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POSTER ABSTRACTS

509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Distribution of Chromosome-Arm Specific Telomere Length in Patients with Telomere Biology Disorders

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Introduction: Telomere biology disorders (TBD) are multisystem diseases often associated with bone marrow failure (BMF) and pulmonary fibrosis. TBD are clinically diagnosed when mean telomere lengths (TL) in blood cells measured by clinical flowFISH assays fall <1 st percentile, in comparison to age-matched reference controls. This information has limitations, e.g. TL in blood cells may not represent TL in other organs (e.g. lung, liver) and moreover, individuals with high clinical suspicion of TBD can show borderline average TL which complicates their diagnosis. The likely reason for this is that cell senescence can be triggered by shortening of a subset, or even a single chromosome arm telomere, a situation that may be missed when measuring average TL. Previous approaches to measure individual chromosome-arm telomere length (CA-TL) are only available for a small number of chromosome arms or can only estimate the number of shortened telomeres without matching them to specific chromosome arms. Taking advantage of recent developments in long-read next generation sequencing (NGS) and the availability of the recently published telomere-to-telomere (T2T) reference human genome, our group developed Telogator, (Stephens Z. *et al*, 2022) a bioinformatic tool that estimates CA-TL for most chromosome arms using long-read NGS data. Here we use Telogator to describe for the first time the CA-TL pattern in TBD patients in comparison with a control non-TBD cohort.

Methods: TBD patients were identified through the Pre-Myeloid and Bone Marrow Failure Specialty Clinic at Mayo Clinic. All patients underwent flowFISH and genetic testing. Age-matched non-TBD patients identified at the Center for Individualized Medicine (Mayo Clinic) were used as reference controls. Informed consent was obtained from all individuals with approval from the Mayo Clinic Institutional Review Board. DNA from peripheral blood mononuclear cells was sequenced using PacBio Sequel II following the manufacturer indications for HiFi sequencing. BAM files were aligned to the T2T reference and CA-TL was calculated using Telogator as described in Stephens Z. et al. 2022. Average TL, CA-TL, and percent of short telomeres (both defined as <5 kb and <3.2 kb) were calculated. Comparisons of average TL and percent of short telomeres were performed using t-test, while Wilcoxon rank-sum test was used to compare CA-TL.

Results: Four TBD patients [median age = 58.5 (52-60), 50% female] and 6 non-TBD controls [Median age = 56 (50-63), 33% female] were included in the analysis. All TBD patients presented average TL below the 1 st centile in both lymphocytes and granulocytes, and TBD-related phenotype (100% with pulmonary fibrosis, 50% with BMF, 25% with liver fibrosis). Three had a pathogenic variant in a TBD related genes [2 in *TERT* (NM_198253.3: c.2030G>A, p.(Gly677Asp) and c.2515_2533del, p.(Thr839Alafs*29)) and 1 in *NHP2* (NM_017838.3: c.459_460delAT; p.(X154Argext29))].

The average TL calculated by Telogator showed high correlation with flowFISH values ($r^2 = 0.9883$, $p = 0.0059$) and was lower in TBD patients than controls ($p = 0.0012$). Next, when comparing individual CA-TL between groups, only half of CA-TL was statistically different in the TBD group compared to controls (1p, 3q, 4p, 5p, 5q, 6q, 7p, 7q, 8q, 9p, 9q, 10q, 11p, 12q, 12q, 16p, 16q, 18q, 19p, 19q, 20p, 20q, 21q - Figure 1). The percentage of telomeres <5kb and <3 kb was significantly increased in TBD patients compared to controls (p= 0.014 and 0.0333, respectively).

Discussion: Using a novel informatic tool, we replicate previous results obtained using classic approaches and were able to expand on these studies by measuring specific CA-TL in TBD patients. We identified statistically significant differences at the CA-TL level in these patients when compared to age-matched controls, while other CA-TL were not statistically different. Future studies and the inclusion of additional TBD patients will help define the clinical relevance of the differential CA-TL shortening and its prevalence among TBD patients. While limited by the small number of samples in the study, we show the feasibility of using this approach to study TL with unprecedented resolution and show that Telogator offers important advantages compared to classic methods to study telomere biology that can be used in other relevant fields like aging and/or cancer. Our results pave the way to advance the mechanistic understanding of TBD.

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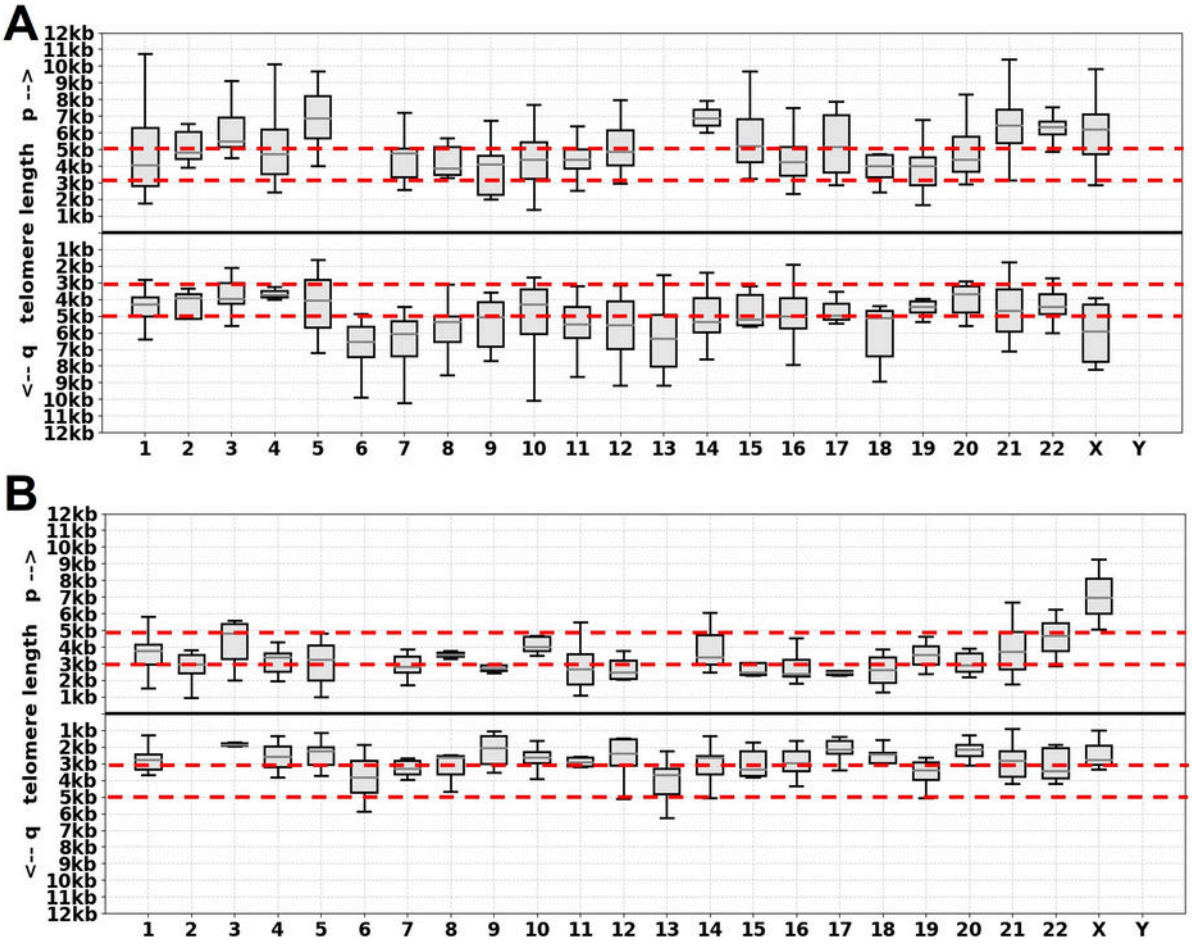

Figure 1: Aggregated measurement of chromosome arm telomere length (CA-TL) in (A) 4 patients with telomere biology disorders and (B) 6 non-TBD, age-matched control samples. Red dotted lines indicate the 3 and 5 kb threshold used to define short telomeres. TBD patients present a distinct pattern with only around 50% of CA-TL being statistically shorter than in non-TBD controls.

Figure 1

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