DOI: 10.1002/hon.2967

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LETTER TO THE EDITOR

A study of Telomerase Reverse Transcriptase rare variants in myeloid neoplasia

Abstract

Telomere dysfunctions are associated with several hematopoietic stem cell (HSC) malignancies. Recent findings have indicated that the occurrence of rare variants of unknown significance (VUS) in the Telomerase Reverse Transcriptase (*TERT*) gene influences the outcomes of patients with myelodysplastic syndromes undergoing allogeneic HSC transplantation. However, the role of *TERT* variants has been historically controversial as initially considered pathogenic variants (H412Y, A202T) presenting functional consequences, were found very frequent in general population questioning their pathogenicity and risk allele significance. Herein, we show that overall *TERT* VUS are non-recurrent in myeloid disorders and cannot be considered risk alleles individually nor can their biological impact.

Dear Editor,

The clinical importance of telomere dysfunctions spans from the frank existence of original telomere syndromes (e.g., dyskeratosis congenita) to telomere biology disorders (TBD; e.g., aplastic anemia [AA], idiopathic pulmonary fibrosis, liver cirrhosis).[1] These conditions, characterized by a perturbation of the control mechanisms preserving telomere length (TL) and homeostasis, frequently arise from genetic alterations in telomerase genes (e.g., TERC, Telomerase Reverse Transcriptase [TERT]).[1] Indeed, short TL represents a major factor contributing to genomic instability and leukemia development.[2] The importance of telomere attrition has also been studied in the context of hematopoietic stem cells transplantation (HSCT), in which HSCs are subjected to the stress of several cell divisions to reconstitute the recipient HSC pool.[3]

Previous studies have shown that shortened leukocyte TL correlates with poor outcomes in AA[4,5] and myelodysplastic syndromes (MDS),[6] higher progression rates to acute myeloid leukemia (AML), and increased non-relapse mortality after HSCT.[7] Although the presence of certain *TERT* variants (e.g., H412Y and A202T) was associated with TL shortening in *in vitro* assays and shorter TL in patients, these variants were found at high frequency in the general population. For instance, in some studies, telomerase variant frequencies in AA were estimated at 1.5%[8] to 4%[9] but some of the putative risk alleles (e.g., H412Y), correlated with shorter TL and reduced telomerase activity *in vitro*, were later found to be more common in general population than in AA patients.[10] Indeed, large genomic datasets of disease and healthy individuals revealed many variants of unknown significance (VUS) within telomere machinery genes. However, the limitations of their risk assessment remain obvious, due to the rarity, differences in penetrance and expressivity, disease anticipation, and lack of informative pedigrees. Consequently, the landscape of genomic variants holding clinical significance in myeloid neoplasia (MN) is not entirely clear and it might deserve to undergo further refinements.

We analyzed the results of a *TERT* mutational screen of coding regions in a large series of unselected heterogeneous MNs ($n = 2560$) outside of the context of HSCT (Figure 1A and *Supplemental material*). Variant annotation of genomic sequencing results was performed according to in-house developed algorithms for variant calls (Figure S1). Overall, we identified a total of 73 *TERT* coding variants. Our filter criteria included a maximum gnomAD population allele frequency AF < 0.001 and pathogenicity scores according to The American College of Medical Genetics and Genomics (ACMG) and VarSome classifiers. After applying these filters, we identified 37/2560 (1.4%) individual patients carrying variants which were classified as rare and VUS (Figure 1A–B). These alterations occurred in the reverse transcriptase domain (RTD, 52%), TERT RNA-binding domain (TRBD)-Linker region (29%) and C-terminal extension (CTE) domain (19%). No variant was detected in the essential N-terminal (10) domain. Besides one splice site (c.2580C > T) and one frameshift (p.Q603KTer15), the remaining variants were missense. A total of 17 VUS were absent from gnomAD despite of adequate mean coverage. *TERT* rare variants were mainly found in patients diagnosed with MDS and in MN cases harboring abnormal karyotype (Table 1; Figure 1C). A fraction of patients (9/37%, 24%) carried the same variant: p.T411A/M ($n = 3$), p.R672C ($n = 2$), p.G822D ($n = 2$), p.V741M ($n = 2$).

A surprisingly high combined prevalence (41/1514; 2.7%) of rare and non-recurrent germline *TERT* variants was recently reported in a cohort of patients with MDS undergoing allogeneic HSCT,[11] but none of the carriers exhibited the typical features of classical telomeropathies. Despite the lack of known clinical impact or disease association (classified as VUS according to ACMG/Association for Molecular Pathology guidelines[12] and Sherloc criteria[13]), these alterations led to functional impairment of telomere elongation *in vitro* and TL *in vivo*.[11] Our molecular screening conducted on an

unselected MN population resulted in a much lower frequency of *TERT* VUS and very low overlap compared to previous analyses (Figure S2A).[11]

We then explored whether the presence of *TERT* rare variants would lead to the perturbation of the control mechanisms preserving TL, thereby causing telomere shortening. Estimation of TL, possible in 12 patients carrying *TERT* rare variants, did not reveal differences compared to wild-type cases (n = 1420; Figure 1D) suggesting that cause-effect of these alterations might be undermined by their low prevalence.

When accounting for mutational burden, variant allelic frequencies (VAFs) of *TERT* rare VUS were higher than those of the most frequent co-occurring mutations such as *DNMT3A* (median 47 vs. 43; p = 0.01), *SF3B1* (median 47 vs. 38; p < 0.0001), and *ASXL1* (median 47 *vs.* 30; p = 0.022; Figure 1E, oncoplot and lower panels). The heterozygous VAFs of *TERT* rare VUS is consistent with the germline nature of these lesions as opposed to the somatic origin of the aforementioned co-occurring hits. When compared with a cohort of *TERT* wild-type cases (n = 1562), patients with *TERT* rare variants were more likely to harbor mutations in *DNMT3A* (p = 0.01), *SF3B1* (p = 0.006), and *FLT3* (p = 0.003) and carried a diverse spectrum of other molecular lesions, including germline VUS of other genes (Figure S2, Tables S1–S2). For instance, four patients harbored concomitant VUS in *BRCA1*, *FANCG*, *SAMD9L* and a likely benign *SAMD9* variant. These observations highlight the difficulty in defining VUS-related features and genotype/phenotype associations in a cohort lacking the "pure" presence of *TERT* rare variants.

Myeloid neoplasia patients with young age at disease onset might also represent a group more likely to carry a strong genetic predisposition. Therefore, we sought to identify a possible germline contribution of *TERT* rare variants in terms of disease-specific characteristics. However, when looking at clinical associations our carriers of *TERT* rare variants had a similar median age at MN diagnosis compared to non-carriers (66 vs. 69.8, p = 0.3856). *Nota Bene*, the median age of our cohort was higher than the one reported in the aforementioned HSCT study,[11] which is only representative of a small fraction (10%–15%) of MDS patients according to the demographics of the disease (i.e., majority of patients are diagnosed at >70 years). No difference was also found when grouping patients according to age ranges (0–40 and > 40;

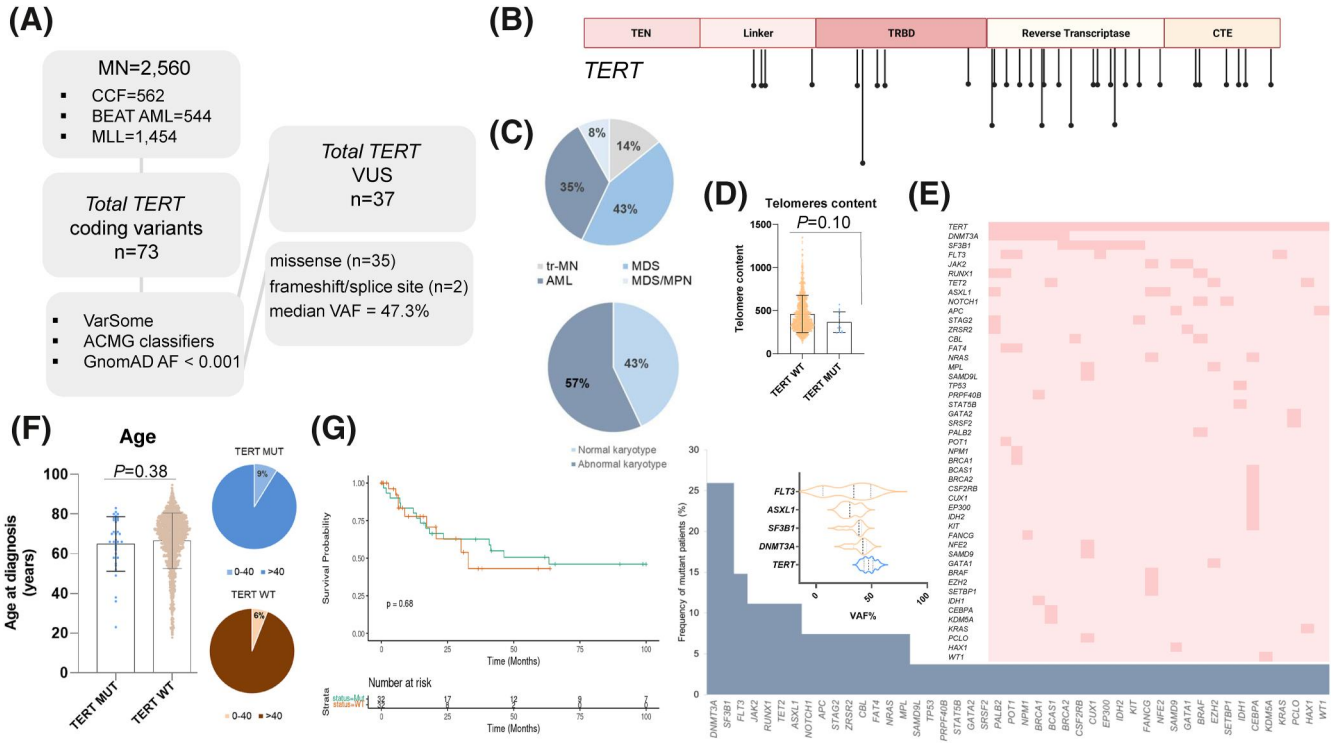

FIGURE 1 Analysis of Telomerase Reverse Transcriptase (*TERT*) rare variants in myeloid neoplasms (MN) (A) Study design representing the cohort of patients with MN, selection of a total number of *TERT* variants and classifiers to identify *TERT* rare variants with unknown significance (VUS) (B) Lollipop of *TERT* rare variants found in our cohort of MN (C) Occurrence of *TERT* rare variants in MN subtypes (D) Bar graph showing analysis of telomeres content between patients with and without *TERT* rare variant (E) Oncoplot of mutations in patients carrying *TERT* rare variants and bar graph of the frequency of each mutation in the cohort of patients with all available information (n = 27). Violin plot showing variant allele frequency (AF) of *TERT* rare variants and most common mutations (*DNMT3A*, *SF3B1*, *FLT3*, *ASXL1*) (F) Bar graph and pie charts show no difference between age at diagnosis and presence of *TERT* rare variants (G) Kaplan–Meier curves of patients with and without *TERT* rare variants showing no difference between the two groups. Propensity score matching (PSM) for age, gender, bone marrow (M)(M)blast percentage, disease type and cytogenetics was developed to remove confounding bias when comparing survival rates (see also Supplemental Material and Fig.S3) *TERT* rare variant, *TERT* MUT; *TERT* wild-type, *TERT* WT

TABLE 1 Clinical and molecular characteristics of Telomerase Reverse Transcriptase (*TERT*) mutant patients

UPN	Age	Sex	BM blast%	WHO 2016	Karyotype	TERT AA change	TERT cDNA change	Type of variant	VAF (%)	GnomAD (AF)	Variant interpretation (VarSome)
1	80	F	4	tr-MN	del (5q)	p.G822D	c.2465G > A	Missense	55.0%	0.0000121	Uncertain significance
2	55	M	1	MDS-MLD	del (7q)	p.R672C	c.2014C > T	Missense	43.3%	0.0002318	Uncertain significance
3	60	F	3	MPN (PMF)	NK	p.V741M	c.2221G > A	Missense	50.6%	3.977E-05	Uncertain significance
4	62	M	3	MDS-MLD	NK	p.E555Q	c.1663G > C	Missense	56.3%	0	Uncertain significance
5	58	F	1	tr-MN	NK	p.V972I	c.2914G > A	Missense	44.9%	1.426E-05	Uncertain significance
6	70	F	0	MPN-U	NK	p.P404R	c.1211C > G	Missense	50.6%	0	Uncertain significance
7	66	F	2	tr-MN	NK	p.R646C	c.1936C > T	Missense	51.4%	3.891E-05	Uncertain significance
8	79	F	7	tr-MN	CK	p.V741M	c.2221G > A	Missense	38.1%	3.977E-05	Uncertain significance
9	52	M	92	AML-NOS	add (7) (q11.2)	p.P627A	c.1879C > G	Missense	44.8%	0	Uncertain significance
10	38	M	70	AML-NOS	der (12; 17) (q10; q10)	p.A257S	c.769G > T	Missense	59.3%	5.316E-06	Uncertain significance
11	64	M	74	AML-NOS	NK	p.S1041C	c.3121A > T	Missense	39.6%	0	Uncertain significance
12	23	F	82	AML-NOS	t (10; 11) (q22; q23)	p.T967R	c.2900C > G	Missense	43.9%	7.124E-06	Uncertain significance
13	66	M	2	tr-MN	CK	p.G674S	c.2020G > A	Missense	54.8%	3.766E-05	Uncertain significance
14	54	M	6	MDS-MLD	CK	p.V791I	c.2371G > A	Missense	55.8%	0.0001013	Uncertain significance
15	58	M	2	MDS-RS-MLD	NK	p.T726M	c.2177C > T	Missense	46.9%	5.656E-05	Uncertain significance
16	63	F	1	MDS-RS-MLD	+8	p.V664L	c.1990G > C	Missense	45.1%	6.508E-06	Uncertain significance
17	49	F	7	MDS-EB-1	NK	p.L837P	c.2510T > C	Missense	40.0%	0	Uncertain significance
18	71	M	1	MDS-RS-SLD	NK	p.E603K	c.1807G > A	Missense	56.0%	0	Uncertain significance
19	65	F	72	APL t (15; 17) (q22; q12)	CK	p.R672C	c.2014C > T	Missense	52.0%	0.0002318	Uncertain significance
20	NA	M	NA	AML-NOS	NK	p.K1050N	c.3150G > C	Missense	54.0%	9.276E-05	Uncertain significance
21	36	M	92	APL t (15; 17) (q22; q12)	t (15; 17) (q24; q21)	p.L234F	c.702G > T	Missense	40.0%	1.047E-05	Uncertain significance
22	78	F	NA	AML-MRC	CK	p.T443K	c.1328C > A	Missense	50.0%	0	Uncertain significance
23	66	M	5	MPN (PMF)	NK	p.G424V	c.1271G > T	Missense	50.0%	0	Uncertain significance
24	70	F	41	AML-NOS	+11	p.R819C	c.2455C > T	Missense	46.0%	7.156E-06	Uncertain significance
25	71	F	78	AML-NOS	NK	p.A326S	c.976G > T	Missense	43.0%	0	Uncertain significance
26	80	M	68	AML-NOS	del (20) (q11q13)	p.V251I	c.751G > A	Missense	43.0%	3.247E-05	Uncertain significance
27	83	M	35	AML t (8; 21) (q22; q22.1)	+8,t(8; 21) (q22; q22)	p.T411M	c.1232C > T	Missense	49.4%	0	Uncertain significance
28	66	M	3	MDS-RS-MLD	−7	p.K112N	c.3384G > T	Missense	48.1%	0	Uncertain significance
29	67	M	3	MDS-MLD	NK	p.P785L	c.2354C > T	Missense	43.4%	4.049E-06	Uncertain significance

TABLE 1 (Continued)

UPN	Age	Sex	BM blast%	WHO 2016	Karyotype	TERT AA change	TERT cDNA change	Type of variant	VAF (%)	GnomAD (AF)	Variant interpretation (VarSome)
30	76	F	2	MDS-RS-MLD	NK	p.V606I	c.1816G > A	Missense	50.0%	0	Uncertain significance
31	77	M	3	MDS-RS-MLD	CK	p.T411M	c.1232C > T	Missense	48.0%	0	Uncertain significance
32	78	M	1	MDS-RS-MLD	NK	p.T411A	c.1231A > G	Missense	47.3%	0	Uncertain significance
33	81	F	4.5	MDS isodel (5q)	del (5q)	p.G822D	c.2465G > A	Missense	38.6%	0.0000121	Uncertain significance
34	70	F	7	MDS-EB-1	CK	p.Q603KTer15	c.1807del	Frameshift	50.3%	0	NA[b]
35	77	M	2	MDS-MLD	del (5q)	p.D860=	c.2580C > T	splice_region	40.9%	5.199E-05	Uncertain significance
36	NA	F	NA	sAML[a]	NA	p.R899L	c.2696G > T	Missense	41.0%	0	Uncertain significance
37	NA	M	NA	MDS[a]	NA	p.R1023C	c.3067C > T	Missense	45.0%	0	Uncertain significance

Abbreviations: −7, monosomy 7; +8, trisomy 8; +11, trisomy 11; AF, allele frequency; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; AML-NOS, acute myeloid leukemia not otherwise specified; APL, acute promyelocytic leukemia; BM, bone marrow; CK, complex karyotype; F, female; isodel(5q), isolated deletion 5q; M, male; MDS, myelodysplastic syndrome; MDS-EB-1, myelodysplastic syndrome with excess blasts-1; MDS-MLD, myelodysplastic syndrome with multilineage dysplasia; MDS/MPN-U, Myelodysplastic/myeloproliferative neoplasm; MDS-RS-MLD, myelodysplastic syndrome with ringed sideroblasts and multilineage dysplasia; MDS-RS-SLD, myelodysplastic syndrome with ringed sideroblasts and single lineage dysplasia; NA information, not applicable/available; NK, normal karyotype; PMF, primary myelofibrosis; TERT, Telomerase Reverse Transcriptase; tr-MN, therapy-related myeloid neoplasm; UPN, unique patient number; VAF, variant allele frequency; WHO, World Health Organization; unclassifiable.

[a]Missing information.

[b]Variant not found in gnomAD and in previous literature reports. On VarSome website reported the E603Kfs*15 (p.Glu603LysfsTer15) variant as likely pathogenic.

Figure 1F). Based on characteristics at diagnosis, only a minority of our patients was eligible for HSCT ($n = 7$ underwent transplant procedure). Most importantly, the presence of a *TERT* rare variant did not have any impact on overall survival by comparison of wild-type patients pair-matched for age, gender, BM blast percentage, disease type and cytogenetics as relevant baseline covariates (confounders; Figure 1G, Figure S3). These discrepancies between our study and the one of Reilly et al. may be explained with the heterogeneity of our study cohort, which reflects a real-life population of unselected patients with MN and hence does not include only younger patients with MDS, who - as mentioned-constitute a minority of the MDS population. Moreover, it is noteworthy that, especially in the group of younger MDS cases and in the subtypes characterized by low blast counts (<5%), some degrees of contamination with an actual TBD manifesting with cytopenias and minimal BM dysplastic changes may be present, thus further contributing to muddy the water of the genomic background of such patients. It is also not a case that the role of *TERT* rare variants has been unveiled by studying MDS patients undergone HSCT, a situation where rapid cell divisions under stress, such as the chemotherapy of the conditioning regimens, may have magnified the inherited germline impairment of telomerase activity, also amplified by the contingent situation generating high telomere attrition.[14] We believe also that in general the heterogeneity of the study cohorts has been one of the main reasons for the controversial results so far described in the literature as to the role of such variants and, more generally, of TL in MN. Nevertheless, when focusing on specific subgroups (younger MDS undergoing HSCT, intermediate-risk AML, acute promyelocytic leukemia), thereby reducing the intra-disease heterogeneity and possible confounding factors, studies have shown how TL may influence disease outcomes and survival.[15,16]

To assess whether carriers of *TERT* rare variants might have been more susceptible to genomic instability, we also reviewed medical charts to identify any manifestations of other cancers or patterns in reported causes of death. We did observe that approximately half of our informative cases had an antecedent or co-existing diagnosis of malignancy (hematological $n = 6$, solid $n = 6$). Primary disease (63%), presence of another malignancy (19%) and infections (13%) constituted the main cause of death in our index cases while, of utmost importance, no patient died because of non-infectious pulmonary causes (Table S3). In a recent survey of the John Hopkins Telomere Syndrome Registry from 2003 to 2019, patients with short telomere syndromes were found to carry an overall risk of cancer (particularly MDS) significantly higher than that of the normal population.[17] In another study focusing on patients developing therapy-related myeloid neoplasms (*t*-MN) after autologous transplantation for lymphoma,[18] an accelerated TL shortening was indeed an independent predictor for subsequent *t*-MN evolution. Short TL was also found associated with a reduced regenerative capacity of HSC compartment, probably deriving from the impaired telomerase activity resulting in chromosomal instability, a mechanism reported to be responsible for the premature acquisition of age-related clonal hematopoiesis and thereby MDS/AML in individuals affected by short telomeres syndromes.[14,17]

In sum, our study further expands the knowledge of *TERT* rare variants in hematological disorders of myeloid origin. Because of their rarity, the impact of individual alterations cannot be assessed and needs to be studied in aggregate to observe any associations with phenotypes, possibly holding significance only in specific circumstances. Indeed, the lack of overlap between our and previous findings points toward a weak role of these rare VUS as risk alleles overall (i.e., outside of the context of younger MDS patients undergoing HSCT). In the future, the availability of integrative big "omics" data from worldwide consortia may help unveiling more detailed genotype/phenotype associations overcoming the pitfalls and the controversies experienced so far in linking genomic and functional information with clinical phenotypes and outcomes for such rare genomic instances.

FUNDING INFORMATION

National Heart, Lung, and Blood Institute (R01HL118281, R01HL123904, R01HL132071, R35HL135795), Vera and Joseph Dresner Foundation, Henry and Marilyn Taub Foundation, VeloSano pilot award, Aplastic Anemia and MDS International Foundation, American-Italian Cancer Foundation.

KEYWORDS

clinical genetics, myeloid neoplasia, telomeres, *TERT* rare variants

ACKNOWLEDGMENTS

We thank all publicly available resources of genomic data (VarSome, COSMIC, GnomAD) and The BEAT AML Master Trial. We thank our sources of funding: the HENRY & MARILYN TAUB FOUNDATION, grants R01HL118281, R01HL123904, R01HL132071, R35HL135795 (all to Jaroslaw P. Maciejewski), AA&MDSIF (to Valeria Visconte and Jaroslaw P. Maciejewski), VeloSano Pilot Award, Vera and Joseph Dresner Foundation–MDS (to Valeria Visconte). Gurnari Carmelo was supported by the American–Italian Cancer Foundation Post-Doctoral Research Fellowship.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

ETHICS STATEMENT

Written informed consents following the Declaration of Helsinki and in accordance to ethics committee approvals of The Cleveland Clinic Foundation and other institutions were obtained from all patients enrolled in the study. Additional information can be found in supplemental material.

AUTHOR CONTRIBUTIONS

Carmelo Gurnari, Valeria Visconte generated and conceived the study design, draw figures and tables, and wrote the manuscript; Adam Wahida provided data of telomere content; Simona Pagliuca, Misam Zawit, Arda Durmaz helped in statistical analysis; Torsten Haferlach provided samples and edited the manuscript; Jaroslaw P. Maciejewski provided patients and wrote the manuscript. All authors participated in the critical review of the final paper and submission.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are available in this published article and supplemental appendix. Any further information may be requested by email to the corresponding author.

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TRANSPARENT PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/hon.2967.

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SUPPORTING INFORMATION

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