of the GI tract is the most common cause of death in patients with Coats plus [18, 26] but there are little data on the clinical management [27–29]. Workshop attendees reported clinically significant GI bleeding in 16 patients with DC, a phenotype rarely reported in the over 100 years of DC/TBD literature (Fig. 2). The majority of patients discussed at the

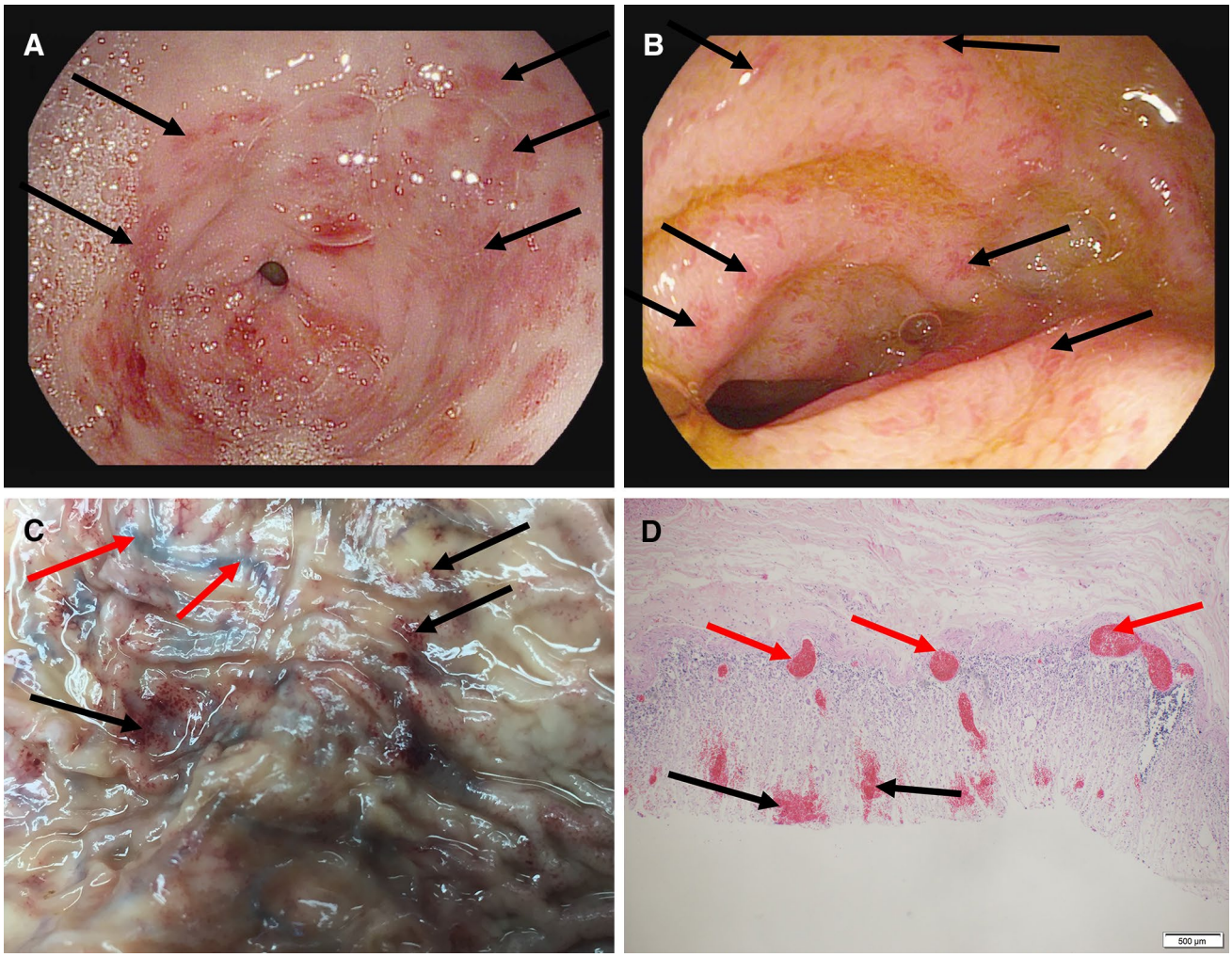

Fig. 2 Representative features of vascular abnormalities in the gastrointestinal tract of patients with TBDs. **a** Stomach, friable, erythematous lesions (shown by black arrows) in the gastric antrum similar in appearance to gastric antral vascular ectasia. **b** Small intestine. Numerous erythematous, telangiectatic-appearing lesions in the proximal small intestine (shown by black arrows). **c** Stomach-gross, at time of autopsy. Petechial hemorrhage (shown by black arrows) is present as are prominent submucosal vessels (shown by red arrows). Courtesy Dr. Hao Wu, Baylor College of Medicine. **d** Stomach-diffuse submucosal (shown by red arrows) congestion with focal congestion of mucosal vessels (shown by black arrows). Courtesy Dr. Hao Wu, Baylor College of Medicine

workshop had a germline mutation in *TINF2*. Patients with mutations in *TERC, TERT*, or *CTC1*, and unknown genetic cause of disease were also reported. The time from diagnosis of DC or HCT to first GI bleed ranged from months to years. GI bleeding could be present at diagnosis of a TBD and was not solely as a post-HCT complication. Upper endoscopy revealed that most patients had erythematous or telangiectatic lesions in the lumen of the stomach or small intestine. The diagnosis of gastric antral vascular ectasia (GAVE) was applied to some of these cases during their work-up.

The presence of vascular telangiectasia could also be compounded by portal hypertensive gastropathy and the development of esophageal varices due to progressive portal hypertension. Whereas esophageal varices are amenable to banding, vascular hypertensive ectasia of the stomach is much more difficult to treat. However, only one of the patients with GI bleeding discussed at the workshop had a history of GI bleeding due to esophageal varices. Workshop participants reported the anecdotal use of estrogen, progesterone, propranolol, octreotide, thalidomide, budesonide, bevacizumab, argon plasma coagulation, and radiofrequency ablation, but there was insufficient data to reach consensus on how to best manage GI bleeding in TBD patients.

Exudative vitreoretinopathy is characteristic of Coats plus and Revesz syndrome but there are limited data on the specific ophthalmologic complications in patients with DC [30]. Case presentations at the workshop showed a wide array of retinal vascular diseases in patients with DC. Laser photocoagulation of severe retinopathy is currently the preferred mode of treatment for retinal vascular disease in DC/TBD. The laser is applied to the avascular peripheral retina, which presumably decreases vascular permeability factors and pro-angiogenic factors that may be contributing to progressive vasculopathy and pathologic neovascularization [31, 32]. Intravitreal injection of bevacizumab is a treatment option [33]. The retinopathy in DC/TBD patients can result in a tractional retinal detachment and vitreous hemorrhage. Such advanced pathology is treated with vitreoretinal surgery to clear the visual axis and reattach the retina. However, advanced and chronic retinal detachment may become inoperable. Early screening of patient with TBD with ultra-wide-field fluorescein angiography is important to detect these subtle vascular abnormalities earlier in the disease course to prevent complications.

Overall, vascular complications including GI bleeding and retinal vascular disease appear to be more widespread in TBDs than expected. Patients with GI bleeding did not necessarily have features of Coats plus and those with exudative vitreoretinopathy were not consistently diagnosed with Revesz syndrome.

Challenges and opportunities in clinical studies of rare TBDs

Table 2 illustrates some of the key questions and potential answers in the setting of vascular complications in TBDs. Multi-disciplinary, international collaborative studies between patients, clinicians, and basic scientists are essential

Table 2 Approaches to understanding vascular complications in TBDs

Question	Possible answer(s)	Ways to address the topic
What are we treating?	Vascular anomalies including gastrointestinal bleeding, exudative vitreoretinopathy, pulmonary arteriovenous malformations	Detailed studies of the clinical manifestations Compile large collaborative case series
What is the pathophysiology?	Unknown	Compare vascular anomalies in TBD with those in other disorders and determine whether there are common biomarkers
What are the biomarkers of interest?	Identify markers to diagnose and track disease progression	Work with vascular biologists Test known biomarkers in TBD patients
Where does telomere biology fit in here?	Understand role of telomere biology genes in vascular biology	Basic science collaborators
What are potential therapeutic agents?	Estrogens, progesterone, androgens, propranolol, octreotide, thalidomide, and bevacizumab have been tried in a few cases but there are not enough data to make evidence-based recommendations	Develop a clinical trial or observational clinical study
What is the definition of response?	Resolution of clinically significant bleeding Improvement in pulmonary function for PAVM patients	Develop a clinical trial or observational clinical study
Could vascular abnormalities cause bone problems?	Unknown	Detailed studies of the clinical manifestations Compile large case series
Could vascular abnormalities underlie onset of bone marrow failure?	Unknown	Investigate bone marrow biopsy samples for similar vascular markers

to improving understanding of all rare diseases, and especially of unique complications in these diseases. The workshop also featured talks by two basic scientists in order to facilitate building bridges between clinicians taking care of patients with DC/TBDs and basic scientists making novel contributions to the telomere field.

Dr. Utz Herbig, Rutgers New Jersey Medical School, presented his research on telomeres and wound healing. There is a growing appreciation of the impact of cellular senescence on wound healing, including via telomere dysfunction-induced senescence and the resulting senescence associated secretory phenotypes (SASP) [34]. The SASPs are pro-inflammatory and postulated to be an important aspect of vascular dysfunction and risk of cardiovascular disease [35]. Since telomeres are sensitive to oxidative damage, it is possible that very short telomeres, such as those seen in TBDs, are even more susceptible to the SASP environment. Although not yet studied, SASP in TBDs could result in abnormal wound healing or cellular responses to inflammation. Another possibility that was raised in the discussion is that short telomeres impair the healing process through cell-autonomous defects.

There may be biological connections underlying the TBDs and vascular complications. For example, the Wnt/beta-catenin pathway is implicated in vascular development and homeostasis [36]. To explore this further, Dr. Brad Johnson, University of Pennsylvania, was invited to present his research on Wnt/β-catenin signaling and telomere capping. He discussed a possible role of this pathway in TBDs [37, 38]. Supporting the importance of a link between abnormal Wnt/β-catenin signaling and vasculopathy driven by telomere dysfunction is the fact that the retinal vascular abnormalities of two diseases caused by mutations in Wnt pathway signaling components, familial exudative vitreoretinopathy, and Coat's disease (from which Coat's plus derives its name) are reminiscent of the retinal abnormalities observed in TBDs [39–42]. Additional preclinical studies are required, but it is intriguing to speculate on whether targeting Wnt/beta-catenin could yield novel therapeutics for TBDs.

The workshop also emphasized the importance of multi-disciplinary collaborations and featured an exploratory study of airway epithelial stem/progenitor cells in one patient with DC. Drs. Susan Reynolds and Don Hayes, Nationwide Children's Hospital and The Ohio State University, presented preliminary data showing reduced proliferative capacity of these cells in the patient compared with controls. These data raise the possibility that telomere shortening decreases airway basal epithelial stem/progenitor cell life-span and contributes to lung pathology in TBD patients. In the clinical evaluation of this particular patient, a significantly elevated vascular endothelial growth factor A (VEGFA) level was found in peripheral blood. Based on published literature, the potential link between basal epithelial stem/progenitor cells and vascular biology of the lung is a high expression of VEGFA by these progenitor cells along with VEGFA-mediated crosstalk between these progenitor cells and the endothelium. This cellular interaction appears to modulate endothelial activation and in turn stimulates and sustains basal epithelial stem/progenitor cell growth [43].

Clinicians, researchers, patient groups, and other stakeholders are in a key information gathering phase to understand TBD-associated complications. Collaborative efforts have grown significantly since the first DC-focused workshop in 2008 [4]. The CCCTAA facilitated peer-review of the first edition of "Clinical Care and Diagnosis of Dyskeratosis Congenita and TBDs" guidelines book (https://teamtelomere.org/resources/#research) in close collaboration with DCO, stimulated collaborative relationships towards a multi-center HCT trial (ClinicalTrials.gov Identifier: NCT01659606), and enabled a case series on PAVM in DC [22]. The consortium is now conducting a systematic retrospective case series of GI bleeding in patients with TBDs to understand the approaches to diagnosis and management of this complex phenotype.

Conclusions

The clinical complications caused by aberrant telomere biology are complex and our understanding of these is still developing. The phenotypic spectrum is evolving as TBDs continue to be connected through genetics, and as clinicians and patient advocacy groups join forces to rigorously document disease manifestations and natural history. Clinicians and basic scientists are leveraging this information to reappraise potential pathophysiological mechanisms linking telomere biology to disease. It is worthwhile to consider that defects in vascular biology caused by telomere dysfunction provide a unifying mechanism driving disparate phenotypic manifestations across the TBD spectrum.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

References

1. Bertuch AA (2016) The molecular genetics of the telomere biology disorders. RNA Biol 13(8):696–706. https://doi.org/10.1080/15476286.2015.1094596
2. Savage SA (2014) Human telomeres and telomere biology disorders. Prog Mol Biol Transl Sci 125:41–66. https://doi.org/10.1016/B978-0-12-397898-1.00002-5
3. Stanley SE, Armanios M (2015) The short and long telomere syndromes: paired paradigms for molecular medicine. Curr Opin Genet Dev 33:1–9. https://doi.org/10.1016/j.gde.2015.06.004
4. Savage SA, Dokal I, Armanios M, Aubert G, Cowen EW, Domingo DL, Giri N, Greene MH, Orchard PJ, Tolar J, Tsilou E, Van Waes C, Wong JM, Young NS, Alter BP (2009) Dyskeratosis congenita: the first NIH clinical research workshop. Pediatr Blood Cancer 53(3):520–523. https://doi.org/10.1002/pbc.22061
5. Dokal I, Vulliamy T, Mason P, Bessler M (2015) Clinical utility gene card for: dyskeratosis congenita—update 2015. Eur J Hum Genet 23 (4). https://doi.org/10.1038/ejhg.2014.170
6. Savage SA (1993) Dyskeratosis congenita. In: Adam MP, Ardinger HH, Pagon RA et al (eds) GeneReviews((R)). University of Washington, Seattle (WA)
7. Mitchell JR, Wood E, Collins K (1999) A telomerase component is defective in the human disease dyskeratosis congenita. Nature 402(6761):551–555. https://doi.org/10.1038/990141
8. Heiss NS, Knight SW, Vulliamy TJ, Klauck SM, Wiemann S, Mason PJ, Poustka A, Dokal I (1998) X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. Nat Genet 19(1):32–38. https://doi.org/10.1038/ng0598-32
9. Stanley SE, Gable DL, Wagner CL, Carlile TM, Hanumanthu VS, Podlevsky JD, Khalil SE, DeZern AE, Rojas-Duran MF, Applegate CD, Alder JK, Parry EM, Gilbert WV, Armanios M (2016) Loss-of-function mutations in the RNA biogenesis factor NAF1 predispose to pulmonary fibrosis-emphysema. Sci Transl Med 8(351):351ra107. https://doi.org/10.1126/scitranslmed.aaf7837
10. Simon AJ, Lev A, Zhang Y, Weiss B, Rylova A, Eyal E, Kol N, Barel O, Cesarkas K, Soudack M, Greenberg-Kushnir N, Rhodes M, Wiest DL, Schiby G, Barshack I, Katz S, Pras E, Poran H, Reznik-Wolf H, Ribakovsky E, Simon C, Hazou W, Sidi Y, Lahad A, Katzir H, Sagie S, Aqeilan HA, Glousker G, Amariglio N, Tzfati Y, Selig S, Rechavi G, Somech R (2016) Mutations in STN1 cause Coats plus syndrome and are associated with genomic and telomere defects. J Exp Med 213(8):1429–1440. https://doi.org/10.1084/jem.20151618
11. Takai H, Jenkinson E, Kabir S, Babul-Hirji R, Najm-Tehrani N, Chitayat DA, Crow YJ, de Lange T (2016) A POT1 mutation implicates defective telomere end fill-in and telomere truncations in Coats plus. Genes Dev 30(7):812–826. https://doi.org/10.1101/gad.276873.115
12. Stuart BD, Choi J, Zaidi S, Xing C, Holohan B, Chen R, Choi M, Dharwadkar P, Torres F, Girod CE, Weissler J, Fitzgerald J, Kershaw C, Klesney-Tait J, Mageto Y, Shay JW, Ji W, Bilguvar K, Mane S, Lifton RP, Garcia CK (2015) Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. Nat Genet 47(5):512–517. https://doi.org/10.1038/ng.3278
13. Vulliamy TJ, Walne A, Baskaradas A, Mason PJ, Marrone A, Dokal I (2005) Mutations in the reverse transcriptase component of telomerase (TERT) in patients with bone marrow failure. Blood Cells Mol Dis 34(3):257–263. https://doi.org/10.1016/j.bcmd.2004.12.008.
14. Ly H, Calado RT, Allard P, Baerlocher GM, Lansdorp PM, Young NS, Parslow TG (2005) Functional characterization of telomerase RNA variants found in patients with hematologic disorders. Blood 105(6):2332–2339. https://doi.org/10.1182/blood-2004-09-3659
15. Calado RT, Regal JA, Kleiner DE, Schrump DS, Peterson NR, Pons V, Chanock SJ, Lansdorp PM, Young NS (2009) A spectrum of severe familial liver disorders associate with telomerase mutations. PLoS ONE 4(11):e7926. https://doi.org/10.1371/journal.pone.0007926
16. Alder JK, Hanumanthu VS, Strong MA, DeZern AE, Stanley SE, Takemoto CM, Danilova L, Applegate CD, Bolton SG, Mohr DW, Brodsky RA, Casella JF, Greider CW, Jackson JB, Armanios M (2018) Diagnostic utility of telomere length testing in a hospital-based setting. Proc Natl Acad Sci USA 115(10):E2358–E2365
17. Glousker G, Touzot F, Revy P, Tzfati Y, Savage SA (2015) Unraveling the pathogenesis of Hoyeraal-Hreidarsson syndrome, a complex telomere biology disorder. Br J Haematol 170(4):457–471. https://doi.org/10.1111/bjh.13442
18. Anderson BH, Kasher PR, Mayer J, Szynkiewicz M, Jenkinson EM, Bhaskar SS, Urquhart JE, Daly SB, Dickerson JE, O'Sullivan J, Leibundgut EO, Muter J, Abdel-Salem GM, Babul-Hirji R, Baxter P, Berger A, Bonafe L, Brunstom-Hernandez JE, Buckard JA, Chitayat D, Chong WK, Cordelli DM, Ferreira P, Fluss J, Forrest EH, Franzoni E, Garone C, Hammans SR, Houge G, Hughes I, Jacquemont S, Jeannet PY, Jefferson RJ, Kumar R, Kutschke G, Lundberg S, Lourenco CM, Mehta R, Naidu S, Nischal KK, Nunes L, Ounap K, Philippart M, Prabhakar P, Risen SR, Schiffmann R, Soh C, Stephenson JB, Stewart H, Stone J, Tolmie JL, van der Knaap MS, Vieira JP, Vilain CN, Wakeling EL, Wermenbol V, Whitney A, Lovell SC, Meyer S, Livingston JH, Baerlocher GM, Black GC, Rice GI, Crow YJ (2012) Mutations in CTC1, encoding conserved telomere maintenance component 1, cause Coats plus. Nat Genet 44(3):338–342. https://doi.org/10.1038/ng.1084
19. Polvi A, Linnankivi T, Kivela T, Herva R, Keating JP, Makitie O, Pareyson D, Vainionpaa L, Lahtinen J, Hovatta I, Pihko H, Lehesjoki AE (2012) Mutations in CTC1, encoding the CTS telomere maintenance complex component 1, cause cerebroretinal microangiopathy with calcifications and cysts. Am J Hum Genet 90(3):540–549. https://doi.org/10.1016/j.ajhg.2012.02.002
20. Keller RB, Gagne KE, Usmani GN, Asdourian GK, Williams DA, Hofmann I, Agarwal S (2012) CTC1 Mutations in a patient with dyskeratosis congenita. Pediatr Blood Cancer 59(2):311–314
21. Walne AJ, Bhagat T, Kirwan M, Gitiaux C, Desguerre I, Leonard N, Nogales E, Vulliamy T, Dokal S (2013) Mutations in the telomere capping complex in bone marrow failure and related syndromes. Haematologica 98(3):334–338
22. Khincha PP, Bertuch AA, Agarwal S, Townsley DM, Young NS, Keel S, Shimamura A, Boulad F, Simoneau T, Justino H, Kuo C, Artandi S, McCaslin C, Cox DW, Chaffee S, Collins BF, Giri N, Alter BP, Raghu G, Savage SA (2017) Pulmonary arteriovenous malformations: an uncharacterised phenotype of dyskeratosis congenita and related telomere biology disorders. Eur Respir J. https://doi.org/10.1183/13993003.01640-2016
23. Gorgy AI, Jonassaint NL, Stanley SE, Koteish A, DeZern AE, Walter JE, Sopha SC, Hamilton JP, Hoover-Fong J, Chen AR, Anders RA, Kamel IR, Armanios M (2015) Hepatopulmonary syndrome is a frequent cause of dyspnea in the short telomere disorders. Chest 148(4):1019–1026. https://doi.org/10.1378/chest.15-0825
24. Anderson BH, Kasher PR, Mayer J, Szynkiewicz M, Jenkinson EM, Bhaskar SS, Urguhart JE, Daly SB, Dickerson JE, O'Sullivan J, Leibundgut EO, Muter J, Abdel-Salem GM, Babul-Hirji R, Baxter P, Berger A, Bonafé L, Brunstom-Hernandez JE, Buckard JA, Chitayat D, Chong WK, Cordelli DM, Ferreira P, Fluss J, Forrest EH, Franzoni E, Garcone C, Hammans SR, Houge G, Hughes I, Jacquemont S, Jeannet PY, Jerfferson RJ, Kumar R, Kutschke

G, Lundberg S, Lourenço CM, Mehta R, Naidu S, Nischal KK, Nunes L, Ounap K, Philippart M, Prabhakar P, Risen SR, Schiffman R, Soh C, Stephenson JB, Stewart H, Stone J, Tolmie JL, van der Knaap MS, Vieira JP, Vilain CN, Wakeling EL, Wermenbol V, Whitney A, Lovell SC, Meyer S, Livingston JH, Baerlocher GM, Black GC, Rice GI, Crow YJ (2012) Mutations in CTC1, encoding conserved telomere maintenance component 1, cause Coats plus. Nat Genet 44(3):338–342

25. Imai J, Suzuki T, Yoshikawa M, Dekiden M, Nakae H, Nakahara F, Tsuda S, Mizukami H, Koike J, Igarashi M, Yabe H, Mine T (2016) Fatal hemorrhagic gastrointestinal angioectasia after bone marrow transplantation for dyskeratosis congenita. Intern Med 55(23):3441–3444
26. Crow YJ, McMenamin J, Haenggeli CA, Hadley DM, Tirupathi S, Treacy EP, Zuberi SM, Browne BH, Tolmie JL, Stephenson JB (2004) Coats' plus: a progressive familial syndrome of bilateral Coats' disease, characteristic cerebral calcification, leukoencephalopathy, slow pre- and post-natal linear growth and defects of bone marrow and integument. Neuropediatrics 35(1):10–19. https://doi.org/10.1055/s-2003-43552
27. Bisserbe A, Tertian G, Buffet C, Turhan A, Lambotte O, Nasser G, Alvin P, Tardieu M, Riant F, Bergametti F, Tournier-Lasserve E, Denier C (2015) Cerebro-retinal microangiopathy with calcifications and cysts due to recessive mutations in the CTC1 gene. Rev Neurol (Paris) 171(5):445–449. https://doi.org/10.1016/j.neurol.2015.01.566
28. Briggs TA, Hubbard M, Hawkins C, Cole T, Livingston JH, Crow YJ, Pigott A (2011) Treatment of gastrointestinal bleeding in a probable case of cerebroretinal microangiopathy with calcifications and cysts. Mol Syndromol 1(4):159–162. https://doi.org/10.1159/000321559
29. Jonassaint NL, Guo N, Califano JA, Montgomery EA, Armanios M (2013) The gastrointestinal manifestations of telomere-mediated disease. Aging Cell 12(2):319–323. https://doi.org/10.1111/acel.12041
30. Tsilou ET, Giri N, Weinstein S, Mueller C, Savage SA, Alter BP (2010) Ocular and orbital manifestations of the inherited bone marrow failure syndromes: fanconi anemia and dyskeratosis congenita. Ophthalmology 117(3):615–622. https://doi.org/10.1016/j.ophtha.2009.08.023
31. Indaram M, Agarwal S, Yonekawa Y (2017) Exudative vitreoretinopathy in dyskeratosis congenita. Ophthalmology 124(8):1246
32. Thanos A, Todorich B, Hypes S, Yonekawa Y, Thomas B, Randhawa S, Drenser K, Trese M (2017) Retinal vascular tortuosity and exudative retinopathy in a family with dyskeratosis congenita masquerading as familial exudative vitreoretinopathy. Retin Cases Brief Rep 11:S187–S190
33. Netravathi M, Kumari R, Kapoor S, Dakle P, Dwivedi MK, Roy SD, Pandey P, Saini J, Ramakrishna A, Navalli D, Satishchandra P, Pal PK, Kumar A, Faruq M (2015) Whole exome sequencing in an Indian family links Coats plus syndrome and dextrocardia with a homozygous novel CTC1 and a rare HES7 variation. BMC Med Genet 16:5. https://doi.org/10.1186/s12881-015-0151-8
34. Patel PL, Suram A, Mirani N, Bischof O, Herbig U (2016) Derepression of hTERT gene expression promotes escape from oncogene-induced cellular senescence. Proc Natl Acad Sci USA 113(34):E5024–E5033. https://doi.org/10.1073/pnas.1602379113
35. Liu Y, Bloom SI, Donato AJ (2018) The role of senescence, telomere dysfunction and shelterin in vascular aging. Microcirculation. https://doi.org/10.1111/micc.12487
36. Gay A, Towler DA (2017) Wnt signaling in cardiovascular disease: opportunities and challenges. Curr Opin Lipidol 28(5):387–396. https://doi.org/10.1097/MOL.0000000000000445
37. Yang TB, Chen Q, Deng JT, Jagannathan G, Tobias JW, Schultz DC, Wang S, Lengner CJ, Rustgi AK, Lynch JP, Johnson FB (2017) Mutual reinforcement between telomere capping and canonical Wnt signalling in the intestinal stem cell niche. Nat Commun 8:14766. https://doi.org/10.1038/ncomms14766
38. Woo DH, Chen Q, Yang TL, Glineburg MR, Hoge C, Leu NA, Johnson FB, Lengner CJ (2016) Enhancing a Wnt-Telomere feedback loop restores intestinal stem cell function in a human organotypic model of dyskeratosis congenita. Cell Stem Cell 19(3):397–405. https://doi.org/10.1016/j.stem.2016.05.024
39. Fernandez RJ 3rd, Johnson FB (2018) A regulatory loop connecting WNT signaling and telomere capping: possible therapeutic implications for dyskeratosis congenita. Ann NY Acad Sci 1418(1):56–68. https://doi.org/10.1111/nyas.13692
40. Lai MB, Zhang C, Shi J, Johnson V, Khandan L, McVey J, Klymkowsky MW, Chen Z, Junge HJ (2017) TSPAN12 is a Norrin Co-receptor that amplifies Frizzled4 ligand selectivity and signaling. Cell Rep 19(13):2809–2822. https://doi.org/10.1016/j.celrep.2017.06.004
41. Panagiotou ES, Sanjurjo Soriano C, Poulter JA, Lord EC, Dzulova D, Kondo H, Hiyoshi A, Chung BH, Chu YW, Lai CHY, Tafoya ME, Karjosukarso D, Collin RWJ, Topping J, Downey LM, Ali M, Inglehearn CF, Toomes C (2017) Defects in the cell signaling mediator beta-Catenin cause the retinal vascular condition FEVR. Am J Hum Genet 100(6):960–968. https://doi.org/10.1016/j.ajhg.2017.05.001
42. Wu JH, Liu JH, Ko YC, Wang CT, Chung YC, Chu KC, Liu TT, Chao HM, Jiang YJ, Chen SJ, Chung MY (2016) Haploinsufficiency of RCBTB1 is associated with Coats disease and familial exudative vitreoretinopathy. Hum Mol Genet 25(8):1637–1647. https://doi.org/10.1093/hmg/ddw041
43. Curradi G, Walters MS, Ding BS, Rafii S, Hackett NR, Crystal RG (2012) Airway basal cell vascular endothelial growth factor-mediated cross-talk regulates endothelial cell-dependent growth support of human airway basal cells. Cell Mol Life Sci 69(13):2217–2231. https://doi.org/10.1007/s00018-012-0922-8

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