Reconsidering Low-Risk *CHEK2* Variants: Evidence for Oligogenic Modifiers in Cancer Predisposition

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BACKGROUND

CHEK2 p.Thr476Met (c.1427C>T) is classified as a low-risk allele for breast cancer (OR < 1.4). However, single-gene penetrance estimates may underestimate cancer risk when co-occurring variants affect related genome-maintenance pathways.

The concept of oligogenic modulation — where a variant of modest individual effect substantially increases risk in combination with a second pathogenic allele — is established in other hereditary conditions.

CASE PRESENTATION

63-year-old woman with complex cancer and systemic phenotype:
Oncologic history: Stage IA invasive ductal carcinoma (ER+96%, PR+95%, HER2−), breast (age 62); premalignant thyroid lesion; multiple skin cancers; extensive colonic polyposis

Physical examination: reticulated red hyperpigmentation with thin, mottled, and prematurely wrinkled skin, sparse hair, and nail dystrophy characterized by ridging, splitting, and soft, fragile nails.

Systemic features: Primary immunodeficiency (IgA, IgG2, IgG3 deficiencies); dysplastic nails; chronic epiphora; stage 3 CKD; renal cysts; congenital solitary kidney

Family history: Father — colon cancer (deceased, 79 y/o); paternal grandfather (deceased) — colon cancer. Mother (Living, 85 y/o) — skin cancer; did NOT carry *CHEK2* or *RTEL1* variants

Keywords: *CHEK2* · *RTEL1* · Telomere Biology Disorder · Oligogenic Inheritance · Genomic Instability · Hereditary Cancer · DNA Damage Response

MOLECULAR FINDINGS

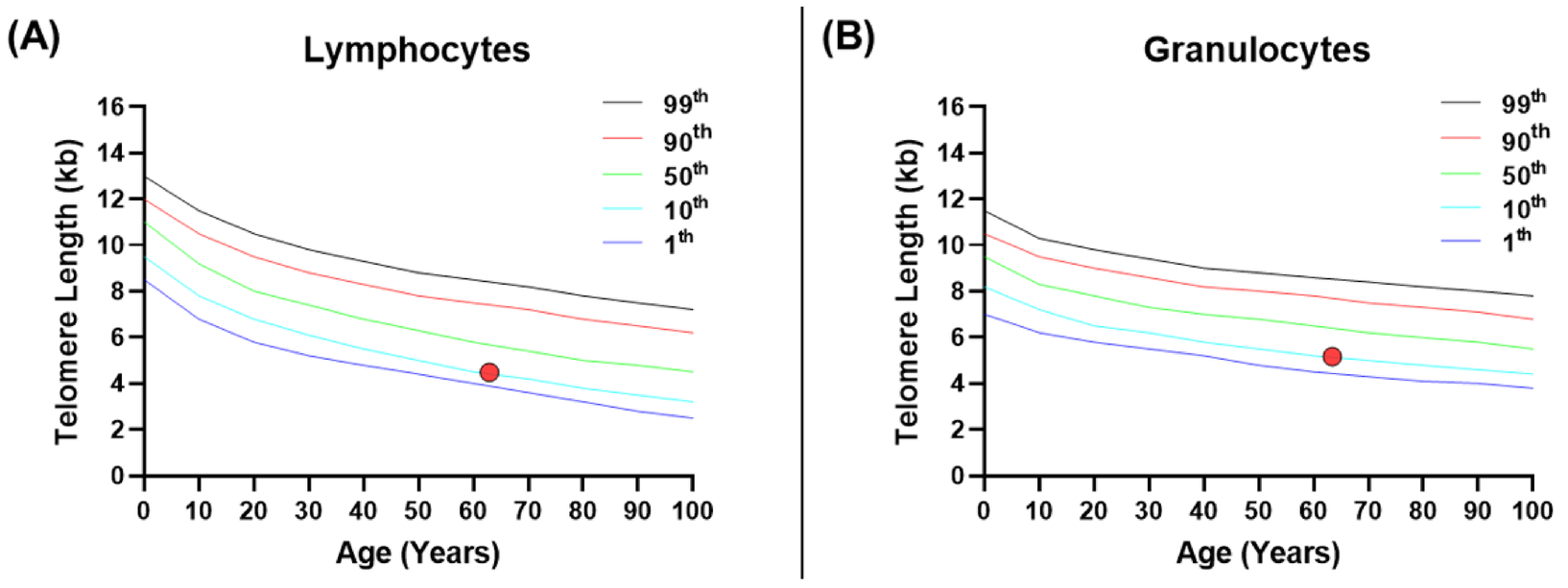
***CHEK2* c.1427C>T (p.Thr476Met)**

Low-risk allele | OR < 1.4 for breast cancer

***RTEL1* c.904G>T (p.Asp302Tyr)**

Variant of Uncertain Significance (VUS) | Conserved helicase domain

FIGURE 1: TELOMERE LENGTH MEASUREMENT (flowFISH)



Patient value (red dot) lies near the 10th percentile in both lymphocytes (A) and granulocytes (B)

PROPOSED OLIGOGENIC MECHANISM

We hypothesize a two-hit functional impairment:

① *RTEL1* p.Asp302Tyr → partial helicase impairment → increased replication stress at telomeres and G-quadruplex structures → telomeric fragility

② *CHEK2* p.Thr476Met → modest reduction in kinase domain stability → attenuated checkpoint activation and DNA damage signaling (DDR)

Combined effect: concurrent impairment of telomere maintenance and DDR creates a cellular environment permissive to structural genomic alterations and cancer predisposition — neither variant sufficient alone.

RTEL1 BIOLOGY & FUNCTIONAL CONTEXT

RTEL1 encodes a helicase essential for T-loop disassembly and G-quadruplex resolution during S-phase, ensuring proper replication fork progression. Even partial reductions in helicase activity can increase replication stress and telomeric fragility, promoting localized genomic instability.

The patient's borderline telomere length (10th percentile) and syndromic clinical features (dysplastic nails, chronic epiphora, immunodeficiency) are suggestive of an intermediate functional state — below threshold for definitive TBD diagnosis yet clinically significant in the context of co-occurring *CHEK2* variant.

CLINICAL IMPLICATIONS

De-escalated surveillance caveat:
As guidelines move toward reduced surveillance for low-risk *CHEK2* variants, clinicians must recognize patients with unusually severe or syndromic presentations who may warrant more intensive management.

Modifier evaluation:
For *CHEK2* carriers with complex phenotypes, evaluation for co-occurring variants in telomere-maintenance (*RTEL1*, *TERT*, *DKC1*) or DDR pathways may provide critical risk context.

Oligogenic models:
Incorporating multi-gene interaction models may refine rare variant interpretation and personalize management in hereditary cancer syndromes.

CONCLUSIONS

Single-gene penetrance estimates represent population averages — not individualized risk. Broader genomic context, including oligogenic modifiers, must be considered for patients with atypical or syndromic cancer presentations.

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