Clinical diagnostic value of telomere length measurement in inherited bone marrow failure syndromes

Shunsuke Miwata,[1] Atsushi Narita,[1] Yusuke Okuno,[1,2] Kyogo Suzuki,[1] Motoharu Hamada,[1] Taro Yoshida,[1] Masayuki Imaya,[1] Ayako Yamamori,[1] Manabu Wakamatsu,[1] Kotaro Narita,[1] Hironobu Kitazawa,[1] Daisuke Ichikawa,[1] Rieko Taniguchi,[1] Nozomu Kawashima,[1] Eri Nishikawa,[1] Nobuhiro Nishio,[1,2] Seiji Kojima,[1] Hideki Muramatsu[1] and Yoshiyuki Takahashi[1]

[1]Department of Pediatrics, Nagoya University Graduate School of Medicine and [2]Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan

Correspondence:

HIDEKI MURAMATSU - hideki-muramatsu@med.nagoya-u.ac.jp

YOSHIYUKI TAKAHASHI - ytakaha@med.nagoya-u.ac.jp

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Supplementary Table 1. Target 184 gene list.

Disease categories	Gene					
Aplastic anemia	*PRF1*	*TERF1*	*TERF2*			
Congenital amegakaryocytic thrombocytopenia	*MPL*					
Congenital dyserythropoietic anemia	*CDAN1*	*KLF1*	*SEC23B*			
Chromosome fragile syndromes	*ATM*	*BLM*	*DCLRE1C*	*LIG4*	*NBN*	*RAD50*
Diamond-Blackfan anemia	*GATA1*	*RPL31*	*RPS10*	*RPS19*	*RPS29*	
	RPL11	*RPL35A*	*RPS14*	*RPS24*	*RPS7*	
	RPL26	*RPL5*	*RPS17*	*RPS26*		
Dyskeratosis congenita	*C16orf57*	*DKC1*	*NOP10*	*TERC*	*TINF2*	*POT1*
	CTC1	*NHP2*	*RTEL1*	*TERT*	*WRAP53*	*TERF2IP*
Fanconi anemia	*BRCA2*	*FANCB*	*FANCE*	*FANCI*	*PALB2*	
	BRIP1	*FANCC*	*FANCF*	*FANCL*	*RAD51C*	
	FANCA	*FANCD2*	*FANCG*	*FANCM*	*SLX4*	
Hemolytic anemia	*ADA*	*ENO1*	*GPI*	*HBB*	*PGK1*	*SPTB*
	ADD1	*EPB41*	*GPX1*	*HK1*	*PIEZO1*	*TPI1*
	AK1	*EPB42*	*GSR*	*NT5C3*	*PKLR*	
	ALDOA	*G6PD*	*GSS*	*PFKM*	*SLC4A1*	
	ANK1	*GCLC*	*HBA1*	*PGD*	*SPTA1*	
Juvenile myelomonocytic leukemia	*ASXL1*	*FLT3*	*KRAS*	*NRAS*	*SETBP1*	
	CBL	*JAK3*	*NF1*	*PTPN11*		
Hematological Malignancies	*AEBP2*	*CSF3R*	*EZH2*	*KIT*	*SF3B1*	*U2AF1*
	ATRX	*CTCF*	*FBXW7*	*LAMB4*	*SH2B3*	*U2AF2*
	B2M	*CUX1*	*GNAS*	*LUC7L2*	*SMC1A*	*UMODL1*
	BCOR	*DAXX*	*GPRC5A*	*MAP3K4*	*SMC3*	*WT1*
	BCORL1	*DCAF7*	*IDH1*	*NCOR2*	*SRP72*	*ZRSR2*
	BRAF	*DIDO1*	*IDH2*	*NPM1*	*SRSF2*	*ZSWIM4*
	BRCC3	*DIS3*	*IRF1*	*PHF6*	*STAG2*	
	CDH23	*DNMT3A*	*JAK1*	*PRPF8*	*STAT3*	
	CEBPA	*EED*	*JARID2*	*RAD21*	*SUZ12*	
	CREBBP	*ETNK1*	*KANSL1*	*RB1*	*TET2*	
	CSMD1	*ETV6*	*KDM6A*	*RIT1*	*TP53*	
MonoMAC syndrome	*GATA2*					
Myeloproliferative disorder	*JAK2*					
Neuronal ceroid lipofuscinosis type 2	*TPP1*					
Pancytopenia	*AK2*	*IKZF1*				
Congenital thrombocytopenia	*ACTN1*	*GP1BA*	*ITGA2B*	*MYH9*	*TUBB1*	
	FLI1	*GP9*	*ITGB3*	*RUNX1*	*VWF*	
Paroximal nocturnal hemogrobinuria	*PIGA*					
Sideroblastic anemia	*ABCB7*	*GLRX5*	*SLC19A2*	*YARS2*		
	ALAS2	*PUS1*	*SLC25A38*			
Severe congenital neutropenia	*ELANE*	*G6PC3*	*GFI1*	*HAX1*	*VPS45*	
Shwachman-Diamond syndrome	*SBDS*					
Wiskott-Aldrich syndrome	*WAS*					
WHIM syndrome	*CXCR4*					
X-linked lymphoproliferative syndrome	*SH2D1A*	*XIAP*				

Supplementary Table 2. Clinical characteristics of patients with inherited bone marrow failure syndromes (IBMFS).

UPN	Diagnosis	Age	Triad of DC			Physical anomaly	Gene	Nucleotide change	Amino acid change	Zygosity	Allelic frequency (GnomAD)	Clinvar ID / Reference	TL (SD)
		Sex	Nail dystrophy	Skin pigmentation	Leuko-plakia								
1	DC	2 F	+	−	−	+	*TINF2*	c.845G>A	p.R282H	Hetero	Not reported	VCV000005625.1	0.83
2	DC	1 F	−	−	−	+	*TINF2*	c.845G>A	p.R282H	Hetero	Not reported	VCV000005625.1	−5.73
3	DC	5 F	+	−	+	+	*TINF2*	c.847C>T	p.P283S	Hetero	Not reported	VCV000038920.2	−2.40
4	DC	7 F	−	+	−	+	*TINF2*	c.851C>G	p.T284R	Hetero	Not reported	Alder *et al*., 2015	−4.45
5	DC	11 F	−	−	−	+	*TINF2*	c.845G>A	p.R282H	Hetero	Not reported	VCV000005625.1	−3.55
6	DC	2 M	−	−	−	−	*TINF2*	c.844C>T	p.R282C	Hetero	Not reported	VCV000005627.3	−3.61
7	DC	17 M	−	+	−	+	*TERT*	c.1892G>A	p.R631Q	Hetero	Not reported	VCV000029899.1	−2.64
8	DC	6 M	−	−	−	+	*TERT*	c.2701C>T	p.R901W	Hetero	Not reported	VCV000029901.2	−2.19
9	DC	19 M	−	−	−	−	*TERT*	Deletion	−	Hetero	Not reported	−	−3.50
10	DC	12 F	−	+	−	+	−	−	−	−	−	−	−2.50
11	DC	11 M	+	+	−	+	−	−	−	−	−	−	−3.82
12	FA	10 M	−	−	−	−	*FANCA*	c.2546delC	p.S849fs*40	Homo	3.98E-06	VCV000408166.3	−1.84
13	FA	8 F	−	−	−	+	*FANCA*	c.2546delC	p.S849fs*40	Hemi	3.98E-06	VCV000408166.3	−1.89
							FANCA	Deletion	−		Not reported	−	
14	FA	13 M	−	−	−	+	*FANCA*	c.2470T>C	p.C824R	Hetero	Not reported	Novel	0.83
							FANCA	c.1418T>C	p.L473P	Hetero	Not reported	Novel	
15	FA	6 F	−	−	−	+	*FANCA*	c.2470T>C	p.C824R	Hemi	Not reported	Novel	−0.26
							FANCA	Deletion	−		Not reported	−	
16	FA	3 F	−	−	−	+	*FANCA*	c.2546delC	p.S849fs*40	Hemi	3.98E-06	VCV000408166.3	−3.29
							FANCA	Deletion	−		Not reported	−	
17	FA	15 M	−	−	−	+	*FANCA*	c.2778+1G>A	−	Hetero	Not reported	VCV000635518.5	−1.71
							FANCA	c.2210C>T	p.A737V	Hetero	Not reported	VCV000456093.1	
18	FA	2 M	−	−	−	−	*FANCG*	c.307+1G>C	−	Homo	Not reported	VCV000006714.5	2.05
19	FA	10 M	−	−	−	+	*FANCG*	c.307+1G>C	−	Homo	Not reported	VCV000006714.5	−4.74
20	FA	5 F	−	−	−	+	*FANCG*	c.1066C>T	p.Q356X	Hetero	Not reported	VCV000006715.6	−3.58
							FANCG	c.194delC	p.65fs*7	Hetero	Not reported	VCV000660043.2	
21	DBA	1 F	−	−	−	−	*RPS19*	c.301C>T	p.R101C	Hetero	3.99E-06	Ilenia *et al*., 2010	0.32
22	DBA	0 F	−	−	−	−	*RPS17*	Deletion	−	Hetero	Not reported	−	1.21
23	DBA	6 F	−	−	−	+	*RPL5*	c.3+1G>A	−	Hetero	Not reported	Novel	−2.10
24	DBA	13 F	−	−	−	+	*RPL5*	c.657C>G	p.Y219X	Hetero	Not reported	Novel	−2.83
25	SDS	6 M	−	−	−	+	*SBDS*	c.184A>T	p.K62X	Hetero	0.000258	VCV000449095.5	−1.99
							SBDS	c.258+2T>C	−	Hetero	Not reported	VCV000003196.15	
26*	BS	13 M	−	−	−	+	*BLM*	c.557_559 delCAA	p.S186X	Homo	Not reported	VCV000005455.2	−1.55

*UPN26: A 13-year-old boy presented with anemia and thrombocytopenia. He was receiving growth hormone replacement therapy for short stature associated with extremely low birth weight. General examination revealed a characteristic facial appearance including an erythematous rash on the nose and cheeks, cryptorchidism, urethral malformation, facial stenosis, and a small nose. Bone marrow aspiration showed hypercellularity with moderate dysplasia. Genetic analysis revealed a homozygous mutation in the *BLM* gene, leading to the diagnosis of Bloom's syndrome (BS). IBMFS, inherited bone marrow failure syndromes; UPN, unique patient number; DC, dyskeratosis congenita; TL, telomere length; SD, standard deviation; FA, Fanconi anemia; DBA, Diamond–Blackfan anemia; SDS, Shwachman–Diamond syndrome; BS, Bloom syndrome.

Supplementary Table 3. Summary of reports analyzed on TL of inherited bone marrow failure syndromes (IBMFS).

Reference	Age, Median (range)	Patients (N)	Patients of TL shortening (%)	Method	Threshold
Fanconi anemia					
Ball, 1998	ND (4–18)	6	4 (67)	Southern, TRF	<Normal range for age
Hanson, 2001	4.5 (0–11)	16	15 (94)	Q-FISH	Loss of telomere signal
Li, 2003	11 (2–48)	71	47 (66)	Southern	<200 bp/year
Pavessi, 2009	6 (2–33)	9	2 (22)	Q-PCR	<1st percentile
Alter, 2015	18 (3–56)	30	2 (7)	Flow-FISH	<1st percentile
Our data	8 (2–15)	9	6 (67)	Flow-FISH	<−1.71 SD
Diamond–Blackfan anemia					
Pavessi, 2009	2 (0–31)	45	1 (2)	qPCR	<1st percentile
Du, 2009	12 (0–62)	41	5 (12)	Flow-FISH	<1st percentile
Alter, 2015	14 (2–58)	34	1 (3)	Flow-FISH	<1st percentile
Our data	4 (0–13)	4	2 (50)	Flow-FISH	<−1.71 SD
Shwachman–Diamond syndrome					
Thornley, 2002	7 (0.5–18)	12	7 (58)	Southern	<Normal range for age
Du, 2009	20 (2–41)	5	1 (20)	Flow-FISH	<1st percentile
Alter, 2015	12 (5–42)	14	2 (14)	Flow-FISH	<1st percentile
Ong, 2018	19	1	1 (100)	qPCR	<1st percentile
Our data	6	1	1 (100)	Flow-FISH	<−1.71 SD

TL, telomere length; IBMFS, inherited bone marrow failure syndromes; ND, not described; SD, standard deviation; TRF, terminal restriction fragment; Flow-FISH, flow-fluorescence in situ hybridization; Q-FISH, quantitative fluorescent in situ hybridization; qPCR, quantitative polymerase chain reaction; Southern, Southern blotting.