Germline mutations in the telomere gene POT1 are associated with long telomere length and risk of lymphoid malignancies

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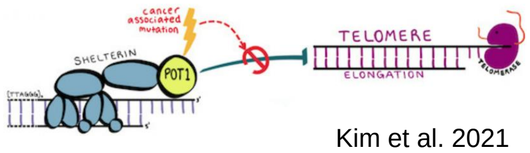
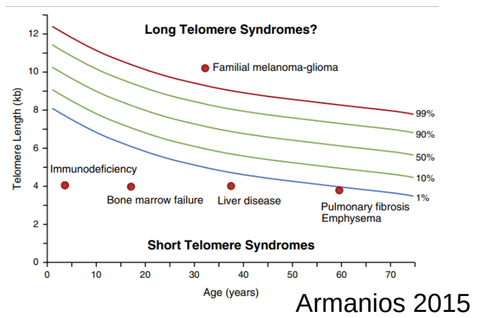
BACKGROUND

- POT1 is a member of the shelterin complex, involved in capping telomeres and regulating telomerase activity
- Heterozygous mutations in POT1 are associated with longer telomere length and with melanoma and glioma



Kim et al. 2021



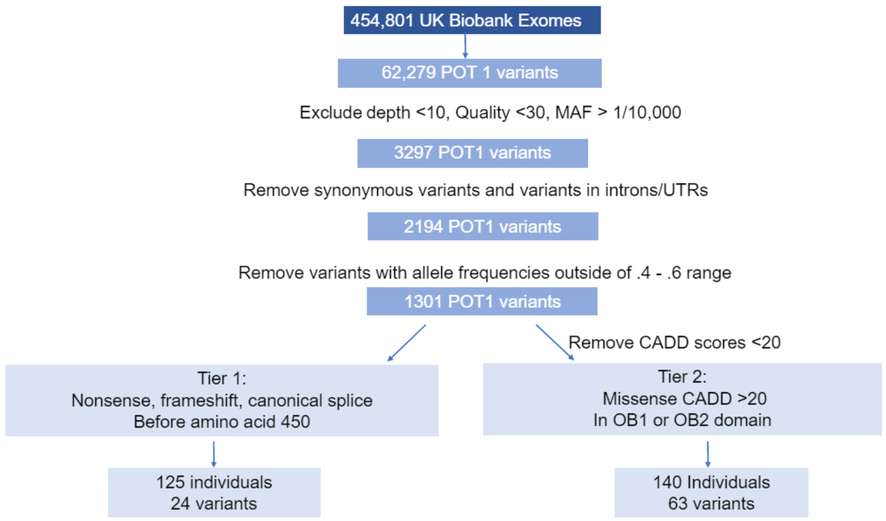
Armanios 2015

STUDY OBJECTIVE

- To determine the spectrum of cancers seen in individuals with pathogenic germline POT1 mutation

METHODS

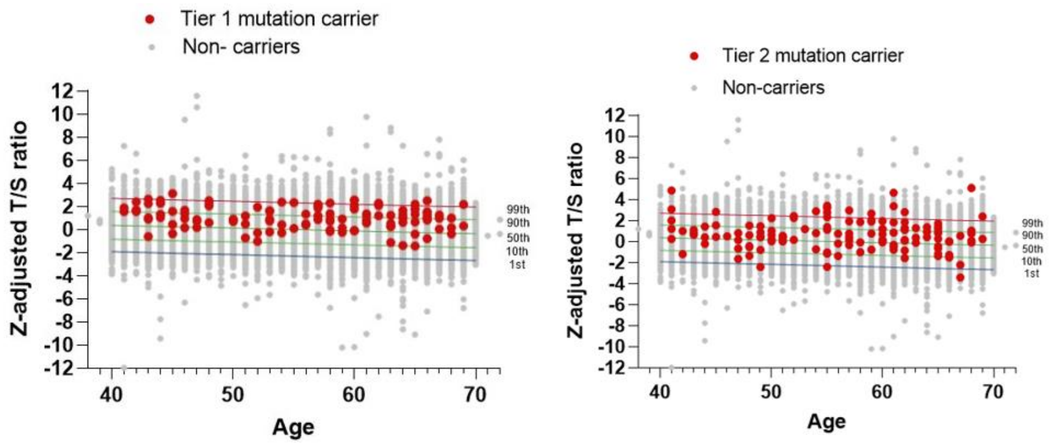
- Study Design: Database retrospective cohort study
- Population: UK Biobank population: 40-69 year-olds from the UK
  - Filtered to include only those with pathogenic POT1 mutations



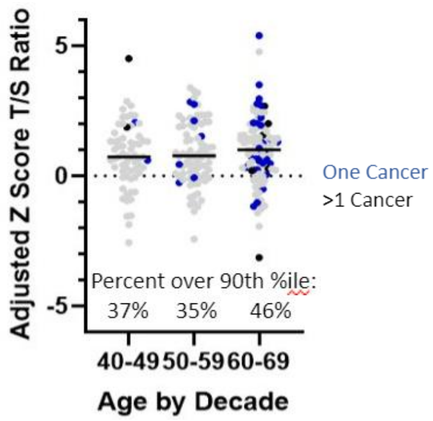
- Main Outcomes: Cancer diagnoses and telomere lengths of POT1 mutation carriers

RESULTS

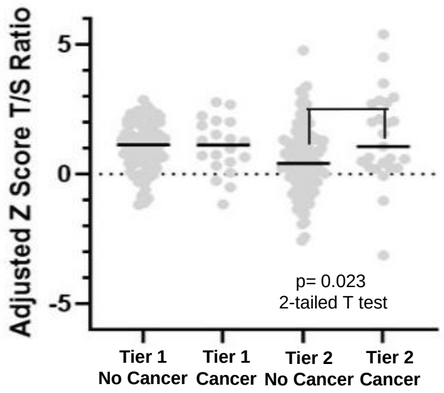
Tier 1 mutation telomeres are longer than Tier 2



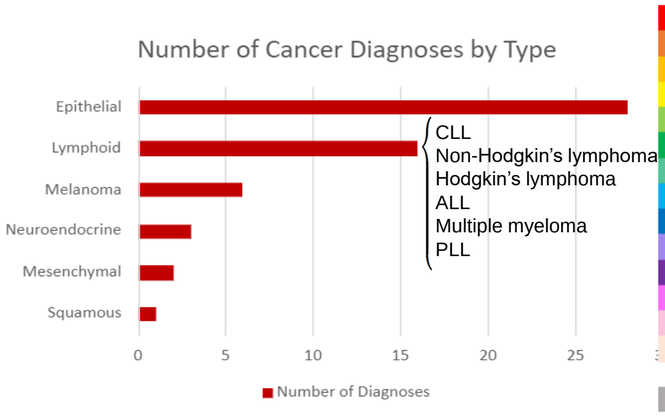
POT1 mutation carriers have telomeres ~1 SD longer than the median (p<.0001)

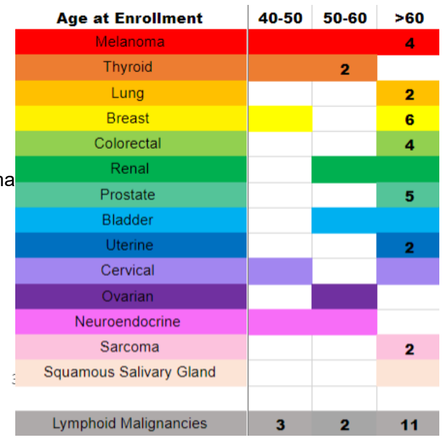


Longer telomeres are associated with an increased cancer risk



Cancer spectrum encompasses melanoma and lymphoid malignancies





CONCLUSIONS

- Almost 20% of UK Biobank POT1 mutation carriers had a malignancy (unadjusted)
- Among POT1 mutation carriers with cancers, lymphoid cancers were most common 16/49 (33%)
- Age and long telomere length are risk factors for malignancy development

LIMITATIONS

- UK Biobank Healthy Volunteer Bias
- Tier 1 POT1 mutations very rare, limits sample size
- New POT1 mutations would not impact telomere length due to genetic anticipation

IMPLICATIONS

- Although long telomere length extends cellular lifespan in vitro, it appears to promote clonal evolution that may lead to lymphoid malignancies in POT1 mutation carriers
- Further work is needed to characterize which malignancies are enriched in the POT1 mutation population compared to the general public