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RE: The Effect on Melanoma Risk of Genes Previously Associated With Telomere Length

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In a recent report by Iles et al. (1), the effects of loci associated with telomere length (TL) were tested on melanoma risk and statistically significant enrichment of association was discovered. Nevertheless, genetically regulated causal effects between TL and melanoma were not investigated.

Several observational studies have reported that telomere length (TL) was longer in patients with melanoma (2–4). However, these studies collected a fairly small number of case patients, and only a limited number of adjustments were made for possible confounders such as age and sex. Results from these studies are prone to confounding and reverse causation, which make it difficult to determine whether TL was one of the causal factors involved in melanoma pathogenesis.

Based on the large-sample summary statistics reported by Iles et al. (1), we conducted Mendelian randomization (MR) analysis using the seven previously replicated TL-causal variants (5): rs10936599, rs2736100, rs7675998, rs9420907, rs8105767, rs755017, and rs11125529, which offered more statistical power and efficiency than a single variant. The seven single-nucleotide polymorphisms (SNPs) were used as instrumental variables (IVs) and combined into a genetic risk score (GRS) in our MR analysis. The causal effect of TL on melanoma, β_{IV}, using each SNP as IV was calculated by dividing each SNP effect on melanoma, β_{SNP_M}, by the effect of the same SNP on TL, β_{SNP_TL}:

$$\beta_{IV} = \frac{\beta_{SNP\_M}}{\beta_{SNP\_TL}}$$

The standard error (SE) of the IV estimator was calculated as:

$$SE_{IV} = abs(\beta_{IV})\sqrt{\left(\frac{SE_{SNP\_TL}}{\beta_{SNP\_TL}}\right)^2 + \left(\frac{SE_{SNP\_M}}{\beta_{SNP\_M}}\right)^2}$$

In order to obtain the pooled estimate of the causal effect of TL on melanoma, we calculated the effect of the GRS based on the seven SNPs using the inverse variance weighted method (6). The GRS was statistically significantly associated with longer TL (β = 0.07, 95% confidence interval [CI] = 0.06 to 0.08) and higher risk of melanoma (odds ratio [OR] = 1.05, 95% CI = 1.03 to 1.07). MR analysis showed that longer TL causes higher risk of melanoma (OR = 2.08, 95% CI = 1.82 to 2.38). The MR-estimated TL effects on melanoma were given and visualized in Figure 1.

Extending the report by Iles et al. (1), we established a causal effect of longer TL on higher risk of melanoma using MR applied to summary-level data. To the best of our knowledge, this provides the first evidence of a causal role of TL in the pathogenesis of melanoma. We found that one standard deviation increase of leukocyte TL would double the risk of melanoma. Our analysis was mainly limited by the MR assumption that all the genetic effects of the seven loci on melanoma risk are mediated through TL. Unfortunately, there is by far no valid statistical test to examine this assumption with sufficient power. However, we checked the functions of these genetic variants as much as we can and found the no pleiotropic assumption could probably hold, therefore it is likely that the observed genetic effects on melanoma were mediated through TL.

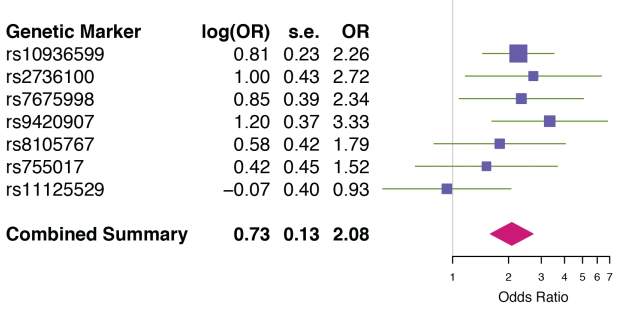

Figure 1. Meta-analysis of the Mendelian randomization telomere length effect on melanoma given the genetic risk score. Ninety-five percent confidence intervals (shown in **error bars**) of the odd ratios (OR;, shown in **boxes**) were calculated based on log(OR) and its standard error (s.e.). The size of each **box** represents the weight of the corresponding marker in the meta-analysis. The **diamond** shows the summarized meta-estimate and its 95% confidence interval (**error bars**).

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The authors declare no conflicts of interest.

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