Role of CTC1 gene in primary immunodeficiency and CLL susceptibility. Can monoallelic loss-of-function mutations in *CTC1* cause late onset PID?

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01 Background and Aims

Chronic lymphocytic leukaemia (CLL) is a prevalent haematological malignancy (HM) among the elderly, characterized by heterogeneity in its clinical presentation. Germline mutations in telomere-related genes are one of the most common genetic causes of HM. The deficiency of one of such genes, *CTC1*, causes a rare autosomal recessive disorder called cerebroretinal microangiopathy with calcifications and cysts (COATS plus syndrome) that associates bone marrow failure. Recently, variants in telomerase-related genes have been positively correlated with telomere shortening in patients with common variable immunodeficiency (*figure 1*).

This study aims searching new disease-causing mutations in telomere-related genes associated with primary immunodeficiency (PID) and susceptibility to HM.

02 Methods

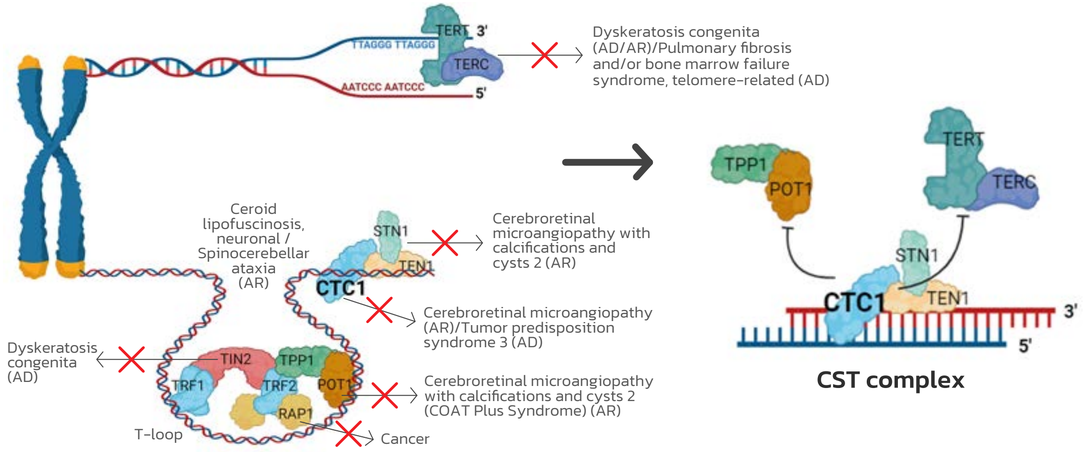
We tested by targeted high throughput sequencing over 500 immune system- related genes in 40 patients with HM and suspicion of PID.

03 Results

Two patients, an 85-year-old male (case 1) and a 63-year-old female (case 2) harbored the same frameshift heterozygous variant in CTC1 (NM_025099.5:c.251_252insGCCA; p.His84Glnfs*8), likely of germline origin. Both patients shared a diagnosis of CLL at 67- and 43-year-old, respectively, accompanied by severe recurrent infections of respiratory, skin and urinary systems. They presented autoimmune thrombocytopenia, one of them hemolytic anaemia subsequent to CLL onset, alongside a normal count of B cell with 0% of class-switched memory B cell and NK deficiency. Other monoallelic truncating variants in *CTC1* have been previously reported in patients with PID (*table 1*).

Patient	Current age	Variant in CTC1 gene	Effect	Clinical history	Immuno-phenotype	Hematological neoplasia	Reference
Case 1	85 yo (male)	NM_025099.5:c.251_252insGCCA; NP_079375.3:p.His84Glnfs*8	Frameshift	Severe recurrent respiratory and skin infections, AHA	Panhipogammaglobulinemia, class-switched memory B-cell deficiency, NK deficiency	CLL (67 yo)	This study
Case 2	63 yo (female)	NM_025099.5:c.251_252insGCCA; NP_079375.3:p.His84Glnfs*8	Frameshift	Recurrent pneumonia, urine infection by pseodomonas, bronchiectasis	Lymphopenia of B-cells, NK deficiency, Thrombocytopenia	CLL (67 yo)	This study
Case 3 (literature review)	69 yo (male)	NM_025099.5:c.1360delG; NP_079375.3:p.Glu454Serfs*9	Frameshift	Recurrent respiratory, bronchiectasis, ILD	N/A	No	PMID: 37404458
Case 4 (literature review)	65 yo	NM_025099.3:c.400dupT; NP_079375.3:p.Tyr134fs*	Frameshift	Pulmonary fibrosis	N/A	N/A	PMID: 29920840

Table 1: Clinical features of patients harboring monoallelic truncating variants in *CTC1*. Case 1 and 2 belonged from this communications. Case 3 and 4 were identified by searching publications in which patients harboring truncating heterozygous variants in *CTC1* gene were reported



Functional steps of CST complex:

1. Binds to telomeric G-rich ssDNA.
2. Protein-protein interactions between POT1-TPP1 and CST complex.
3. Assitance to synthesis of the telomeric C-strand.
4. Telomerase inhibition to prevent telomereover-elongation.

Related-disease risk to telomeres shortening in Adults.

Immunodeficiency (CVID).
Aplasic anemia.
Hematological malignancies.
Pulmonary fibrosis.
Solid tumors.
Bone marrow failure.
Hepatic cirrhosis.

Figure 1: Representative interaction of CST complex (CTC1-STN1-TEN1) and molecular mechanism of telomere maintenance. Genetic defects in the genes involved in different steps, causing telomere shortening, were associated with each previously described disease. Additional phenotypes characteristic in adults were indicated in patients with telomeres shortening.

04 Conclusions

We uncovered two patients with genetic telomeric dysregulation as potential driver mutations in CLL pathogenesis, associated with autoimmune cytopenia, undetectable class-switched memory B cells and NK cells. As well as recent reports have proposed monoallelic pathogenic mutations in telomere-related genes are cause of CVID with variable expression, LoF in *CTC1* may be a primary cause of CVID.