Mitochondrial Genetic Variation Orchestrates COPZ1 Transcript Heterogeneity and Reveals Telomere-Mediated Vulnerabilities in Osteosarcoma

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INTRODUCTION: While telomere biology has been implicated in osteosarcoma, potential connections with mitochondrial function remain unexplored despite emerging evidence of bidirectional telomere-mitochondria crosstalk in cancer pathogenesis. Telomere dysfunction can trigger p53-mediated suppression of mitochondrial biogenesis, while mitochondrial dysfunction accelerates telomere attrition, creating potential feedback loops that may influence tumor development. However, whether mitochondrial genetic variation causally contributes to osteosarcoma risk has not been systematically investigated using robust causal inference methods. We investigated causal roles of telomere length and mitochondrial DNA (mtDNA) copy number in osteosarcoma risk using Mendelian randomization and characterized regulatory mechanisms potentially linking these cellular processes through tissue-specific splicing analysis.

METHODS: We performed Mendelian randomization using 94 telomere length-associated and 113 mtDNA copy number-associated variants against FinnGen osteosarcoma statistics. Multiple analytical approaches were employed including inverse variance weighted regression, MR-Egger, weighted median, and MR-PRESSO methods. Splicing quantitative trait loci (sQTL) analysis using GTEx v10 skeletal muscle data identified regulatory variants. Variant Effect Predictor annotation assessed functional consequences. Expression profiling was conducted in GTEx muscle tissue and 212 osteosarcoma samples from Recount3 (SRP090849). Sex distribution data was not available for the osteosarcoma expression samples as Recount3 provides de-identified transcriptomic data without accompanying demographic metadata.

RESULTS SECTION: Using Mendelian randomization, we found that longer telomeres significantly reduced osteosarcoma risk (β= -0.5358, 95% CI: -0.72 to -0.36, p=0.0029). Leave-one-out analysis confirmed this protective effect was consistent across all genetic variants. In contrast, mtDNA copy number showed no causal association with osteosarcoma risk (β= 0.2963, 95% CI: -0.1542 to 0.7468, p=0.511), with consistent null findings across MR-Egger (β= 0.4135, p=0.289) and weighted median (β= 0.1405) approaches. Among 113 mitochondrial variants tested, rs11451044 emerged as a significant skeletal muscle-specific sQTL for COPZ1 (slope= -0.2714, 95% CI: -0.3165 to -0.2263, p<0.001), while rs2853828 showed no splicing association (p=0.403). Variant Effect Predictor analysis predicted that rs11451044 alters splicing or transcript processing across 18 COPZ1 isoforms. Expression analysis in skeletal muscle identified ENST00000262061.7 as the dominant COPZ1 transcript (mean TPM= 48.5), with the next highest isoforms showing substantially lower expression (ENST00000552362: TPM= 5.00; ENST00000455864: TPM= 4.61). In osteosarcoma tumor samples, this primary transcript exhibited expression heterogeneity (range: 18,758-215,617 raw counts; median= 56,599), with an 11.5-fold difference between highest and lowest expressing samples. Comparative analysis revealed COPZ1 expression nearly 3.3-fold higher than its paralog COPZ2 across all statistical measures (median: 50,080 vs 14,902 reads/kb), establishing COPZ1 as the predominant coatomer zeta subunit in metastatic osteosarcoma (Figure 1).

DISCUSSION: The identification of rs11451044 as a functional splicing regulator of COPZ1 reveals how mitochondrial genetic variation modulates stress response pathways critical for osteosarcoma survival. The 3.3-fold expression dominance of COPZ1 over COPZ2 indicates compensatory upregulation responding to the unique metabolic demands of rapidly proliferating tumor cells, where conventional stress buffering mechanisms become overwhelmed [1]. This creates a tumor-specific dependency where enhanced coatomer-mediated trafficking is essential for maintaining cellular viability under proteotoxic and oxidative stress. The underlying telomere-mitochondria crosstalk operates through bidirectional signaling where telomere dysfunction triggers p53-mediated suppression of PGC-1α, creating a feed-forward loop that may drive COPZ1 expression heterogeneity [2]. The selective dependency created by widespread COPZ2 silencing across cancer types establishes a therapeutic vulnerability that could minimize toxicity to normal tissues, particularly relevant given the young patient demographic. Study limitations include reliance on skeletal muscle as proxy tissue for sQTL discovery and lack of direct functional validation. Nevertheless, the isoform-specific regulation provides a foundation for precision therapeutic approaches targeting stress response dependencies unique to aggressive osteosarcoma phenotypes.

SIGNIFICANCE/CLINICAL RELEVANCE: The identification of rs11451044-mediated COPZ1 splicing regulation and the 3.3-fold overexpression of COPZ1 in metastatic osteosarcoma establishes a tumor-specific vulnerability that could enable precision therapeutic targeting while sparing normal tissues. This mechanism provides a potential biomarker-driven approach for developing novel treatments in a disease where conventional therapies have remained largely unchanged for decades, particularly critical given the young patient population and devastating long-term consequences of current cytotoxic regimens.

REFERENCES: [1] Sahin E, Colla S, Liesa M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature. 2011 Feb 17;470(7334):359-65 [2] Sahin E, DePinho RA. Axis of ageing: telomeres, p53 and mitochondria. Nat Rev Mol Cell Biol. 2012 May 16;13(6):397-404.

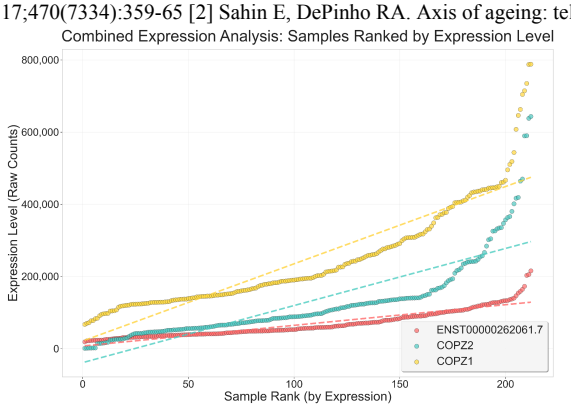

Figure 1. Expression Heterogeneity of COPZ1, COPZ2, and ENST00000262061.7 in Metastatic Osteosarcoma Samples