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A functional *POT1* variant and risk of thyroid subsequent malignant neoplasm: A report from the Childhood Cancer Survivor Study

Short Title:
POT1 and thyroid SMN in CCSS

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Abstract:
Purpose: Reduced telomere content has been associated with an increased risk for subsequent malignant neoplasms of the thyroid (thyroid SMN) in survivors of childhood cancer (PMID 24277454). However, variation in nine common single nucleotide polymorphisms (SNPs) that influence leukocyte telomere length was not associated with thyroid SMN (PMID 30377209). Here, we report results of a candidate gene approach investigating associations between thyroid SMN and genes functionally related to telomere maintenance. **Methods**: Genome-wide SNP data were generated using the Illumina HumanOmni5Exome array in 5,324 5-year survivors of childhood cancer enrolled to the Childhood Cancer Survivor Study (CCSS), and imputed to the 1000 Genomes reference haplotypes. Of these 5,324 survivors, 117 developed thyroid SMN. We mapped 4,290 variants to 18 genes involved in telomere maintenance (*TERC, TERT, RAD50, NHP2, POT1, TERF1, NBN, TPP1, MRE11A, TINF2, NOP10, PARN, ACD, TERF2, RAP1* (*TERF2IP*), *WRAP53, CTC1*, and *RTEL1*) and used RegulomeDB to annotate each variant by its projected functional impact. Time-to-event Cox regression was used for thyroid SMN, censored by date of any SMN, death, or last follow-up. For each functional SNP, hazard ratios (HR) were estimated, adjusting for sex, primary cancer diagnosis, neck radiation exposure (yes/no), alkylating agent exposure (yes/no), and thyroid nodules. **Results:** Our analysis included 103 SNPs with a RegulomeDB score ≤ 2, signifying high likelihood for affecting transcriptional regulation. After Bonferroni correction (α=0.000485), an imputed variant in an intronic region of *POT1* (Protection of Telomeres 1), rs58722976 (CCSS minor allele frequency = 0.2%), was associated with risk for thyroid SMN (adjusted HR=6.1, 95% CI: 2.4, 15.5, p=0.0001) and was present in 3 cases and 14 controls. **Conclusions:** Using a candidate gene approach, we observed an association between an intronic regulatory *POT1* variant and risk for thyroid SMN in survivors. *POT1* is a highly conserved gene encoding a key component of the

shelterin complex, which protects telomere ends against DNA damage recognition and facilitates telomerase-mediated telomere elongation. The ENCODE Consortium identifies rs58722976 as a strong enhancer and DNase in multiple tissues, including the hematopoietic compartment. ENCODE ChIP-Seq data suggest that rs58722976 genotypes also affect protein binding of RAD21, SMC3, and CTCF, components of cohesin and a co-localizing protein that play key roles in maintaining genomic integrity. Germline variants in *POT1* have been described in familial glioma, melanoma, colorectal cancer, chronic lymphocytic leukemia, and non-*TP53* familial cancer syndromes. The results of this study suggest that intronic variation in *POT1* may affect key protein binding interactions related to defects in telomere maintenance and affecting genomic integrity.
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