The effect on melanoma risk of genes previously associated with telomere length

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Supplementary Material

Supplementary Methods

Note on associations of variants in the TERT region with cancer risk

The C allele of rs401681 has been associated with shorter telomere length and increased risk of cancer of the lung, urinary bladder, prostate, cervix and basal cell carcinoma (1,2), but decreased risk of melanoma (3), pancreatic cancer (4) and, less statistically significantly, colorectal cancer ($p=8.4x10^{-3}$) (1). The minor allele (A) of rs7726159, which is associated with increased telomere length, is associated with increased risk of breast and ovarian cancer, but a decreased risk of prostate cancer (5). The G allele of rs2736100 is associated with longer telomere length (6) and confers an increased risk of glioma (7) and lung adenocarcinoma (8,9), but is protective for testis cancer (10) and probably colorectal cancer ($p=2.5x10^{-5}$) (11). The minor allele at rs2736108 is associated with longer telomeres and is protective against a subtype of breast cancer while the minor allele at rs7705526 is associated with longer telomeres and higher risk of subtypes of ovarian cancer (12). The

minor alleles of rs10069690 and rs2242652 increase risk of subtypes of breast and ovarian cancer, but have no apparent effect on telomere length (12). Thus we see that variants in *TERT* demonstrate increased risk for basal cell carcinoma and cancer of the lung, urinary bladder, prostate and cervix. The same variants are protective against melanoma, testis cancer, pancreatic cancer and, quite likely, colorectal cancer. The effect on breast and ovarian cancer is less clear and seem to depend on cancer subtype.

Samples and Genotyping

GenoMEL

Phase 1 of the original GenoMEL GWAS consisted of cases and controls collected from 8 centers across 6 different European countries. Standard quality control (QC) measures were applied to both samples and SNPs, giving a total of 1,353 cases and 3,571 controls. Most GenoMEL Phase 1 samples were genotyped on the Illumina HumanHap300 BeadChip version 2 duo array (with 317k tagging SNPs), with the exception of the French cases, which were genotyped on the Illumina HumanCNV370k array.

Phase 2 of the GenoMEL GWAS consisted of cases and controls from 10 centers (4 not in Phase 1) in 8 different European countries and Israel, supplemented with controls from the Wellcome Trust Case Control Consortium (WTCCC) (13). In both phases cases were preferentially selected to have a family history of melanoma, multiple primary tumours or an early

age of onset. After QC 1,450 cases and 2,668 controls remained (see (3) for details of QC and samples). The GenoMEL Phase 2 samples were genotyped on the Illumina 610k array.

UK Data

1,085 cases from Leeds and 1,392 from Cambridge (UK) were matched with controls from the WTCCC. The Leeds cases were obtained from a population-based study of incident melanoma cases diagnosed between September 2000 and December 2012 from a geographically defined area of Yorkshire and the Northern region of the UK (14,15,16). Controls were ascertained by contacting general practitioners (family doctors) to identify eligible individuals. These controls were frequency-matched with cases for age and sex from general practitioners who had also had cases as part of their patient register. A further 220 controls were sex- and age-matched and from the same primary care practice as incident cases of colorectal cancer recruiting from hospitals in Leeds (17). The Cambridge cases were recruited as part of the SEARCH study (18,19), an ongoing population-based study in Eastern England. Cases were ascertained through the Eastern Cancer Registry and Information Centre, and were aged between 18 and 70 years at diagnosis. All cases were genotyped on the Illumina HumanOmniExpressExome-8 v1.0. Controls are taken from the WTCCC.

In all the studies included here, written informed consent was obtained from each subject and the investigations were performed after approval by the

institutional review board for each recruiting center.

Houston (M.D. Anderson)

931 cutaneous melanoma (CM) non-Hispanic white patients were recruited together with 1,026 cancer-free controls (friends or acquaintances of patients reporting to other clinics at the M.D. Anderson Cancer Center) frequency matched on age and sex. These were supplemented with an additional 873 individuals presenting for treatment for CM at MD Anderson which did not have BMI recorded. All samples were collected between March 1998 and August 2008.

Samples were genotyped using the Illumina HumanOmni1-Quad_v1-0_B array and called using the BeadStudio algorithm. No adjustment was made for ethnicity as the genomic inflation factor was 1.02. Data were analysed by regressing case-control status on genotype (coded according to an additive model). This study has been previously published (20) and a more detailed description of the QC procedures applied to these data can be found there.

Australia

Cases were genotyped on Illumina Omni1-Quad or HumanHap610 while controls were genotyped on Illumina Omni1-Quad or HumanHap610 or HumanHap670 (21). A more detailed description of the QC procedures applied to these data can be found in a previous publication (21).

AMFS: 549 cases collected by the Australian Melanoma Family Study (AMFS) (22), whose recruitment occurred from 2001-2005 and case probands identified from population-based state cancer registries. 430 control probands were selected from the electoral roll and frequency-matched to cases by city, age and sex. Blood was requested from all probands. A 20ml blood sample was collected in EDTA tubes by local pathology services and transported to a central laboratory in Sydney within 48h of collection. White blood cells were separated on a Ficoll gradient and plasma obtained by centrifugation, and stored at -70ºC. Guthrie Spots were obtained from 1ml blood. Remaining blood was used for DNA extraction. Buccal swabs were collected from participants who did not wish to give blood. All AMFS case probands and population control probands were aged between 18-39 years inclusive.

QMEGA: 1,617 Australian melanoma cases of European descent were collected through the Queensland study of Melanoma: Environment and Genetic Associations (Q-MEGA) (23) The combined 4342 controls represent 3 control sets: 1,799 unrelated individuals from the Brisbane Adolescent Twin Study (21,24), 2,155 endometriosis patients recruited by QIMR Berghofer Medical Research Institute (QIMR) from 1995 to 2002 (25); and 553 healthy controls from the Study of Digestive Health (SDH)recruited through the Genomics Research Centre (Griffith University, Queensland, Australia) (26).

Western Australia: 1,253 melanoma cases of European descent recruited through the Western Australian Melanoma Health Study (WAMHS) (27) were

combined with 898 controls, who were Australian Caucasian participants from a Inflammatory Bowel disease study (593 controls, 96 mild ulcerative colitis, 176 with severe ulcerative colitis, 33 with Ulcerative Colitis NOS) recruited from the IBD Clinical and Research Programme at the Royal Brisbane & Women's Hospital (RBWH), Brisbane, Queensland (28).

French Data

535 French melanoma cases and 856 French controls were genotyped using the Illumina Human660W-Quad array at the Centre National de Genotypage (CNG, Evry, France). The melanoma patients and controls came from the same collections as those included in Genomel, the French MELARISK collection for the patients (29) and the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) study for the controls (30). Quality control procedures applied to these data were similar to those previously described (3).

Imputation

Imputation was conducted genome-wide on the GenoMEL Phase 1 samples, excluding SNPs with MAF<0.03 (or in some studies MAF<0.01), HWE p-value<10^{-4} (in controls) and missingness >0.03. IMPUTEv2 (31,32) was used and the reference panel used was 1000 Genomes Phase 1 integrated variant set (March 2012 release, excluding SNPs with MAF<0.001 in the CEU European samples). rs10936599 (*TERC*) was genotyped in all samples, while

the remaining 6 SNPs were imputed in at least some samples, with INFO>0.97 in all studies. We note that the telomere GWAS data (33) are imputed from a much smaller reference panel (HapMap2: 3.1M SNPs in 270 individuals, 30 of them European trios) than the melanoma reference panel (1000 Genomes Phase 1 integrated variant set: 38M SNPs, 1092 individuals, 500 of them European) and the authors themselves note particular problems with imputation in the *TERT* region. Of the three regions (*TERT*, *OBFC1* and *RTEL1*) where a much more statistically significant melanoma hit is found close to the telomere hit, the top melanoma hit is not present in the HapMap2 reference panel. The LD between the most statistically significant telomere SNP and the most statistically significant melanoma SNP is quite high in *TERC* (r^2=0.77), *OBFC1* (r^2=0.66) and *RTEL1* (r^2=0.003, but D'=0.47, suggesting that the LD is reasonably high given the difference in allele frequencies). LD is weaker in *TERT* (r^2=0.02, D'=0.16), but then LD is generally low across the *TERT* region and there is good evidence that multiple causal loci may exist (12). In other words, the level of LD between the telomere and melanoma hits and the absence of the most statistically significant melanoma SNPs in HapMap2 suggest that the telomere length meta analysis and the melanoma study may be identifying the same underlying signal in each region.

Statistical Analysis

For the single SNP analysis, imputed genotypes were analysed as expected genotype counts based on the posterior probabilities (gene dosage) using

SNPTEST2 (34) assuming an additive model (two-sided). For the telomere score analysis, melanoma case-control status was regressed in a logistic regression on the telomere score (two-sided significance reported). In both analyses the European samples were analysed as four separate datasets (GenoMEL Phase 1, Phase 2, UK (Leeds and Cambridge) data, French data), the US data as a single dataset and the Australian data as four separate datasets (AMFS, QMEGA-610k, QMEGA-Omni, WAMHS). For the analysis of GenoMEL Phase 1 and 2 data, geographical region was included as a covariate as has been done previously (14). In addition adjustment for principal components was applied to all datasets but made little difference to the results (the French data were slightly less statistically significant and the US and Australian datasets slightly more statistically significant), so were not used in the final analysis. All datasets were combined using an inverse weighted fixed effects meta analysis, with the exception of rs2736100 and rs7675998 which showed evidence of heterogeneity (I^2=0.63 and 0.34, respectively). These two were combined using the method of Dersimonian and Laird (35) to estimate the between-studies variance, $\hat{\tau}^2$. An overall random effects estimate was then calculated using the weights $1/(v_i + \hat{\tau}^2)$ where v_i is the variance of the estimated effect.

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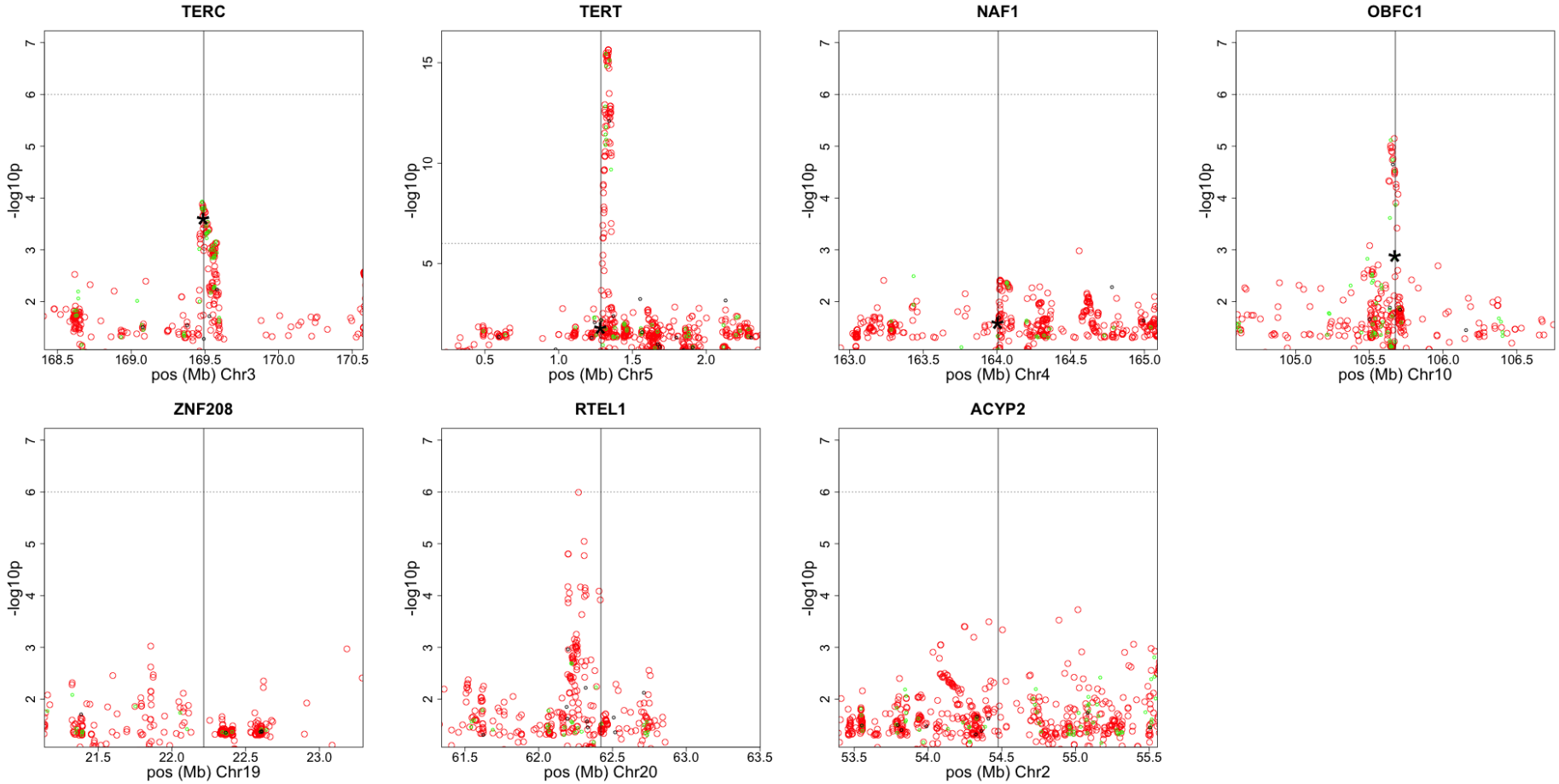
Supplementary Tables

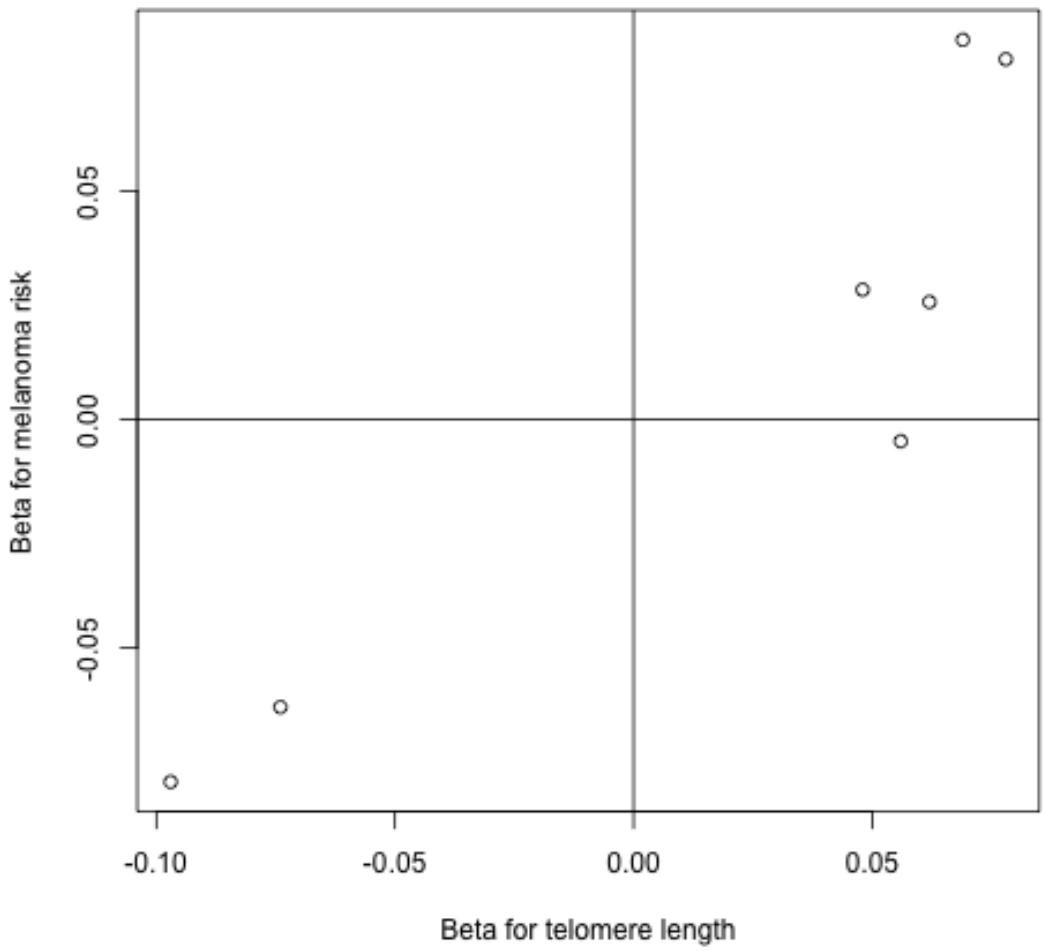
Supplementary Table 1 Numbers of cases and controls from each study

	Cases	Controls
GenoMEL Phase 1	1,354	2,341
GenoMEL Phase 2	1,450	1,399
UK data	2,570	2,682
Houston	1,804	1,026
AMFS	549	430
QMEGA	1,617	4,342
Western Australia	1,253	898
France	511	815
Total	**11,108**	**13,933**

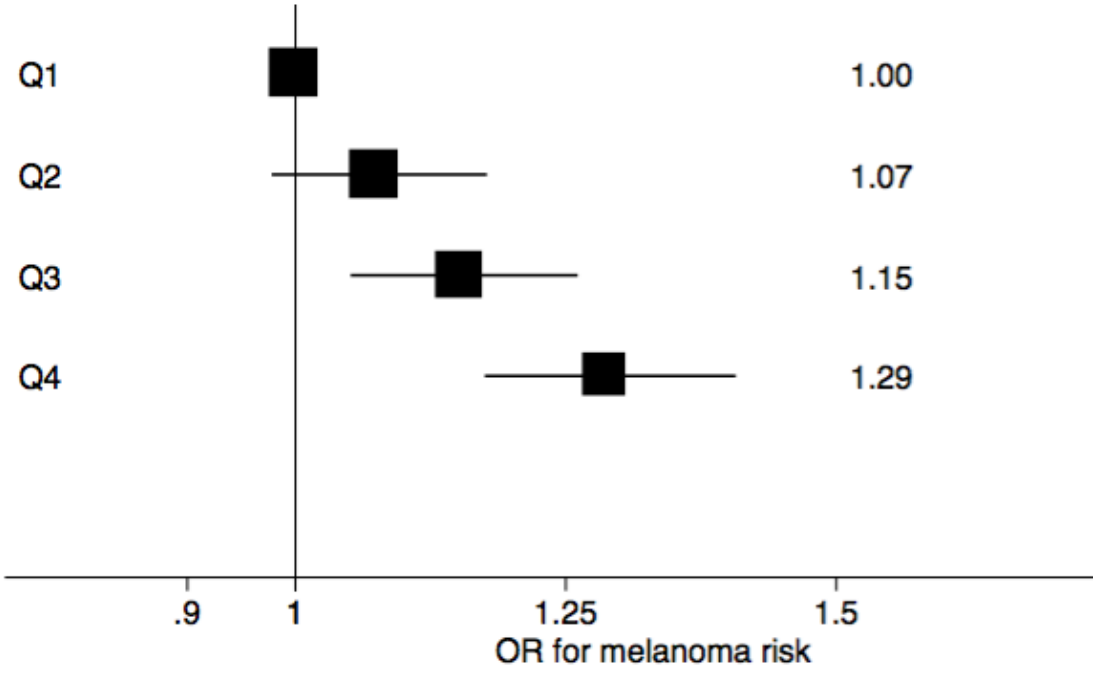
Supplementary Figures



Supplementary Figure 1. Manhattan plots of association with melanoma risk 1 megabase (Mb) either side of the strongest SNP at each telomere-associated locus. SNPs that were genotyped in the all studies in the melanoma GWAS are idicated by black circles, those that were imputed in all studies by red circles and those that were genotyped in some and imputed in others by green circles. The location of the telomere-associated SNP is indicated by a vertical line. The SNP itself is marked with an asterisk if it reached $p<0.05$ (otherwise it is absent). The y-axis ranges from 0 ($p=1$) to 7 ($p=10^{-7}$) except for the TERT plot where SNPs in the region reached far higher statistical significances. Results based on meta-analysis of two-sided results from SNPTEST2 (34) using gene dosage and assuming an additive model. Chromosome (Chr) indicated on the x-axis of each plot.



Supplementary Figure 2. Estimated effect of each telomere-asociated SNP on telomere length (beta from linear regression) plotted against estimated effect on melanoma risk (beta from logistic regression).



Supplementary Figure 3. Plot showing effect of telomere score on melanoma risk. Here the telomere score is divided into quartiles and melanoma case-control status regressed on the resulting categorical variable with the lowest quartile (by telomere length) as the baseline. This analysis does not include the Australian data. 95% confidence interval is indicated by horizontal bars, relative sample size of each group is indicated by the size of the squares. Exact odds ratios (ORs) are given in the right hand column.

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