Sender's message: No association found between telomere length and cancer as determined by GWAS

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1. Front Med. 2015 Dec;9(4):478-86. doi: 10.1007/s11684-015-0420-0. Epub 2015 Nov 18.

U-shaped association between telomere length and esophageal squamous cell carcinoma risk: a case-control study in Chinese population.

Du J[1,2], Xue W[1], Ji Y[3], Zhu X[1], Gu Y[1,2], Zhu M[1,2], Wang C[1,2], Gao Y[4], Dai J[1,2], Ma H[1], Jiang Y[1], Chen J[1,2], Hu Z[1,2], Jin G[1,2], Shen H[1,2].

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Abstract

Telomeres play a critical role in biological ageing by maintaining chromosomal integrity and preventing chromosome ends fusion. Epidemiological studies have suggested that inter-individual differences of telomere length could affect predisposition to multiple cancers, but

evidence regarding esophageal squamous cell carcinoma (ESCC) was still uncertain. Several telomere length-related single nucleotide polymorphisms (TLSNPs) in Caucasians have been reported in genome-wide association studies. However, the effects of telomere length and TL-SNPs on ESCC development are unclear. Therefore, we conducted a case-control study (1045 ESCC cases and 1433 controls) to evaluate the associations between telomere length, TL-SNPs, and ESCC risk in Chinese population. As a result, ESCC cases showed overall shorter relative telomere length (RTL) (median: 1.34) than controls (median: 1.50, $P < 0.001$). More interestingly, an evident nonlinear U-shaped association was observed between RTL and ESCC risk ($P < 0.001$), with odds ratios (95% confidence interval) equal to 2.40 (1.84-3.14), 1.36 (1.03-1.79), 1.01 (0.76-1.35), and 1.37 (1.03-1.82) for individuals in the 1st (the shortest), 2nd, 3rd, and 5th (the longest) quintile, respectively, compared with those in the 4th quintile as reference group. No significant associations were observed between the eight reported TL-SNPs and ESCC susceptibility. These findings suggest that either short or extremely long telomeres may be risk factors for ESCC in the Chinese population.

PMID: 26581417 [Indexed for MEDLINE]

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2. World J Gastroenterol. 2015 Aug 21;21(31):9328-36. doi: 10.3748/wjg.v21.i31.9328.

Influence of the hTERT rs2736100 polymorphism on telomere length in gastric cancer.

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Byung Joon Choi, Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul 137-701, South Korea.

Abstract

AIM:

To investigate the functional consequences of rs2736100 polymorphism in telomere length and examine its link to gastric cancer risk.

METHODS:

Telomere length and human telomerase reverse transcriptase (hTERT) mRNA expression were measured in 35 gastric cancer tissues and 5 cell lines and correlated to rs2736100 polymorphism. The relationship between rs2736100 polymorphism and the risk of gastric cancer were examined in 243 gastric cancer patients and 246 healthy individuals.

RESULTS:

The rs2736100 A allele carrier is closely associated with reduced hTERT mRNA expression and shortened telomere length in gastric cancer tissue and cell lines. When gastric cancers were stratified by histological subtype, telomere length and hTERT mRNA levels were significantly increased in those with the C/C genotype in intestinal-type gastric cancer, but not in diffuse-type gastric cancer. Interestingly, there was no significant difference in the genotype and allele frequencies of the rs2736100 polymorphism between the patients with gastric cancer and healthy controls.

CONCLUSION:

The rs2736100 polymorphism of the hTERT gene is involved in the regulation of hTERT expression and telomere length, but not in the risk of gastric cancer.

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3. Carcinogenesis. 2015 Sep;36(9):963-70. doi: 10.1093/carcin/bgv075. Epub 2015 May 29.

Telomere length, genetic variants and gastric cancer risk in a Chinese population.

Du J[1], Zhu X[2], Xie C[2], Dai N[3], Gu Y[3], Zhu M[3], Wang C[3], Gao Y[4], Pan F[4], Ren C[5], Ji Y[6], Dai J[3], Ma H[2], Jiang Y[2], Chen J[3], Yi H[2], Zhao Y[2], Hu Z[1], Shen H[7], Jin G[8].

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Abstract

Telomeres maintain chromosomal stability and integrity and are crucial in carcinogenesis. Telomere length is implicated in multiple cancer risk, but the results are conflicting. Genome-wide association studies have identified several genetic loci associated with telomere length in Caucasians. However, the roles of telomere length and related variants on gastric cancer development are largely unknown. We conducted a case-control study including 1136 gastric cancer cases and 1012 controls to evaluate the associations between telomere length, eight telomere length-related variants identified in Caucasians and gastric cancer risk in Chinese population. We observed an obvious U-shaped association between telomere length and gastric cancer risk ($P < 0.001$), with odds ratios (95% confidence intervals) being 3.81 (2.82-5.13), 1.65 (1.21-2.26), 1.28 (0.93-1.77) and 1.78 (1.30-2.44) for individuals in the first (the shortest), second, third and fifth (the longest) quintile as compared with those in the fourth quintile as reference group. The weighted genetic score (WGS) of eight variants was significantly associated with telomere length ($P < 0.001$), and in particular, the G allele of rs2736100 in TERT at 5p15.33 exhibited a significant association with long telomeres ($P = 0.047$). However, we did not observe significant associations between these genetic variants and gastric cancer risk for both single-variant and WGS analyses. These findings suggest that either short or extreme long telomeres may be risk factor for gastric cancer. Genetic variants identified in Caucasians may also contribute to the variation of telomere length in Chinese but seems not to gastric cancer susceptibility.

PMID: 26025910 [Indexed for MEDLINE]
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4. Cancer Epidemiol Biomarkers Prev. 2017 Mar 6. pii: cebp.0100.2017. doi: 10.1158/1055-9965.EPI-17-0100. [Epub ahead of print]

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 PDAC cases and 1,500 controls, frequency-matched on age and sex was performed. Eight of nine polymorphisms previously associated with variation in LTL were analyzed. Genetic risk scores (GRS) consisting of the TL-related polymorphisms 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:

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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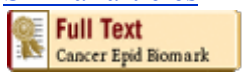

5. Oncotarget. 2017 Feb 7;8(6):9849-9857. doi: 10.18632/oncotarget.14219.

Genetic polymorphisms in the telomere length-related gene ACYP2 are associated with the risk of colorectal cancer in a Chinese Han population.

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Abstract

We investigated the association between single nucleotide polymorphisms (SNPs) in ACYP2, which has been associated with telomere length in several types of cancer, and the risk of CRC in a Chinese Han population. In a case-control study that included 247 cases and 300 healthy controls, 14 SNPs in ACYP2 were selected and genotyped using the Sequenom MassARRAY platform. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression after adjusting for age and gender. We determined that rs843711 and rs843706 were associated with an increased risk of CRC (rs843711: OR = 1.376, 95% CI = 1.082-1.749, p = 0.009; rs843706: OR = 1.361, 95% CI = 1.069-1.733, p = 0.012). Additionally, rs6713088, rs843645, rs843711, and rs843706 were associated with an increased risk of CRC under additive and recessive models ($p < 0.05$). Finally, the "TTCTCGCC" and "CG" haplotypes decreased the risk of CRC, while the "AG" haplotype increase the risk of CRC. The association between rs843711 and CRC remained significant after Bonferroni correction for multiple comparisons ($p \leq 0.00036$). Our data shed new light on the associations between genetic variants in the ACYP2 gene and CRC susceptibility in a Chinese Han population.

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