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

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Case Presentation

A 63-year-old woman presented with dysplastic nails, chronic epiphora, and a complex medical history suggestive of cancer susceptibility and systemic cellular maintenance defects. Medical history reveals diagnosis of right-sided invasive ductal carcinoma at 62 years of age characterized as stage IA (T1bN0), grade 1, ER-positive (96%), PR-positive (95%), HER2-negative, with Ki-67 of 21%. She previously underwent left thyroidectomy for a premalignant thyroid lesion and has persistent contralateral thyroid nodules. Her history is also notable for multiple skin cancers, extensive colonic polyposis, and primary immunodeficiency characterized by IgA, IgG2, and IgG3 deficiencies. Additional findings include dysplastic nails, chronic epiphora, stage 3 chronic kidney disease, renal cysts, and a congenital solitary kidney. Germline exome sequencing revealed a *CHEK2* c.1427C>T (p.Thr476Met), classified as a low-risk allele for breast cancer, and an *RTEL1* c.904G>T (p.Asp302Tyr), which is considered a variant of uncertain significance. Family medical history includes the patient's 85-year-old mother with a history of skin cancer, although exome sequencing did not identify *CHEK2* or *RTEL1* variant. Her father and paternal grandfather both died due to colon cancer, but genetic testing results are unavailable to both. Her telomere length was also assessed and found to be in the 10^{th} percentile in both lymphocytes and granulocytes.

Discussion

The *CHEK2* missense variant p.Thr476Met (c.1427C>T) has been shown to be a low-risk allele with an odds ratio less than 1.4 for breast cancer. However, penetrance derived from single-gene analyses may not fully capture cancer susceptibility in individuals harboring additional germline variation affecting genome stability. Variants considered to be low-risk have been demonstrated to contribute to a higher-penetrance phenotype when identified in the context of an additional variant of a separate gene. The *CHEK2* encodes for protein involved in the DNA-repair response (DDR). *RTEL1* encodes a helicase required for disassembly of T-loops and resolution of G-quadruplex structures during S-phase to ensure proper replication fork progression. Although *RTEL1* p.Asp302Tyr remains a variant of uncertain significance, its position within a highly conserved region of the helicase domain raises the possibility of hypomorphic activity. Our interpretation of the results in combination with a clinical presentation consistent with potential telomere pathology point toward the idea that partially impaired *RTEL1* activity can become clinically relevant with concurrent *CHEK2*-mediated DDR. We hypothesize that together, these variants may partially impair telomere maintenance and DDR, creating a cellular environment that could favor the accumulation of structural genomic alterations and contribute to genomic instability. We also raise the notion that incorporating oligogenic models of risk may improve interpretation of rare variants and refine management strategies for complex hereditary cancer syndromes.