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Genetically predicted telomere length is not associated with pancreatic cancer risk

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Abstract

Background—Epidemiologic associations of leukocyte telomere length (LTL) and pancreatic ductal adenocarcinoma (PDAC) have been inconsistent owing, in part, to variation in telomere length (TL) assessment across studies. To overcome this limitation and address concerns of potential reverse causation, we used carriage of telomere-related alleles to genetically predict TL and examined its association with PDAC.

Methods—A case-control study of 1,500 incident PDAC cases and 1,500 controls, frequency-matched on age and sex was performed. Eight of nine single nucleotide polymorphisms (SNPs) previously associated with variation in LTL were analyzed. Genetic risk scores (GRS) consisting of the TL-related SNPs were computed as the number of long TL alleles carried by an individual scaled to published kilobase pairs of TL associated with each allele. Participants were further categorized based on the number of short TL alleles they carry across all eight SNPs. Associations were examined in additive and dominant models using logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results—In age- and sex-adjusted models, one short TL allele (rs10936599, T) was associated with reduced risk, whereas another short TL allele (rs2736100, A) was associated with increased risk, with per-allele ORs of 0.89 (95% CI: 0.79–0.99) and 1.13 (95% CI: 1.01–1.24), respectively. No association was observed with GRS or short TL allele counts, and no associations were observed in the dominant models.

Conclusions—The findings suggest that genetically predicted short TL is not associated with PDAC risk.

Impact—Common genetic determinants of short TL do not appear to influence PDAC risk.

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Compliance with Ethical Standards: Written informed consent was obtained from all participants. The study was approved by the Mayo Clinic Institutional Review Board.

Conflict of interest: The authors do not have any conflicts of interest related to this study.

Keywords

Telomeres; telomere length; telomere genes; pancreatic cancer; pancreatic ductal adenocarcinoma

Introduction

Telomere length (TL), the repetitive DNA sequence (TTAGGG) that spans the ends of linear chromosomes, protect genetic material from degradation, prevent end-to-end fusion, and ensure proper chromosomal segregation (1). Variation in TL can result from individual differences in demographic, genetic, and lifestyle factors. Blackburn *et al.* estimated that as much as 80% of inter-individual variation in TL is attributable to genetic factors (1). Epidemiologic studies have reported conflicting results for association between leukocyte TL (LTL) and pancreatic ductal adenocarcinoma (PDAC) (reviewed in (2)). Long LTL was associated with increased PDAC risk in one prospective study, but reduced risk in another, and a "U-shape" association was reported by one case-control and one prospective study (2). In light of the conflicting findings, we genotyped nine single nucleotide polymorphisms (SNPs) that have been associated with variation in LTL to predict TL and examined its association with PDAC.

Methods

Following approval by the Mayo Clinic Institutional Review Board, epidemiologic data and leukocyte DNA were obtained from the Mayo Clinic pancreatic cancer patient registry (http://tinyurl.com/MayoClinicPancreasResearch). The registry utilizes an ultra-rapid case ascertainment process for prospective patient recruitment. Previously enrolled non-cancer control patients by the registry were frequency-matched to incident PDAC cases on age and sex. The study included 1,500 cases and 1,500 controls enrolled between October 2000 and June 2016. Participants completed risk factor questionnaires that solicited various information including demographics, smoking history, personal history of diabetes, and usual adult weight and height.

Genotyping of the leukocyte DNA was performed by the Mayo Clinic Genome Analysis Core. Nine SNPs previously associated with variation in LTL (Table 1) were genotyped using the Sequenom multiplex assay. Genotyping call rates and concordance with blinded duplicates were 100% each. Hardy-Weinberg equilibrium among controls was violated for one SNP (rs755017, p-value<0.05). This SNP was eliminated from further analyses. One control sample failed genotyping, leaving 1,500 cases and 1,499 controls for analyses.

Per-allele odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with logistic regression, using alleles previously associated with long LTL as the referent alleles. Genetic risk scores (GRS) were computed by combining data on all eight TL-related SNPs and calculated according to published β-estimates of kilobase pairs of LTL associated with each allele, as described (3). The GRS were categorized into quartiles (based on control distribution), using the lowest quartile as the referent group. Participants were further categorized according to the number of short TL-associated alleles they carry. We explored associations of LTL-related SNPs and short TL allele counts in dominant models:

participants with one or two copies of the short TL allele were combined into one group and compared with those who carry two copies of the long TL allele. Analyses were performed in SAS® (v9.4).

Results

By design, the cases and controls were similar in age and sex (Supplementary Table 1). There were greater proportion of current smokers, individuals with personal history of diabetes, and a slightly higher BMI among cases than controls (28 *vs.* 27 kg/m^2). After adjusting for age and sex, the short TL-associated allele of rs10936599 was associated with lower PDAC risk (OR=0.89, 95% CI: 0.79–0.99), while the short TL-associated allele of rs2736100 was associated with higher risk (OR=1.13, 95% CI: 1.02–1.24) (Table 2a). None of these associations remained significant after additional adjustment for diabetes, smoking, and BMI. No associations were observed with GRS or short TL allele counts. Similarly, no associations were observed in the dominant models (Table 2b).

Discussion

Epidemiologic studies of LTL and PDAC risk have yielded mixed results (2). This may be due to differences in the studied populations (e.g., heavy smokers (4) *vs.* population with < 15% smoking prevalence (5)), inter-laboratory variation in LTL measurement, differences in the time between blood collection and cancer diagnosis, or a combination of these factors. To help clarify the conflicting reports, we used TL-related SNPs to genetically predict TL and examined association with PDAC. In age- and sex-adjusted models, short TL-associated alleles of rs10936599 and rs2736100 had opposite associations with PDAC risk. Results from GRS and short TL allele counts were null.

Our sample had sufficient statistical power to detect an association at the 0.05 significance level. Based on 1,500 cases and 1,499 controls we had >80% to detect an OR of 1.20 in the dominant model with three categories of short TL allele counts (Table 2b). Although validation in a consortium setting may be warranted, the findings indicate that genetically predicted TL is not associated with PDAC. LTL may represent an integrative biological marker of long-term exposure to risk factors of PDAC (e.g., smoking, obesity, and diabetes). Thus, further delineation of the association between LTL and PDAC, using current industry standard methods (e.g., monochrome multiplex quantitative PCR) to measure TL in longitudinal studies, with multiple measures at biologically relevant stages in life may provide new insights.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	confidence intervals
GRS	genetic risk scores
LTL	leukocytes telomere length
OR	odds ratio
PDAC	pancreatic ductal adenocarcinoma
SNPs	single nucleotide polymorphisms
TL	telomere length

Table 1

Polymorphic variants associated with leukocyte telomere length in genome-wide association studies, and minor allele frequencies in the present study.

SNP ID	Position (GRCh37/hg19)	Nearby gene	Short Allele	Long Allele [a]	MAF	Published β[b]	Published p-value	Reference paper	MAF controls [c]
rs10936599	chr3:169492101	TERC	T	C	0.25	0.117	2.5×10^{-31}	Codd (6)	0.261
rs2736100	chr5:1286516	TERT	A	C	0.49	0.094	4.4×10^{-19}	Codd (6)	0.492
rs7675998	chr4:164007820	NAF1	A	G	0.22	0.090	4.3×10^{-16}	Codd (6)	0.210
rs9420907	chr10:105676465	OBFC1	A	C	0.14	0.083	6.9×10^{-11}	Codd (6)	0.143
rs6772228	chr3:58376019	PXK	A	T	0.05	0.120	3.9×10^{-10}	Pooley (7)	0.048
rs8105767	chr19:22215441	ZNF208	A	G	0.30	0.058	1.1×10^{-9}	Codd (6)	0.295
rs755017*	chr20:62421622	RTEL1	A	G	0.12	0.074	6.7×10^{-9}	Codd (6)	0.004
rs11125529	chr2:54475866	ACYP2	C	A	0.14	0.067	4.5×10^{-8}	Codd (6)	0.140
rs3027234	chr17:8136092	CTC1	T	C	0.23	0.057	2.3×10^{-8}	Mangino (8)	0.231

[a] Allele associated with longer leukocytes telomere length

[b] β-estimate is reported in kilobase pairs per long telomere length allele

[c] MAF, minor allele frequencies among controls in the present study (n= 1,499)

* This polymorphism was not in Hardy-Weinberg equilibrium (p-value <0.05) and was excluded from the analysis.

Table 2a

Associations of telomere-related SNP, genetic risk scores, and short telomere length allele counts with pancreatic cancer risk: Additive model (cases: n=1,500; controls: n=1,499)

		Unadjusted model		Age- and sex-adjusted		Multivariable-adjusted [a]	
SNP ID	**MAF**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
rs10936599	0.261	0.89 (0.79, 0.99)	0.044	**0.89** (0.79, 0.99)	**0.046**	0.94 (0.83, 1.06)	0.294
rs2736100	0.492	1.12 (1.01, 1.24)	0.023	**1.13** (1.02, 1.24)	**0.021**	1.09 (0.99, 1.22)	0.100
rs7675998	0.210	1.03 (0.91, 1.17)	0.621	1.03 (0.91, 1.17)	0.599	1.05 (0.93, 1.20)	0.459
rs9420907	0.143	0.98 (0.85, 1.13)	0.775	0.98 (0.85, 1.13)	0.763	1.02 (0.88, 1.18)	0.838
rs6772228	0.048	1.15 (0.91, 1.45)	0.242	1.15 (0.91, 1.45)	0.245	1.09 (0.85, 1.40)	0.477
rs8105767	0.295	1.02 (0.91, 1.13)	0.763	1.02 (0.91, 1.14)	0.752	1.02 (0.92, 1.15)	0.690
rs11125529	0.140	1.02 (0.88, 1.18)	0.773	1.02 (0.88, 1.18)	0.787	1.00 (0.86, 1.16)	0.975
rs3027234	0.231	1.03 (0.91, 1.16)	0.662	1.03 (0.91, 1.15)	0.677	1.04 (0.92, 1.18)	0.500
GRS Quartiles	Case: control						
1: ≤ 0.473	378: 370	1.00 (ref)	0.588	1.00 (ref)	0.585	1.00 (ref)	0.556
2: > 0.473 - ≤ 0.567	337: 368	0.90 (0.73, 1.10)		0.90 (0.73, 1.10)		0.90 (0.73, 1.12)	
3: > 0.567 - ≤ 0.662	385: 372	1.01 (0.83, 1.24)		1.01 (0.83, 1.24)		1.04 (0.84, 1.28)	
4: > 0.662	383: 369	1.02 (0.83, 1.24)		1.02 (0.83, 1.25)		1.04 (0.84, 1.29)	
Continuous [b]		1.02 (0.97, 1.07)	0.492	1.02 (0.97, 1.07)	0.483	1.03 (0.97, 1.08)	0.325
Short Allele Counts [c]							
2-6	434: 435	1.00 (ref)	0.137	1.00 (ref)	0.137	1.00 (ref)	0.117
7	329: 369	0.89 (0.73, 1.09)		0.89 (0.73, 1.09)		0.88 (0.71, 1.09)	
8	362: 315	1.15 (0.94, 1.41)		1.15 (0.94, 1.41)		1.16 (0.94, 1.43)	
≥ 9	358: 360	1.00 (0.82, 1.21)		1.00 (0.82, 1.23)		1.02 (0.82, 1.25)	
Continuous [b]		1.02 (0.98, 1.07)	0.380	1.02 (0.98, 1.07)	0.375	1.03 (0.98, 1.07)	0.264

[a] Adjusted for age (continuous), sex, self-reported personal history of diabetes (yes, no), smoking history (never, former, current), and usual adult body mass index (continuous)

[b] Calculated as per 0.10 increase in kilobase pair of telomere length or per 1 short TL allele

[c] Allele counts were categorized based on distribution among controls. Lower “short allele count” values predict longer telomere length (3).

Abbreviations: CI, confidence interval, GRS, genetic risk score, MAF, minor allele frequency (among controls), OR, odds ratio, SNP, single nucleotide polymorphism

Table 2b

Associations of telomere-related SNP and short telomere length allele counts with pancreatic cancer risk: Dominant model (cases: n=1,500, controls: n=1,499)

	Long-allele genotype [a]	Short-allele genotypes [b]	Unadjusted model		Age- and sex-adjusted		Multivariable-adjusted [c]	
SNP ID	**Case: control**	**Case: control**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
rs10936599	872: 826	627: 670	0.88 (0.76, 1.02)	0.097	0.89 (0.77, 1.02)	0.101	0.95 (0.81, 1.11)	0.507
rs2736100	352: 385	1136: 1097	1.14 (0.96, 1.35)	0.126	1.14 (0.97, 1.35)	0.121	1.12 (0.94, 1.34)	0.196
rs7675998	927: 931	570: 563	1.02 (0.88, 1.18)	0.835	1.02 (0.88, 1.18)	0.813	1.03 (0.88, 1.20)	0.718
rs9420907	35: 35	1465: 1461	1.00 (0.62, 1.61)	0.991	1.00 (0.62, 1.61)	0.999	0.98 (0.60, 1.63)	0.953
rs6772228	1,338: 1,352	161: 144	1.14 (0.90, 1.44)	0.288	1.14 (0.90, 1.44)	0.290	1.08 (0.84, 1.39)	0.541
rs8105767	129: 147	1369: 1348	1.15 (0.90, 1.48)	0.271	1.15 (0.90, 1.48)	0.268	1.15 (0.89, 1.50)	0.285
rs11125529	35: 34	1464: 1462	1.00 (0.62, 1.62)	0.991	1.00 (0.62, 1.62)	0.994	0.93 (0.56, 1.53)	0.770
rs3027234	876: 894	618: 601	1.04 (0.90, 1.21)	0.565	1.04 (0.90, 1.21)	0.574	1.07 (0.92, 1.25)	0.362
Short Allele Count [d]		Case: control						
2-4		491: 506	1.00 (ref)		1.00 (ref)		1.00 (ref)	
5		546: 541	1.04 (0.88, 1.24)	0.654	1.04 (0.88, 1.24)	0.648	1.04 (0.86, 1.24)	0.702
>6		446: 432	1.06 (0.89, 1.28)	0.503	1.07 (0.89, 1.28)	0.494	1.11 (0.92, 1.35)	0.280
Continuous [e]			1.03 (0.96, 1.10)	0.419	1.03 (0.96, 1.10)	0.408	1.04 (0.97, 1.12)	0.228

[a] Referent group for calculation of odds ratio estimates

[b] Patients with one or two copies of the minor allele were combined into one group

[c] Adjusted for age (continuous), sex, self-reported personal history of diabetes (yes, no), smoking history (never, former, current), and usual adult body mass index (continuous)

[d] Allele counts were categorized based on distribution among controls. A lower value of “short allele counts” predicts longer telomere length (3).

[e] Per 1 short TL allele

Abbreviations: CI, confidence interval, GRS, genetic risk score, MAF, minor allele frequency (among controls), OR, odds ratio, SNP, single nucleotide polymorphism