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Germline *POT1* Variants Can Predispose to Myeloid and Lymphoid Neoplasms

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AUTHOR CONTRIBUTIONS

TLL and DVB collected and analyzed the data, performed literature review, and wrote and revised the manuscript. DBL and JJDM established the hematologic malignancies molecular panel at the Hospital of the University of Pennsylvania and performed clinical *POT1* MPS. ARD and A. Bagg oversaw clinical hematopathology review and provided archived pathology specimens for germline validation. AWL contributed to clinical care for myeloid malignancy patients and provided leukemia and transplant expertise. RH and A. Bigdeli assisted with bioinformatic analysis of *POT1* variants. YL performed statistical review. JP assisted with human subjects study design and provided clinical genetics expertise. Regeneron Genetics Center performed WES for PMBB control cohort. SAC provided lymphoma expertise and assisted clinicopathological correlation of lymphoma patients. AR and KLN provided clinical genetics expertise. KLN additionally provided critical manuscript revisions and variant classification expertise. KNM assisted with PMBB variant analysis and provided technical expertise for FFPE DNA extraction. EOH assisted with clinicopathological correlation of myeloid malignancy patients. DVB conceived and oversaw the study. All authors assisted with data analysis and edited and approved the final version of the manuscript.

DISCLOSURE OF CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest.

TO THE EDITOR:

Since the introduction of myeloid neoplasms with germline predisposition as a new category by the World Health Organization(1), the list of genes linked to predisposition to hematologic malignancies has continued to grow. Recently, germline variants in a shelterin complex component Protection of Telomeres 1 (*POT1*) have been implicated in several familial cancer syndromes, including familial chronic lymphocytic leukemia (CLL), and, more recently, a Li-Fraumeni-like multicancer predisposition, suggesting the spectrum of *POT1*-related malignancies remains incompletely characterized(2–5). A highly conserved protein, POT1, is recruited to single-stranded telomeric DNA through its interaction with ACD shelterin complex subunit and telomerase recruitment factor (TPP1), where it functions to regulate telomere length and prevent induction of DNA damage response(6). However, the role of *POT1* variants in hematologic neoplasms beyond CLL remains unknown. To explore the role of *POT1* variants in hematologic neoplasms, we analyzed *POT1* variants in 3,323 consecutive patients who were evaluated for cytopenias or hematologic malignancies at the University of Pennsylvania.

The case population consisted of 3,323 consecutive patients who had clinical MPS testing for variants associated with hematologic malignancies during evaluation of cytopenias or hematologic malignancies from April 2015 to October 2018. Comprehensive description of study methodology is provided in the Supplement, including Supplemental Tables S1–S5. The variant pathogenicity was determined using ACMG criteria(7). Germline/somatic status was assigned using clinicopathological data and confirmed in non-hematopoietic tissues when available. The prevalence of germline *POT1* predicted loss-of-function (pLOF) variants in cases was compared to cancer-free controls from the Penn Medicine BioBank (PMBB) and Genome Aggregate Database (gnomAD)(8,9).

From 3,323 evaluated patients, 2,744 patients (83%) had a hematologic malignancy with 1,401 patients with lymphoid, 1,225 patients with myeloid, and 118 patients with both lymphoid and myeloid malignancies, whereas 579 patients (17%) did not have a hematologic malignancy. Fifty-seven patients, all with hematologic malignancies, had 52 distinct *POT1* variants classified as pathogenic (n = 8), likely pathogenic (n = 2), or variants of uncertain significance (VUS, n = 42); only these variants were included in subsequent analyses (Supplemental Figure 1). The prevalence of these *POT1* variants was significantly higher in patients with hematologic malignancies (57 of 2744, 2.1%) than in those with non-neoplastic blood conditions (0 of 579, 0%) (OR 24.8, 95% CI 1.5-402, $p < 0.001$). This association is largely due to somatic *POT1* variants, which comprised 54% of the identified variants. Thirty-nine percent were germline or presumed germline, and another 7% had an indeterminate germline/somatic status.

Of the 19 unique germline *POT1* variants, 13 were missense and located within mapped functional protein domains, whereas 6 were classified as pLOF (Figure 1A). Germline enrichment analyses using only pLOF variants revealed that patients with hematological malignancies had a ~4 to 8-fold increased odds of having a germline (n = 4) or presumed germline (n = 3) pLOF *POT1* variant compared to cancer-free individuals in gnomAD (OR = 7.6, 95% CI 3.3-16.7, $p < 0.001$) or PMBB (OR = 4.2, 95% CI 1.2-15.2, $p = 0.020$).

Germline (n = 3) and presumed germline (n = 3) pLOF *POT1* variants were ~6 to 12-fold more common in patients with lymphoid neoplasms compared to cancer-free individuals in gnomAD (OR 11.8, 95% CI 4.9-27.8, p < 0.001) and PMBB (OR 6.4, 95% CI 1.8-24.4, p = 0.005). Interestingly, in patients with myeloid neoplasms, confirmed germline pLOF *POT1* variants also occurred at a ~4 to 7-fold enrichment compared to the cancer-free populations (gnomAD: OR 6.7, 95% CI 1.7-20.2, p = 0.012, PMBB: OR 3.6, 95% CI 0.7-16.7, p = 0.10) (Table 1).

Clinicopathological analyses, detailed fully in the Supplement, revealed distinctive spectra of lymphoid and myeloid malignancies (Supplemental Table S1). All patients with germline or presumed germline *POT1* variants and lymphoid neoplasms presented with indolent lymphoid neoplasms, approximately half with diagnoses other than CLL. Consistent with prior studies(4), both germline (n = 6) and somatic (n = 13) *POT1* variants in patients with lymphoid malignancies were most frequently associated with CLL. Lymphoid neoplasms in patients with germline *POT1* variants had no other disease-associated variants detected by MPS (median 0, range 0-2), compared to a median of one variant in patients with somatic *POT1* variants (range 0-6). The most frequent co-occurring variants were in *TP53*, observed in five patients with somatic *POT1* alterations (Figure 1B).

For patients with germline *POT1* variants and myeloid neoplasms, the most common diagnosis was myeloproliferative neoplasms (MPNs) (n = 6) at 1.2% prevalence of germline *POT1* variants in 492 MPN patients in our cohort. In contrast, somatic *POT1* variants in patients with myeloid malignancies were seen predominantly in AML (n = 6). Patients with myeloid malignancies and germline *POT1* variants had a median of two pathogenic variants in other cancer-associated genes (range 0-6). The most commonly mutated genes in patients with germline *POT1* variants were *TET2* and *JAK2*, each identified in five patients. In patients with somatic *POT1* variants and myeloid malignancies, additional hematologic malignancy-associated pathogenic variants were observed at a median of three variants (range 0-6), with *NRAS* most commonly mutated in four patients (Figure 1B).

Patients with germline *POT1* variants had a median of two (range 1-4) distinct cancer diagnoses per patient. Four patients had malignancies previously reported in patients with germline *POT1* variants (melanoma, oligodendroglioma, and follicular thyroid cancer) (2,3,5). Sixteen patients (73%) had a family history of malignancy, with hematologic, lung, and skin cancers being most common. Within the families of patients with myeloid malignancies and germline *POT1* variants, myeloid malignancies occurred as part of a broader spectrum of *POT1*-associated familial cancers. The affected patients and their families frequently had a strong cancer history with multiple types, including known *POT1*-associated neoplasms and other cancers (Figure 1C). For example, patient PENN07 was diagnosed with monoclonal B cell lymphocytosis and *JAK2 V617F*-positive MPN at the age of 55 years and had a family history of CLL, basal cell carcinoma, melanoma, bladder cancer, kidney cancer, neuroendocrine cancer, glioblastoma, and several benign tumors.

Notably, among patients with germline *POT1* variants and myeloid neoplasms, none were noted to have classical mucocutaneous features of short telomere syndromes, such as nail dystrophy or oral leukoplakia, and none had bone marrow failure prior to the development

of myeloid malignancy. One patient did have severe pulmonary pathology suggestive of telomere dysfunction: patient PENN19 died at the age of 45 years from pulmonary complications after a myeloablative Cyclophosphamide/Total Body Irradiation-conditioned allogeneic stem cell transplant (Supplemental Figure S2).

In sum, in this first comprehensive analysis of *POT1* variants in a hematologic malignancy population, we have shown that germline variants in *POT1* are among the growing list of hematologic malignancy predisposition syndromes and newly found that they are associated with increased risk of not just lymphoid but also myeloid malignancies. *POT1* variants were ~25-fold enriched in patients with hematologic malignancies compared to nonmalignant conditions, expanding upon prior reports of *POT1* as a tumor driver in solid malignancies(5).

The association of germline *POT1* variants with chronic lymphoproliferative (e.g., CLL) and myeloproliferative neoplasms is likely not coincidental and probably reflects the synergy between telomere shortening and dysfunction in these neoplasms and the telomere elongation caused by *POT1* variants. Genome-wide association studies have identified 17 genetic loci associated with increased risk of MPN, including two polymorphisms within the telomerase reverse transcriptase (*TERT*) locus, previously associated with increased leukocyte telomere lengths(10,11). While *POT1* was not among the 17 identified MPN risk loci, the authors estimated that the identified 17 loci explain only ~18% of familial relative risk for MPN acquisition, suggesting that other, more rare, germline predisposition factors not identified in the analysis may jointly explain the remaining risk. Our findings suggest that germline *POT1* variants predispose to MPNs through a mechanism similar to *TERT* variants, by increasing telomere lengths and protecting MPN hematopoietic cells from premature cell senescence. In contrast to germline *POT1* variants, somatic *POT1* variants likely emerge as a compensatory event in response to telomere attrition, allowing *POT1*-mutant malignant cells to bypass telomere shortening-induced DNA damage response.

Although short telomere syndromes (STS) carry an increased risk of MDS/AML (12), heterozygous *POT1* variants do not cause STS but instead have been linked to abnormally long telomeres(2,13). Accordingly, patients with germline *POT1* variants in our cohort did not have recognized features of STS. One notable clinical finding in a patient with germline *POT1* variant was severe pulmonary toxicity after myeloablative allogeneic stem cell transplant. Although we are not able to definitively link *POT1*-associated telomere dysfunction to this patient's pulmonary toxicity, the type and unusual severity of pulmonary failure is very reminiscent of pulmonary transplant toxicity seen in STS patients(14). Future studies of SCT outcomes in germline *POT1* variant carriers will help better assess potential transplant-related complications and safety of myeloablative conditioning in this patient population.

In conclusion, our data provide the first evidence for an association between germline *POT1* variants and myeloid neoplasms and expand our understanding of the role of telomere regulation in hematologic neoplasms. Our findings suggest that patients with identified pathogenic *POT1* variants merit evaluation for their germline/somatic status and surveillance for any underlying malignancies(15) and underscore the importance of recognizing germline hematologic malignancy predisposition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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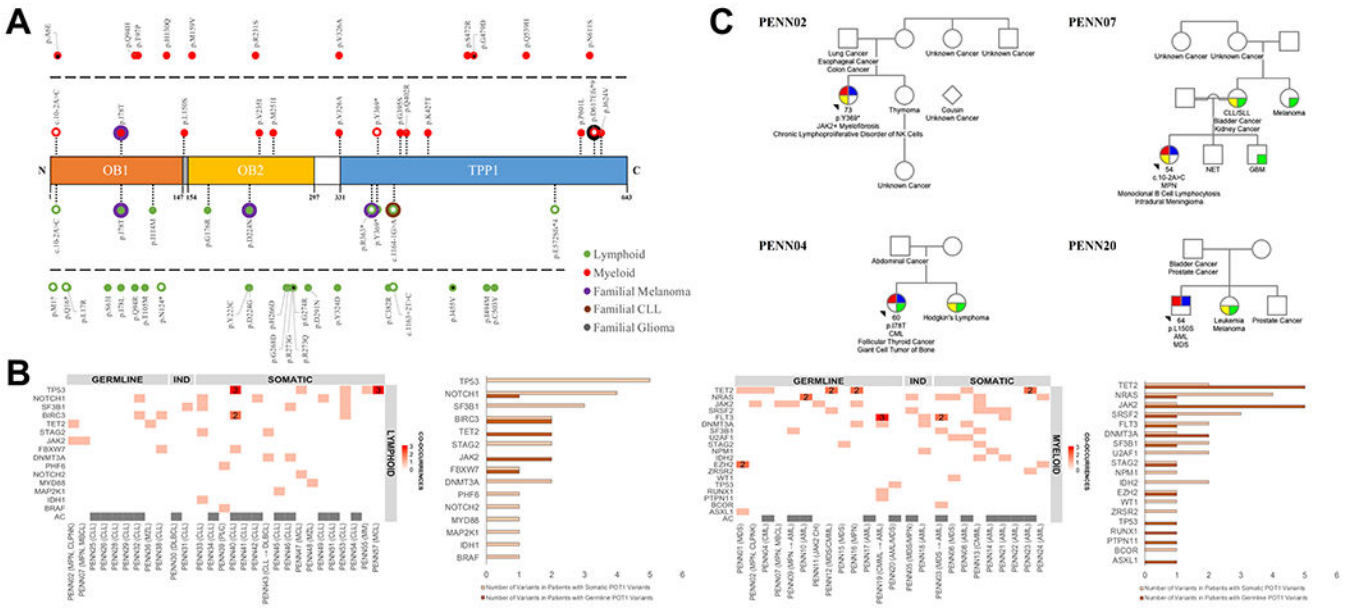

Figure 1. *POT1* variants in hematologic neoplasms.

(A) A schematic diagram of the identified *POT1* variants. Variants identified in patients with lymphoid neoplasms are depicted below the protein structure in green, and variants identified in patients with myeloid neoplasms are plotted above the protein diagram in red. pLOF variants are shown as open circles. Variants previously identified in the literature are signified with a border that is color-coded with a previously described familial *POT1* cancer type (melanoma, purple; CLL, brown; glioma, black). Germline variants are plotted closest to the protein diagram with a dashed line connected to the POT1 protein structure, whereas somatic and indeterminate variants are plotted in the outside rows and are not connected by dashed lines. Indeterminate variants are marked with a central black circle. The germline pLOF variant p.D617Efs*9, identified in a patient with a myeloid neoplasm and located near the C-terminus of the POT1 protein in the TPP1 binding domain, has been previously associated with familial glioma (3). Previous studies identified variants in that region in several *POT1*-associated familial CLL kindreds and have demonstrated that they result in disruption of POT1 interaction with TPP1, loss of DNA binding, increased telomere fragility, and significantly increased telomere lengths (2,13). Four additional variants (p.I78T, p.D224N, p.R363*, and c.1164-1G>A) were previously reported in association with familial *POT1* syndromes, whereas 14 were newly identified in our study. **(B)** A schematic representation of disease-associated variants in genes associated with hematologic malignancies in patients with *POT1* variants. Only genes with at least one disease-associated gene variant are shown in the figure; all genes assessed for disease-associated variants are listed in Supplemental Table S2. The malignancies in each of the affected patients are listed next to each patient's study number: myeloproliferative neoplasm (MPN), monoclonal B cell lymphocytosis (MBCL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), plasmacytoma (PLC), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), multiple myeloma (MM), myelodysplastic syndrome (MDS), chronic lymphoproliferative disorder of natural killer cells (CLPNK), acute myeloid leukemia (AML), *JAK2*+ V617F Clonal Hematopoiesis (JAK2 CH), chronic

myelomonocytic leukemia (CMML), high grade B-cell lymphoma (HGBCL). Abnormal cytogenetics (AC) are indicated by a gray tile. Synchronous malignancies are denoted with a comma, whereas transformations are marked with an arrow. **C)** Pedigrees of patients with germline *POT1* variants and myeloid neoplasms. Black arrows indicate the index case in the pedigree, and symbols are colored depending on key malignancy features (red quadrant, germline *POT1* variant cancer; blue quadrant, myeloid malignancy; yellow quadrant, lymphoid malignancy; green quadrant, *POT1*-associated cancer). Ages at cancer diagnosis (when available), *POT1* variant, and tumor type are listed below the individual symbol.

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Table 1.

Patients with germline *POT1* variants.

Subject	Age at Diagnosis, Years	Sex	Diagnosis	Other Cancers	*POT1* Variant	Chr Position	Consequence	VAF	Domain	Pathogenicity	Cytogenetics	Disease-Associated Co-Varaints	Germline Status
PENN01	59	F	MDS	-	c.C1802T p.P601L	chr 7:124464119	Missense	0.53	TPP1	LP	Normal	*TET2, EZH2, ASXL1*	Presumed Germline
PENN02	73	F	MPN (MF)	Chronic Lymphoproliferative Disorder of NK Cells	**c.1107delT p.Y369***	chr 7:124482917	Stop Gained	0.49	TPP1	P	-	*JAK2, TET2*	Germline
PENN04	60	F	MPN (CML)	Follicular Thyroid Cancer, Giant Cell Tumor of Bone	c.T233C p.I78T	chr 7:124510987	Missense	0.52	OB1	VUS	t(9;22)	*TET2*	Germline
PENN07	54	F	MPN (ET)	Intradural Meningioma, Monoclonal B Cell Lymphocytosis	**c.10-2A>C p.?**	chr 7:124532436	Splice Site	0.51	OB1	LP	Normal	*JAK2*	Germline
PENN09	68	M	MPN (MF) → AML	Gastric Adenocarcinoma, Prostate Cancer, Colon Adenoma	c.T977C p.V326A	chr 7:124487025	Missense	0.48	TPP1	VUS	del(13q)	*JAK2, SF3B1*	Germline
PENN10	44	M	AML	-	c.G703A p.V235I	chr 7:124493192	Missense	0.49	OB2	VUS	−Y, t(8;21)	*NRAS*	Germline
PENN11	51	M	*JAK2 V617F*+ Clonal Hematopoiesis†	Brain Oligodendroglioma	c.G1183A p.G395S	chr 7:124481213	Missense	0.46	TPP1	VUS	Normal	*JAK2*	Presumed Germline
PENN12	81	M	CMML	Basal Cell Carcinoma, Squamous Cell Carcinoma	c.A1280C p.K427T	chr 7:124481116	Missense	0.50	TPP1	VUS	Normal	*TET2, SRSF2*	Germline
PENN15	72	M	MDS	Renal Cell Carcinoma	c.G753A p.M251I	chr 7:124493142	Missense	0.50	OB2	VUS	Normal	*STAG2*	Germline
PENN16	87	M	MPN (PV)	Skin Cancer, Prostate Cancer	c.A1870G p.I624V	chr 7:124464051	Missense	0.51	TPP1	VUS	Normal	*DNMT3A, NPM1, FLT3*	Germline
PENN17	60	M	AML	-	c.A1205G p.Q402R	chr 7:124481191	Missense	0.50	TPP1	VUS	−Y, t(8;21)	None	Presumed Germline
PENN19	44	F	CMML → AML	-	***c.1851_1852del p.D617Efs*9***	chr 7:124464069	Stop Gained	0.52	TPP1	P	Normal	*DNMT3A, PTPN11, FLT3, RUNX1*	Germline

Subject	Age at Diagnosis, Years	Sex	Diagnosis	Other Cancers	*POT1* Variant	Chr Position	Consequence	VAF	Domain	Pathogenicity	Cytogenetics	Disease-Associated Co-Varaints	Germline Status
PENN20	64	M	AML/MDS	-	c.T449C p.L150S	chr 7:124493075	Missense	0.53	OB-FOLD	VUS	Complex	*TP53*	Germline
PENN25	59	F	CLL	Bilateral Breast Cancer	c.C342G p.I114M	chr 7:124503608	Missense	0.53	OB1	VUS	−X, del(13q)	None	Presumed Germline
PENN26	48	F	CLL	-	**c.1713_1717del p.E572Sfs*4**	chr 7:124465381	Frameshift	0.49	TPP1	P	del(13q)	None	Presumed Germline
PENN27	67	M	Hairy Cell Leukemia	-	***c.1164-1G>A p.?***	chr 7:124481233	Splice Site	0.53	TPP1	P	Normal	None	Germline
PENN28	63	M	CLL	-	*c.T233C p.I78T*	chr 7:124510987	Missense	0.49	OB1	VUS	+12, +19	None	Presumed Germline
PENN29	59	F	CLL	-	c.G526A p.G176R	chr 7:124503424	Missense	0.48	OB2	VUS	+X, del(13q)	None	Presumed Germline
PENN32	56	M	CLL	Metastatic Melanoma	*c.G670A p.D224N*	chr 7:124499043	Missense	0.48	OB2	VUS	del(11q), del(13q	*NOTCH1, BIRC3*	Germline
PENN35	72	M	CLL	Melanoma	***c.C1087T p.R363****	chr 7:124482937	Stop Gained	0.49	TPP1	P	del(13q)	None	Presumed Germline
PENN36	71	M	Marginal Zone Lymphoma	Prostate, Lung	c.G526A p.G176R	chr 7:124503424	Missense	0.51	OB2	VUS	Normal	*TET2*	Germline
PENN38	65	F	CLL	-	***c.1164-1G>A p.?***	chr 7:124481233	Splice Site	0.51	TPP1	P	Borderline +12	*FBXW7, BIRC3*	Presumed Germline

Chr, chromosome, Variant allele frequency (VAF), myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), essential thrombocythemia (ET), myelofibrosis (MF), acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML), polycythemia vera (PV), natural killer (NK), chronic lymphocytic leukemia (CLL), Female (F), Male (M), TPP1 binding domain (TPP1), oligonucleotide/oligosaccharide DNA-binding domains 1 (OB1) and 2 (OB2), oligonucleotide/oligosaccharide fold (OB-FOLD). Pathogenicity assessment categories of variant of uncertain significance (VUS), likely pathogenic (LP), and pathogenic (P) are determined using ACMG criteria (7). pLOF variants are bolded. Italicized variants have been previously reported in literature. Chromosomal coordinates are based on GRCh37 (hg19) genome assembly.

[†]PENN12 had erythrocytosis and a positive *JAK2 V617F* variant but did not meet formal 2016 WHO criteria for a specific MPN subtype.