Recent Advances in the Genetics of Telomere Biology Disorders

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The term telomere biology disorder (TBD) encompasses the spectrum of germline genetic disorders caused by rare germline pathogenic variants (GPVs) genes essential in telomere maintenance and stability usually resulting in short and/or dysfunctional telomeres and a range of phenotypes. Dyskeratosis congenita (DC), the first described TBD, is classically diagnosed by the presence of the mucocutaneous triad of oral leukoplakia, nail dysplasia, and abnormal skin pigmentation or the presence of two of three of the triad and bone marrow failure (BMF). TBDs are associated with high risk of pulmonary fibrosis, AML, MDS, head/neck squamous cell carcinoma, cryptogenic liver disease, stenosis of the urethra, esophagus or lacrimal ducts, avascular necrosis of the hips or shoulders, and many other complications.

Lymphocyte telomeres less than the 1st percentile for age measured by flow FISH is sensitive and specific for differentiating patients with TBDs from their unaffected relatives and those with other inherited BMF syndromes and is the primary diagnostic test for TBDs. However, many adults with TBDs may have telomeres in the first to 10th percentile for age. HT-STELA is relatively new diagnostic test for TBDs and hasn't yet been widely implemented but holds promise to make diagnosis quicker and easier.

To date, TBDs have been attributed to PGVs in at least 17 genes related to telomere maintenance including *ACD, CTC1, DCLRE1B, DKC1, NAF1, NHP2, NOP10, POT1, RPA1, RTEL1, PARN, STN1, TERC, TERT, TINF2, WRAP53,* and *ZCCHC8.* PGVs in additional genes have been associated with TBDs although their causal relationship remains incompletely established (*MDM4, NPM1, POLA1*, *POLA2, RPA2, SON, SHQ1,* and *TYMS-ENOSF1*).

The clinical manifestations of TBDs can be very complex based on the affected gene and mode of inheritance of disease. TBD features can develop at any age and do not always develop in a consistent sequence. Classic DC, Hoyeraal-Hreidarsson syndrome (HH), and Coats plus typically present early in childhood and are caused by autosomal or X-linked recessive inheritance, or heterozygous *TINF2* PGVs. In contrast, middle aged or older adults may present with just one feature of a TBD (e.g., isolated pulmonary fibrosis). The most common adult-onset TBDs are caused by heterozygous pathogenic variants in *TERT, TERC, RTEL1*, or *PARN*. Although they may present with only one TBD feature, such patients remain at risk of other complications, especially BMF if lung transplant is required for pulmonary fibrosis.

This presentation will focus on TBD genetic etiology, new gene discoveries, recently quantified genotype-phenotype associations, and clinical management options.

References of interest: PMIDs: 36151328, 40097157, 39462986, 39661387, 34852175, 39198715, 35609925.