haematologica
Journal of the Ferrata Storti Foundation

Telomere attrition is common in patients with germline *RUNX1* pathogenic variants

by Rialnat A. Lawal, Fernanda Gutierrez-Rodrigues, David J. Young, Erica Bresciani, Emma M. Groarke, Natalie T. Deuitch, Molly McGuinness, Kathleen Craft, Shawn Chong, Michael Sierk, Daoud Meerzaman, Bhavisha A. Patel, Neal S. Young, Nan-ping Weng and Paul P. Liu

Received: June 25, 2025.
Accepted: December 15, 2025.

Citation: Rialnat A. Lawal, Fernanda Gutierrez-Rodrigues, David J. Young, Erica Bresciani, Emma M. Groarke, Natalie T. Deuitch, Molly McGuinness, Kathleen Craft, Shawn Chong, Michael Sierk, Daoud Meerzaman, Bhavisha A. Patel, Neal S. Young, Nan-ping Weng and Paul P. Liu. Telomere attrition is common in patients with germline RUNX1 pathogenic variants.
Haematologica. 2026 Jan 8. doi: 10.3324/haematol.2025.288522 [Epub ahead of print]

Telomere attrition is common in patients with germline *RUNX1* pathogenic variants

Running Heads: Telomere shortening in FPDMM

Rialnat A Lawal[1,2], Fernanda Gutierrez-Rodrigues[3], David J Young[4], Erica Bresciani[1], Emma M Groarke[3], Natalie T Deuitch[1], Molly McGuinness[5], Kathleen Craft[1], Shawn Chong[1], Michael Sierk[6], Daoud Meerzaman[6], Bhavisha A Patel[3], Neal S Young[3], Nan-ping Weng[7], Paul P Liu[1*]

[1]Oncogenesis and Development Section, Translational and Functional Genomics Branch, Division of Intramural Research, National Human Genome Research Institute, NIH. [2]Sickle Cell Branch, [3]Hematology Branch, and [4]Translational Stem Cell Biology Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, NIH. [5]Division of Hematology-Oncology, Department of Pediatrics, Lucile Packard Children's Hospital. [6]Center for Biomedical Informatics & Information Technology, National Cancer Institute, NIH. [7]Lymphocyte Differentiation Section, Laboratory of Molecular Biology and Immunology, Division of Intramural Research, National Institute on Aging, NIH.

*Corresponding author: pliu@mail.nih.gov

Data Sharing Statement: We follow the NIH policy to share scientific data to the maximum extent possible, considering ethical, legal, and technical factors. All data are included in the manuscript including associated supplemental files. Any specific request maybe directed to Paul Liu at pliu@mail.nih.gov.

Funding: This research was supported by the Intramural Research Programs of the National Human Genome Research Institute, the National Heart, Lung, and Blood Institute, and the National Institute for Aging, NIH.

Acknowledgements: The contributions of the NIH author(s) are considered Works of the United States Government. The findings and conclusions presented in this paper are those of the author(s) and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services. We thank all members of the Paul Liu lab for support, technical assistance, and discussions, Beverly Doran for helpful discussions, and Dan Kastner for critical reading of the manuscript. We are extremely grateful to all the patients for their enthusiastic participation in the RUNX1-FPDMM natural history study.

Authors' Disclosures: The authors declare no competing interests.

Author Contributions: RAL drafted the manuscript, analyzed the data, and collected the data. FG, EMG, BAP, and NSY provided guidance and data on SAA and TBD patients. MM contributed data on patients. NTD, KC, and SC collected the data and cared for patients. EB, MS, and DW contributed and analyzed data on patients. NW, DJY and PL supervised the work and drafted the manuscript. All authors critically reviewed the manuscript for submission.

Familial platelet disorder with associated myeloid malignancy (FPDMM) is a hematologic malignancy (HM) predisposition syndrome caused by germline *RUNX1* pathogenic variants (1), characterized by a high lifetime incidence of HM. Telomeres are important for maintaining genomic stability and shortened telomeres have been identified in several inherited blood diseases (2). FPDMM patients exhibit thrombocytopenia, marrow dysplasia, and increased malignancy risk, but telomere dynamics in FPDMM have not been studied. In this study, we used flow fluorescence *in situ* hybridization (FISH) to determine leukocyte telomere length (TL) in FPDMM patients. Leukocyte TL was significantly below the age-adjusted 50th percentile in all patients for both lymphocytes, $p=1.8\text{x}10^{-30}$; and granulocytes, $p=6.5\text{x}10^{-42}$; across all age groups. More patients had very short telomeres (<1st percentile) in granulocytes than in lymphocytes (57.5% vs 30%). Moreover, the severity of TL shortening in FPDMM is similar to that in telomere biology disorder (TBD) and other inherited blood diseases linked to leukemia. Our data indicate that premature TL shortening is a common genomic alteration in germline *RUNX1* variants and FPDMM, pointing to a new and potentially critical disease attribute.

The natural history study on patients with FPDMM was approved by the NIH IRB (protocol number 19HG0059) and was registered at ClinicalTrials.gov with identifier NCT03854318. We prospectively assessed 40 participants from the largest, single-center natural history study of FPDMM (NCT03854318) (1) between May 2024 and March 2025. All 40 participants carry germline *RUNX*1 pathogenic (P) or likely pathogenic (LP) variants, encompassing 23 families with 19 unique *RUNX1* variants (Supplemental Table 1). Informed consent in accordance with the declaration of Helsinki was obtained for all participants. We did not include participants with hematologic malignancy, *RUNX1* benign/likely benign variants, or variants of uncertain significance. The median age of the cohort was 30 years (range 2-66). Lymphocyte TL in 87.5% (35/40) of the patients was shortened: 57.5% measured short (<10th age-adjusted percentile), and 30% very short (<1st age-adjusted percentile) (Fig. 1A, Supplemental Table 2A). In granulocytes, 95% (38/40) of the patients had shortened TL, including 37.5% short and 57.5% very short (Figure 1B and Supplemental Table 2A). Overall, TL was significantly below the age-adjusted 50th percentile in all patients (Fig. 1C, lymphocytes, $p=1.8\text{x}10^{-30}$; granulocytes, $p=6.5\text{x}10^{-42}$), demonstrating a 100% negative predictive value for identifying a germline P/LP variant in *RUNX1*. Furthermore, granulocytes had significantly greater TL shortening than lymphocytes (Fig. 1D, $p=8.59\text{x}10^{-7}$). For both leukocytes, TL shortening happened in all age groups, (Figure 1A and B, Supplemental Table 2A), with no statistically significant differences in severity (Fig. 1E and F).

Thirteen of 40 (32.5%) patients in this study had somatic mutations in myeloid cancer genes with variant allele frequency >2% (Supplemental Figure 1A). However, we found no significant TL difference in the presence or absence of the somatic variants (Supplemental Figure 1B-D, $p\geq0.9$). We also did not see any significant difference in expression of telomere-related genes between FPDMM patients and health controls, nor did we identify any mutations in such genes in the FPDMM patients. Moreover, no correlations were identified between the severity of TL

shortening and the *RUNX1* variant types. Finally, age-adjusted FPDMM TL did not correlate with peripheral blood counts, bone marrow cellularity or ISTH (International Society on Thrombosis and Hemostasis) bleeding criteria. These findings suggest that the TL shortenings observed in these FPDMM patients correlate mainly with the presence of *RUNX1* P/LP variants, rather than any secondary contributing factors.

For two siblings with *RUNX1* frameshift Arg346Profs*249 variant, we analyzed chronological changes of TL data at 3 timepoints each, over 9 years. For both patients, TL continued to shorten with age and accelerated between the second and third timepoints (Fig. 2A and 2B). We also calculated the relative rates of TL attrition in these two siblings. As shown in Figure 2C and D, the telomere attrition rate accelerated with age for both patients and both cell types, relative to the normal attrition rates (Supplemental Table 2B and green curves in Fig. 2C and D), suggesting accelerated telomere attrition with increasing age for both patients.

Next, we considered the possibility of genetic anticipation for the TL shortening phenotype. Of the 23 families, 9 had 2 generations with measured TL. There were no families with TL measurements of 3 generations. TL data in those 9 families does not demonstrate a consistent trend pointing to anticipation (Fig. 2E and 2F). The data would suggest that the TL erosion is acquired due to *RUNX1* loss with telomere reset in each generation.

Very short leukocyte TL, typical of TBD, results from telomere dysfunction in HSC harboring germline mutations in telomere-related genes. However, telomere shortening can also arise from impaired hematopoiesis observed in other inherited bone marrow failure syndromes (IBMFS), such as Fanconi anemia, Diamond-Blackfan and Shwachman-Diamond Syndrome (3). Additionally, TL shortening may also be a consequence of increased HSC proliferation, as seen in severe aplastic anemia (SAA) (4). Comparing the TL profile of our FPDMM patients to those with TBD, other IBMFS, and SAA (5), we found that the percentage of abnormal TLs in FPDMM significantly exceeds that of all inherited IBMFS except dyskeratosis congenita (DC), a TBD with telomeres that are almost exclusively very short (below the 1st percentile) (Figure 3A).

We next compared age-adjusted ΔT between our FPDMM cohort and previously published patients consisting of 62 SAA and 40 TBD, where a majority had germline variants in *TERT*, *TERC*, *RTEL1*, *TINF2*, or *DKC1* (6, 7). Measured FPDMM lymphocyte ΔTL was -1.7kb (Figure 1D), which was greater than -0.5kb ΔTL in SAA patients (p<0.0001), but less than TBD at -2.9kb (p<0.0001) (Figure 3B). The same pattern of differences was observed in granulocytes (Figure 3C). The Δ (ΔTL) between leukocyte subsets $\Delta(\Delta TL_{lymphocytes} - \Delta TL_{granulocytes})$ showed a significant increase in SAA compared to both FPDMM and TBD (p<0.0001), while there was no significant difference between FPDMM and TBD (Figure 3D).

Two observations emerge from our findings: the leukocyte subtype discordance seen in FPDMM resembles the pattern typically detected in SAA (4, 6); yet, the frequency and early onset of abnormal telomere lengths is similar to that seen in IBMFS. The significant decrease in granulocytes may result from the fact that lymphocytes (T and B cells) can activate telomerase during cell division to counteract telomere shortening (8, 9), whereas granulocytes do not express telomerase to reduce the loss of TL (10). In addition, the greater TL attrition in granulocytes could be due to hematopoietic stress placed on the FPDMM HSCs (11). Since lymphocytes are long-lived cells while granulocytes require constant HSC replenishment, HSC dysfunction would manifest immediately in granulocytes but take years to decades in lymphocytes. In the case of acquired aplastic anemia, the pathophysiology is thought to be due to immune-mediated damage to hematopoietic stem and progenitor cells. Recent studies identified increased CD74 signaling driving inflammation in FPDMM patients (12), suggesting a likely contributor to TL erosion in this population. However, TL attrition in FPDMM exceeds that in SAA, suggesting immune mechanisms alone are insufficient; additional factors likely contribute. It is plausible that there is a direct role for *RUNX1* regulation of TL through the telomerase complex (4, 5, 13-15). However, we do not currently have data to demonstrate this.

The TBD cohort compared in Figure 3B-D (7) included pathogenic germline variants in *TERT*, *TERC*, *RTEL1*, *TINF2*, and *DKC1*. Although *RUNX1* has been shown to modulate the expression of *TERT*, no significant change in the expression of telomere-related genes was detected in FPDMM patients compared to healthy donors. In addition, the percentage of patients with very short or short telomeres in each leukocyte subset in FPDMM is similar to but more severe than IBMFSs we analyzed here, except DC. Yet, unlike SAA, FPDMM attrition occurs before marrow failure, often in the absence of cytopenia apart from the characteristic thrombocytopenia. Thus, our findings suggest a new disease phenotype for FPDMM with possible pathogenic implications for cancer and point to a new direction for understanding the biology of the disease. Additionally, our data show for the first time that germline pathogenic variants in a transcription factor gene are associated with telomere shortening. The exact mechanism is unclear, but given the similarity with IBMFS, RUNX1 may regulate genes involved in the telomerase complex and/or the shelterin complex (Figure 3E). To uncover connections between RUNX1 and telomere length, further studies are required to expand our understanding of FPDMM biology.

Clinically, high frequencies of FPDMM patients with short or very short telomeres have direct implications for the differential diagnosis of IBMFS. TL testing turnaround is much shorter than genetic testing, and reports of short or very short telomeres increase the suspicion of underlying TBD. Patients with thrombocytopenia, short telomeres, and increased risk of malignancy can have different etiologies, and distinguishing these patients by clinical presentation may not be enough, implying a need for genetic testing.

References

1. Cunningham L, Merguerian M, Calvo KR, et.al. Natural history study of patients with familial platelet disorder with associated myeloid malignancy. Blood. 2023;142(25):2146-2158.

2. Lansdorp PM. Telomeres, aging, and cancer: the big picture. Blood. 2022;139(6):813-821.

3. Alter BP, Giri N, Savage SA, Rosenberg PS. Telomere length in inherited bone marrow failure syndromes. Haematologica. 2015;00(1):49-54.

4. Alder JK, Hanumanthu VS, Strong MA, et al. Diagnostic utility of telomere length testing in a hospital-based setting. Proc Natl Acad Sci U S A. 2018;115(10):E2358-E2365.

5. Alter BP, Baerlocher GM, Savage SA, et al. Very short telomere length by flow fluorescence in situ hybridization identifies patients with dyskeratosis congenita. Blood. 2007;110(5):1439-1447.

6. Patel BA, Groarke EM, Lotter J, et al . Long-term outcomes in patients with severe aplastic anemia treated with immunosuppression and eltrombopag: a phase 2 study. Blood. 2022;139(1):34-43.

7. Gutierrez-Rodrigues F, Groarke EM, Thongon N, et al. Clonal landscape and clinical outcomes of telomere biology disorders: somatic rescue and cancer mutations. Blood. 2024;144(23):2402-2416.

8. Patrick M, Weng NP. Expression and regulation of telomerase in human T cell differentiation, activation, aging and diseases. Cell Immunol. 2019;345:103989.

9. Weng NP, Granger L, Hodes RJ. Telomere lengthening and telomerase activation during human B cell differentiation. Proc Natl Acad Sci U S A. 1997;94(20):10827-10832.

10. Broccoli D, Young JW, de Lange T. Telomerase activity in normal and malignant hematopoietic cells. Proc Natl Acad Sci U S A. 1995;92:9082-9086.

11. Rufer N, Brummendorf TH, Kolvraa S, et al. Telomere fluorescence measurements in granulocytes and T lymphocyte subsets point to a high turnover of hematopoietic stem cells and memory T cells in early childhood. J Exp Med. 1999;190(2):157-167.

12. Mohammadhosseini M, Enright T, Duvall A, et al. Targeting the CD74 signaling axis suppresses inflammation and rescues defective hematopoiesis in RUNX1-familial platelet disorder. Sci Transl Med. 2025;17(780):eadn9832.

13. Dutta B, Osato M. The RUNX Family, a Novel Multifaceted Guardian of the Genome. Cells. 2023;12(2):255.

14. Moses EJ, Azlan A, Khor KZ, et al. A RUNX1/ETO-SKP2-CDKN1B axis regulates expression of telomerase in t (8;21) acute myeloid leukemia. Cell Mol Life Sci. 2023;80(3):70.

15. Yamaguchi H, Calado RT, Ly H, et al. Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. N Engl J Med. 2005;352(14):1413-1424.

16. Aubert G, Baerlocher GM, Vulto I, Poon SS, Lansdorp PM. Collapse of telomere homeostasis in hematopoietic cells caused by heterozygous mutations in telomerase genes. PLoS Genet. 2012;8(5):e1002696.

Figure Legends

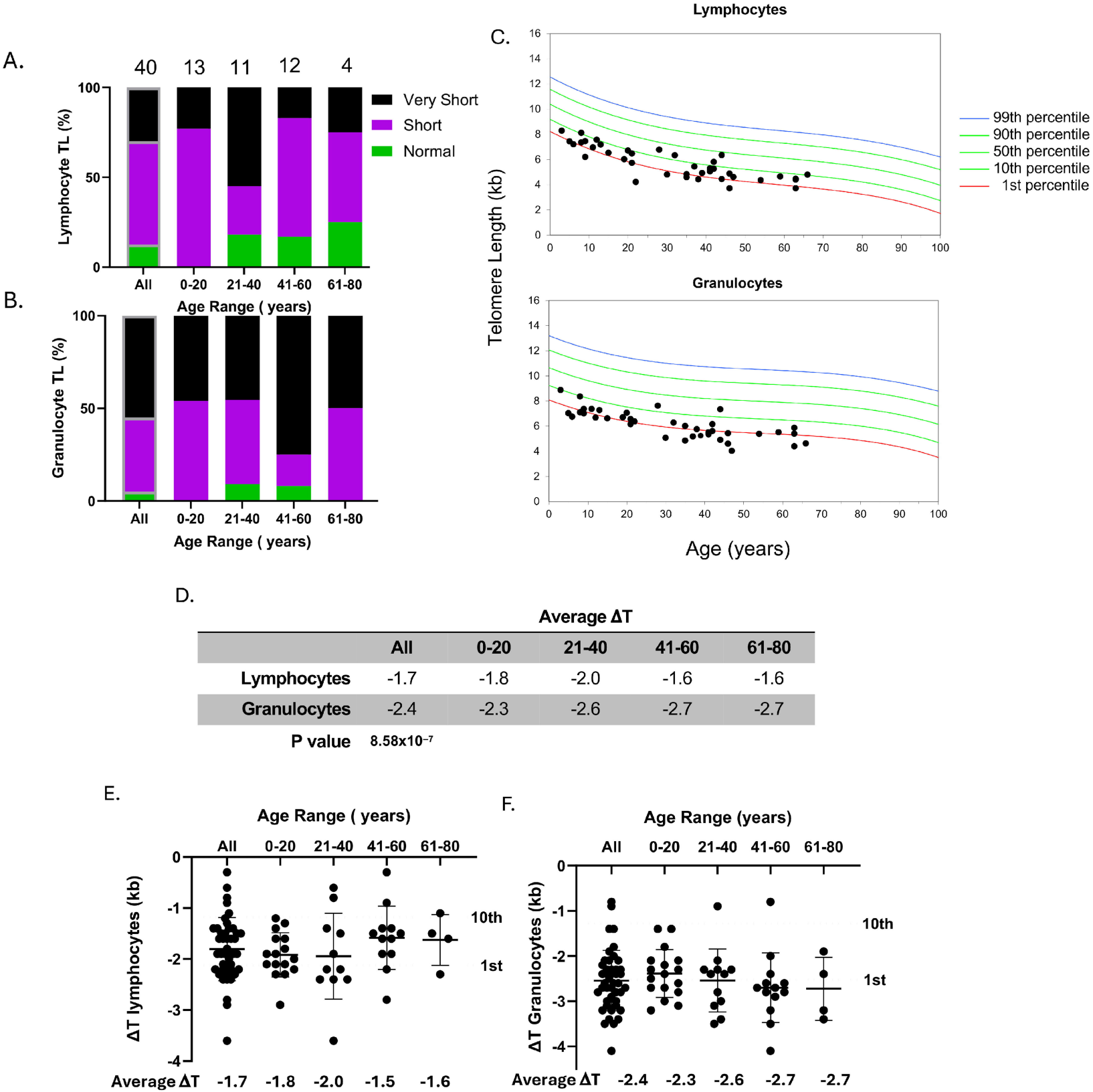
Figure 1. Distribution and changes of age adjusted leukocyte telomere lengths (TL) in patients with germline *RUNX1* FPDMM. Stacked bar graphs of normal, short and very short TL percentage in lymphocytes (A) and in granulocytes (B) from patients with FPDMM in 2-decade intervals. The numbers of patients (n) in each age group are presented on the top of panel A. (C) Nomograms of lymphocyte and granulocyte TLs from FPDMM patients with normal control percentile lines as indicated. (D) Statistical comparison between lymphocyte and granulocyte averages of ΔT for each age range. E and F: The TL mean deviation from age-adjusted median (ΔT) in lymphocytes (E) and granulocytes (F) over 20-year age groups. Average ΔT for each age range are listed under each graph. ΔT: deviation of TL from the age-adjusted median; kb: kilobase. TL measurements were conducted with lymphocytes and granulocytes from fresh blood samples using CLIA-certified fluorescence *in situ* hybridization and flow cytometry (flow - FISH) by the Repeat Diagnostics Inc. (Vancouver, British Columbia, Canada).

Figure 2. Telomere length in families. TL longitudinal assessments of two siblings with germline *RUNX1* FPDMM are plotted on nomograms for patient 1 (P1) and patient 2 (P2) of lymphocytes (A) and granulocytes (B) over 9-year interval with three time points each. Plots of the attrition rates for lymphocytes (C) and granulocytes (D) in each patient against the published control data (16). The rate of attrition [(ending TL – starting TL)/time elapsed] is plotted as a function of time, with the indicated point being the mid-point between observations. Green curved lines depict normal, cell type-specific rate of attrition with a 95% CI interval indicated by the shading. Black symbols are for the two patients (dots for P1 and triangles for P2). Green symbols are expected observations if the patients were to follow the population-based rate of attrition. E and F: TL erosion in families over 2 generations, showing distribution of age-adjusted deviation in telomere length according to an individual family and their *RUNX1* variant in lymphocytes (E) and granulocytes (F). Parent: triangles; Offspring: circles. ΔT- deviation of TL from the age-adjusted median; kb- kilobase. There are 2 families with the same Arg201* variant, hence the blue circles represent an individual family separated from another family sharing the same variant.

Figure 3. Comparing TL abnormalities in FPDMM to other telomere biology disorders. A: Percentage of patients with short (1-10%) and very short (<1%) telomeres in lymphocytes and granulocytes in FPDMM compared to inherited bone marrow failure syndromes (IBMFS). DC: dyskeratosis congenita; DBA: Diamond-Blackfan anemia; FA: Fanconi anemia; SDS: Shwachman-Diamond syndrome. Percentages for IBMFS were obtained from ref 3. Changes in age-adjusted telomere length in FPDMM, SAA and TBD in lymphocytes (B) and granulocytes (C). D: Comparisons among FPDMM, SAA and TBD for the differences between lymphocyte and granulocyte for their changes in age-adjusted telomere length, $\Delta(\Delta TL_{lymphocytes} - \Delta TL_{granulocytes})$. Only P/LP variants are included. Each dot represents one patient. FPDMM-familial platelet disorder with associated myeloid malignancy; SAA- severe aplastic anemia; TBD: telomere biology disorder; ΔT: deviation of TL from the age-adjusted median; kb:

kilobase. E: Schematic of telomere biology in FPDMM. As a defining feature, telomeres in hematopoietic cells in FPDMM patients are shorter than those in healthy controls. The exact mechanism is unclear, but RUNX1 may regulate genes involved in the telomerase complex and/or the shelterin complex.

Figure 1



D.

Average ΔT	All	0-20	21-40	41-60	61-80
Lymphocytes	-1.7	-1.8	-2.0	-1.6	-1.6
Granulocytes	-2.4	-2.3	-2.6	-2.7	-2.7
P value	8.58×10^{-7}				

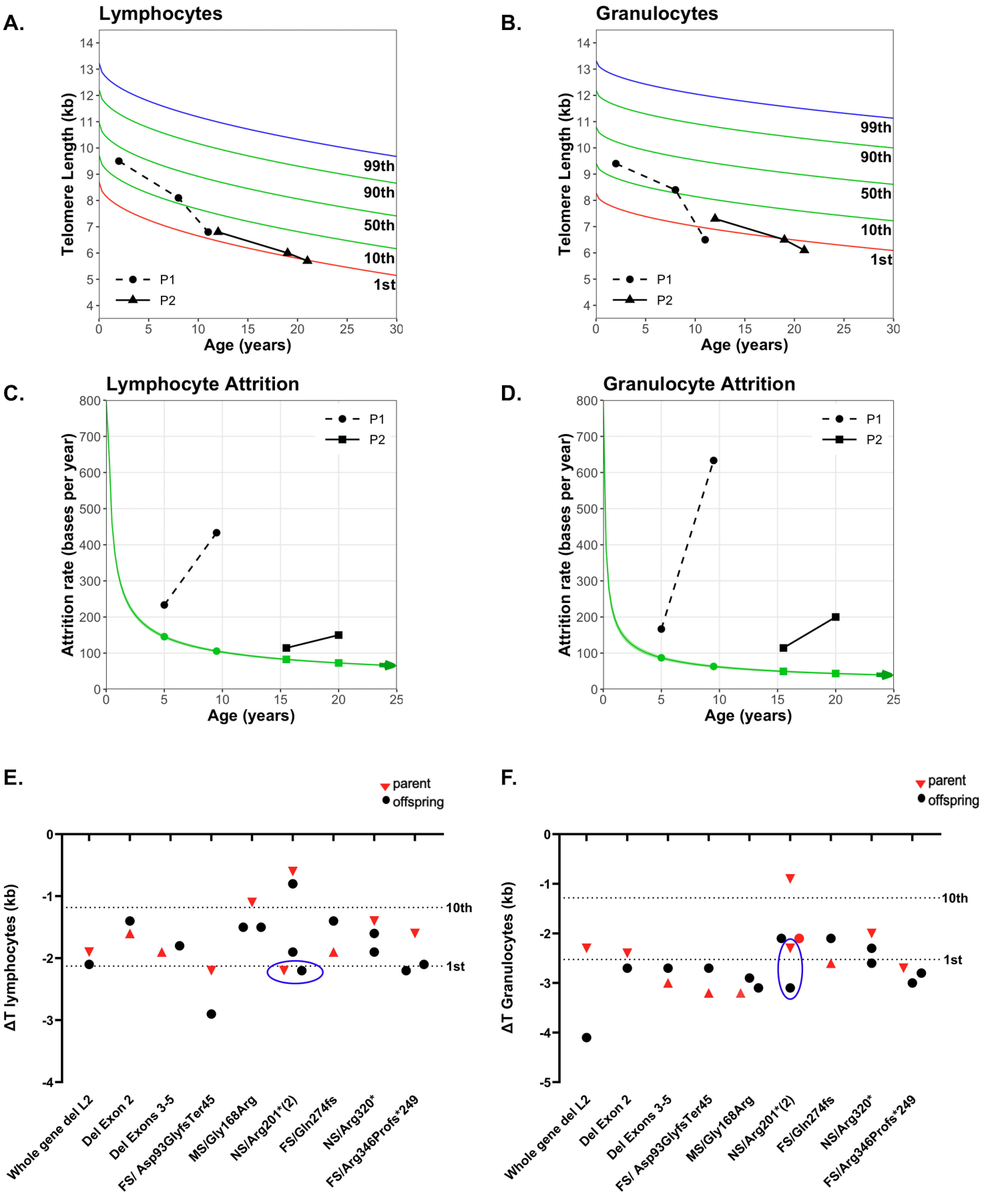
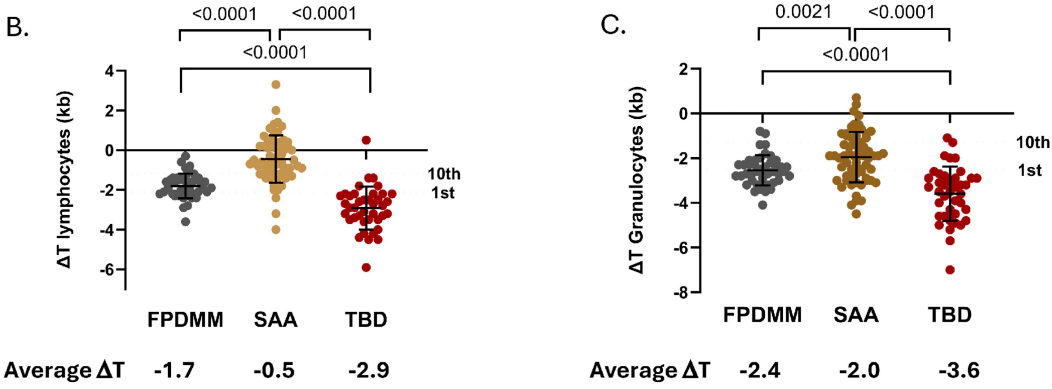
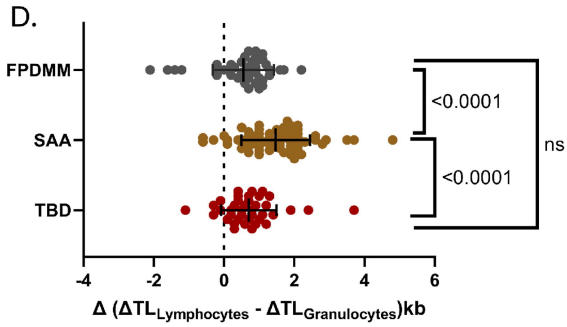

A.
Lymphocytes
Telomere Length (kb)
Age (years)
99th
90th
50th
10th
1st
P1
P2
B.
Granulocytes
Telomere Length (kb)
Age (years)
99th
90th
50th
10th
1st
P1
P2
C.
Lymphocyte Attrition
Attrition rate (bases per year)
Age (years)
P1
P2
D.
Granulocyte Attrition
Attrition rate (bases per year)
Age (years)
P1
P2
E.
parent
offspring
ΔT lymphocytes (kb)
10th
1st
Whole gene del L2
Del Exon 2
Del Exons 3-5
FS/ Asp93GlyfsTer45
MS/Gly168Arg
NS/Arg201*(2)
FS/Gln274fs
NS/Arg320*
FS/Arg346Profs*249
F.
parent
offspring
ΔT Granulocytes (kb)
10th
1st
Whole gene del L2
Del Exon 2
Del Exons 3-5
FS/ Asp93GlyfsTer45
MS/Gly168Arg
NS/Arg201*(2)
FS/Gln274fs
NS/Arg320*
FS/Arg346Profs*249

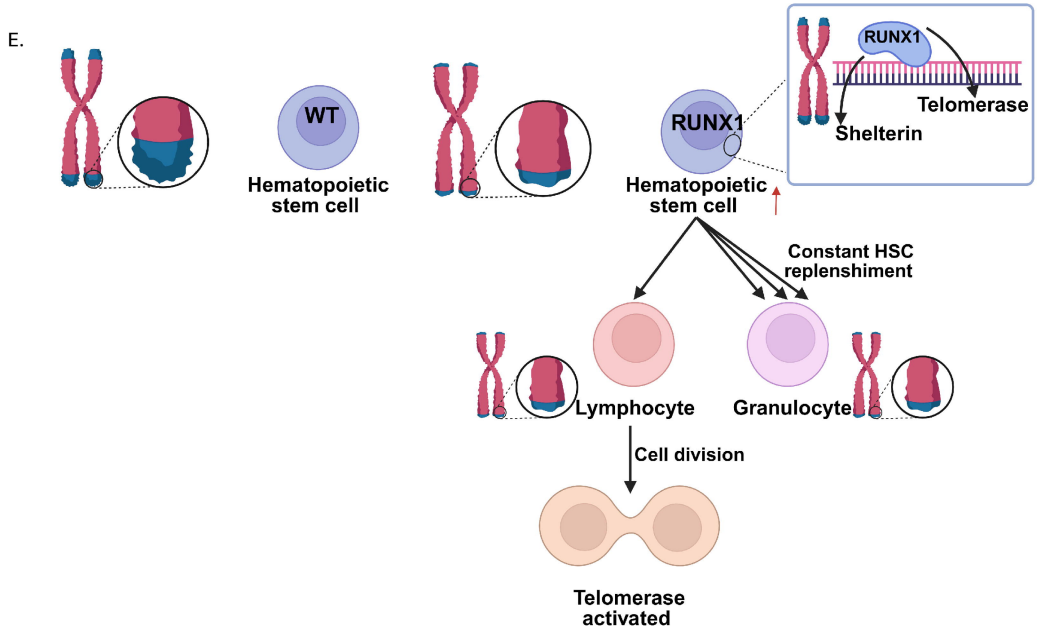
Figure 3

A.

Diagnosis	Lymphocytes		Granulocytes	
	Short (%)	Very Short (%)	Short (%)	Very Short (%)
RUNX1 FPD	57.5	30	37.5	57.5
IBMFS				
DC	8	92	4	96
FA	20	13	33	40
DBA	36	7	21	21
SDS	20	20	40	20







Supplemental Table 1. Individual patient age, sex, MTL and RUNX1 variant (P, LP)

Age/Sex	Family ID	PATHOGENICITY	RUNX1 Variant	MTL (kb) Lymphocytes	MTL (kb) Granulocytes
2*F	1.1	LP	Arg346Profs*249	9.5	9.4
3M	2.1	P	Ala134Glnfs*2	8.3	8.9
5F	3.1	P	Arg201*	7.4	7
6F	4.1	P	Arg201*	7.2	6.8
8*F	1.1	LP	Arg346Profs*249	8.1	8.4
8M	5.1	P	Deletion Exons 3-5	7.4	7.1
9M	6.1	P	Arg320*	7.5	7.4
9F	7.1	P	Asp93GlyfsTer45	6.2	7
11*F	1.1	LP	Arg346Profs*249	6.8	6.5
11F	8.1	P	Arg201*	7	7.4
12^F	1.2	LP	Arg346Profs*249	6.8	7.3
12F	9.1	P	SS/NA	7.6	6.7
13M	10.1	LP	Gln274fs	7.2	7.3
15M	6.2	P	Arg320*	6.5	6.6
19M	12.1	P	21q22.12del	6	6.7
19^F	1.2	LP	Arg346Profs*249	6	6.5
20M	13.1	P	Pro277HisfsTer35	6.7	7.1
21M	13.2	P	Pro277HisfsTer34	6.5	6.6
21^F	1.2	LP	Arg346Profs*249	5.7	6.1
22M	14.1	LP	Glu316Aspfs*12	4.2	6.4
28F	15.1	P	Arg201*	6.8	7.6
30M	16.1	P	Deletion Exons 5-6	4.8	5.1
32F	15.2	P	Arg201*	6.3	6.3
35M	16.2	P	Deletion Exons 5-6	4.6	4.8
36M	3.2	P	Arg201*	4.8	6

37F	**17.1**	**LP**	**Gly168Arg**	**5.4**	**5.2**
38F	**18.1**	**P**	**21q22.11q22.12del**	**4.4**	**5.8**
39M	**5.2**	**P**	**Deletion Exons 3-5**	**4.9**	**5.2**
41F	**19.1**	**P**	**Arg201***	**5.1**	**5.4**
41F	**20.1**	**LP**	**Deletion Exon 2**	**5.3**	**5.5**
41F	**17.2**	**LP**	**Gly168Arg**	**5.2**	**5.3**
42M	**6.3**	**P**	**Arg320***	**5.3**	**6.2**
42M	**16.3**	**P**	**Deletion Exons 5-6**	**5.8**	**5.6**
44M	**7.2**	**P**	**Asp93GlyfsTer45**	**4.4**	**4.9**
44F	**21.1**	**P**	**Leu56Profs*6**	**6.3**	**7.3**
46M	**22.1**	**P**	**508+3delA**	**3.7**	**4.6**
46F	**1.3**	**LP**	**Arg346Profs*249**	**4.9**	**5.4**
47F	**12.2**	**P**	**21q22.12del**	**4.6**	**4**
55M	**10.2**	**LP**	**Gln274fs**	**4.4**	**5.4**
59F	**23.1**	**P**	**806-1G>A**	**4.6**	**5.5**
63F	**24.1**	**LP**	**Deletion Exon 2**	**4.4**	**5.4**
63M	**25.1**	**P**	**Arg201***	**4.5**	**5.9**
64F	**26.1**	**P**	**Leu472fs**	**3.7**	**4.4**
66F	**17.3**	**LP**	**Gly168Arg**	**4.8**	**4.6**

2*F, 8*F, 11*F - serial TL measurements for patient P1 (Figure 2A-D).

12^F, 19^F, 21^F - serial TL measurements for patient P2 (Figure 2A-D).

MTL – median telomere length.

Supplemental Table 2. Telomere shortenings in FPDMM patients by age groups and in two pediatric patients.

2A. Numbers of patients and percentages of total patients in each indicated percentiles of TLs in lymphocytes and granulocytes for the indicated age groups.

		Age				
		0-20	**21-40**	**41-60**	**61-80**	**Percentile**
Lymphocytes						
	5/40 (12.5%)	0/13 (0%)	2/11 (18%)	2/12 (17%)	1/4 (25)	10^{th} -50^{th} (Normal)
	23/40(57.5%)	10/13 (77%)	3/11(27%)	8/12 (66%)	2/4 (50%)	1^{st}-10^{th} (Short)
	12/40(30%)	3/13 (23%)	6/11(55%)	2/12(17%)	1/4 (25%)	<1^{st} (Very Short)
Granulocytes						
	2/40 (5%)	0/13 (0%)	1/11 (9%)	1/12 (8%)	0/4 (0)	10^{th} -50^{th} (Normal)
	15/40 (37.5%)	6/13 (46%)	5/11(45.5%)	2/12 (17%)	2/4 (50%)	1^{st}-10^{th} (Short)
	23/40 (57.5%)	7/13 (54%)	5/11(45.5%)	9/12 (75%)	2/4 (50%)	<1^{st} (Very Short)

2B. Telomere base pair loss per year for 2 related pediatric patients in lymphocytes (upper table) and granulocytes (lower table).

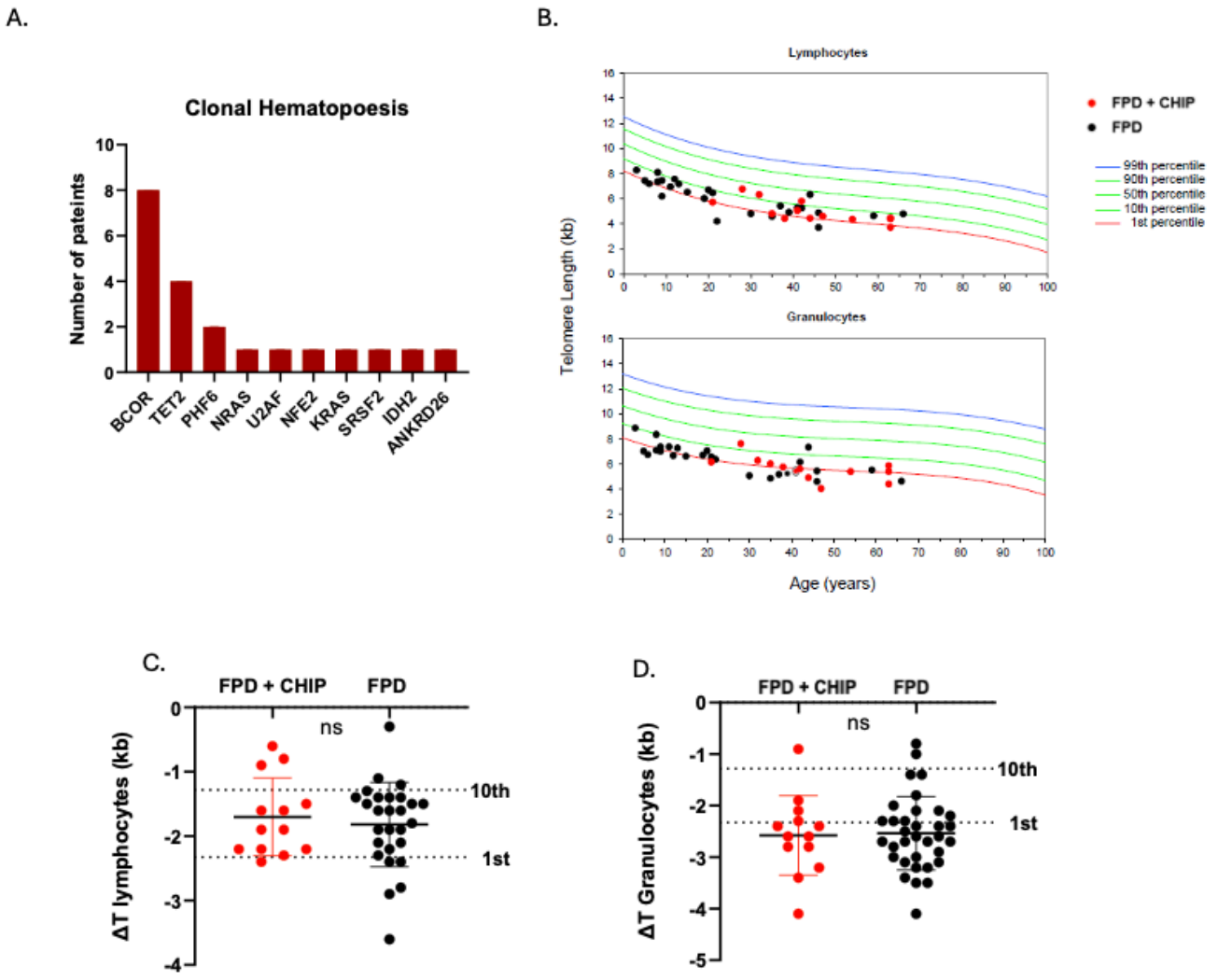
Lymphocytes

	Age (yr)	MTLN (kb)	MTLP (kb)	**MTLN Rate (bp/yr)**	**MTLP Rate (bp/yr)**
FPD P1	2	10.1	9.5		
	8	9.2	8.1	**-900/6y= -150**	**-1400/6y=- 233**
	11	8.9	6.8	**-300/3y= -100**	**-1300/3y= -433**
FPD P2	12	8.8	6.8		
	19	8.1	6.0	**-700/7y= -100**	**-800/7y= -114**
	21	7.9	5.7	**-200/2y= -100**	**-300/2y= -150**

Granulocytes					
	Age (yr)	MTLN (kb)	MTLP (kb)	**MTLN Rate (bp/yr)**	**MTLP Rate (bp/yr)**
FPD P1	2	10.4	9.4		
	8	9.8	8.4	**-600/6y= -100**	**-1000/6y= -166**
	11	9.5	6.5	**-300/3y= -100**	**-1900/3y= -633**
FPD P2	12	9.5	7.3		
	19	9.0	6.5	**-500/7y= -71**	**-800/7y= -114**
	21	8.9	6.1	**-100/2y= -50**	**-400/2y= -200**

Kb- kilobase; bp- base pairs; L- lymphocyte; G- granulocyte; MTLN[1]- normal median telomere length for age; MTLP- patient median telomere length for age; yr- year; FPD – familial platelet disorder; P1- patient1; P2- patient 2.

1. Aubert, G., Baerlocher, G.M., Vulto, I., Poon, S.S. & Lansdorp, P.M. Collapse of telomere homeostasis in hematopoietic cells caused by heterozygous mutations in telomerase genes. *PLoS Genet* **8**, e1002696 (2012).



Supplemental Figure 1. Telomere lengths according to CHIP status in patients with germline *RUNX1* FPDMM. (A) Bar graph showing the number of patients with somatic mutations (VAF >2%) in the indicated CHIP or leukemia genes. (B) Nomograms of lymphocyte and granulocyte TLs from FPDMM patients with (red circles) or without (black circles) CHIP. Distribution of age-adjusted deviation in telomere length according to CHIP status (with CHIP: red circles; without CHIP: black circles) in lymphocytes (C) and granulocytes (D). FPD- familial platelet disorder; CHIP- clonal hematopoiesis of indeterminate potential, ΔT- deviation of TL from the age-adjusted median; kb- kilobase. CHIP is defined as somatic mutations in genes related to clonal hematopoiesis or leukemia with variant allele frequency (VAF) > 2%.