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Genetic Variants in Eleven Telomere-Associated Genes and the Risk of Incident Cardio/Cerebrovascular Disease: The Women's Genome Health Study

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Abstract

Background—Candidate genes associated with telomere-length maintenance, an important molecular marker for biological aging, represent potential risk predictors for cardiovascular disease (CVD). To date, no prospective data are available.

Methods—The associations between 154 tag-single nucleotide polymorphisms (tSNPs) of 11 telomere-associated candidate genes (*TERT*, *POT1*, *TNKS*, *TERF1*, *TNKS2*, *UCP2*, *TEP1*, *ACD*, *TERF2*, *TERF2IP*, *TERC*) were investigated in 23,294 Caucasian participants of the Women's Genome Health Study. All were free of known CVD and cancer at baseline. The primary outcome measure was a composite CVD endpoint (incident ischemic stroke, myocardial infarction (MI), or death due to ischemic CVD); other measures were incident MI, and ischemic stroke. During follow-up, 1178 total incident CVD, 315 incident MI cases, and 323 incident ischemic stroke events were identified. Multivariable Cox regression analysis and a haplotype-based approach were performed to investigate the relationship between genotypes/haplotypes and CVD risk assuming an additive model.

Results—In a marker-by-marker analysis, 7 (*TEP1*, *TNKS*, *ACD*), 11 (*TEP1*, *ACD*, *TERT*), and 24 (*TEP1*, *TNKS*, *TERT*, *TERF2IP*, *TNKS2*, *UCP2*) SNPs were associated -at the level of $p<0.05$- with total CVD, MI, and ischemic stroke risk, respectively. Further analysis using a haplotype-based approach showed similar findings. Although, none remained significant after correction of multiple testing, the false discovery rate analysis revealed 28% of the nominally significant SNPs with true associations in relation to ischemic stroke risk.

Conclusions—The present large prospective study encourages further investigation of the biological role of telomere-associated pathway genes in the pathogenesis and early assessment of vascular events.

Introduction

Cardio/Cerebrovascular disorder (CVD), a leading cause of morbidity and mortality in the western societies, represents a heavy social and economic burden. While biological/life style

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Conflict of Interest
None declared

factors including aging, smoking, hyperlipidemia, hypertension, and obesity are well known risk factors for CVD, the genetic risk factors contributing to CVD remains largely elusive.

Telomeres are tandem repeats of DNA sequences located at the ends of eukaryotic chromosomes and special nucleating chromatin structures. One function of these structures is to protect the telomeric regions from recombination and degradation, thus avoiding a genomic instability leading to cellular senescence and apoptosis [1]. It has been shown that biological factors such as inflammatory responses, oxidative stress, and/or abnormal cellular senescence accelerate leukocyte telomere-length attrition/shortening; biological processes that may have consequences for vascular remodeling and its overall stability [2,3]. Telomere-associated pathway genes are essential for the preservation of genomic integrity and stability. A dysfunctional telomere pathway may lead to impaired DNA damage repair, genomic instability, and ultimately, in the vascular setting, the initiation of atherosclerosis, the most important cause of CVD [3,4]. Data from a candidate gene approach [5] and a recent genome-wide association study [6], examining the genetic determination of telomere length, have shown that a functional polymorphism (rs2735940) of *hTERT* (the catalytic subunit of telomerase and a major determinant of telomerase activity) [5] and common variants near *TERC* (the RNA template component of telomerase that regulates the addition of the telomere repeat sequence) [6], were associated with mean telomere length, suggesting a critical involvement of telomere-associated gene loci in the maintenance of telomere biology. In addition, the *hTERT* rs2735940 has also been associated with coronary artery disease (CAD) in a case-control study of unrelated Japanese sample population [7]. Examining genetic variation in candidate genes derived from pathways-based analysis may be an efficient way to understand biological relationships in human common, complex disorders [8–10]. Thus, in the present investigation, we examined the possible association of 154 tag-single nucleotide polymorphisms (tSNPs) from 11 telomere-associated pathway genes with CVD risk in a large cohort of initially healthy US Caucasian women.

Material and Methods

Study design

Details of the study design have been previously described [11]. In brief, participants in the Women's Genome Health Study (WGHS) –a whole genome survey substudy of the Women's Health Study [12,13]– included initially healthy North American women aged 45 or older with no previous history of cardiovascular disease, cancer, or other major chronic illness. A baseline blood sample was collected during the enrollment phase of the parent cohort, Women's Health Study, between 1992 and 1995, among participants who gave consent for blood-based analyses related to risks of incident chronic diseases. All study participants were followed up through March 2007 for incident events that were adjudicated by an endpoints committee using standardized criteria and full medical record review. Only confirmed end points were included in this analysis. The present investigation included 23,294 Caucasian participants of the WGHS; all were free of known cardiovascular disease and cancer at baseline. Participants were followed for the composite endpoint of incident total CVD (nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death) and the individual endpoints of nonfatal myocardial infarction and ischemic stroke. During a 13-year follow-up period, 1178 total incident CVD, 315 incident MI, and 323 incident ischemic stroke cases identified. As described elsewhere, DNA extracted from the baseline WGHS blood samples underwent tSNP genotyping (r^2=~0.80) using the genome-wide Illumina Infinium II Human HAP300 panel with an additional focused panel of 45,751 SNPs selected to enhance coverage of genomic regions without regard to allele frequency in which we had a strong a priori interest owing to presence of genes thought to be of relevance to metabolic, lipid, inflammatory, and

other biological functions [11,14–17]. The Brigham and Women's Hospital Institutional Review Board for Human Subjects Research approved the study protocol.

Statistical analysis

Genotype frequencies were compared with values predicted by Hardy-Weinberg equilibrium using the chi-square test. Hazard ratios (HRs) associated with each of the individual SNPs were calculated separately by Cox regression analysis adjusting for age, current smoking status, and further adjusting for BMI, randomized treatment assignment, history of hypertension, and hyperlipidemia, and current hormone use, assuming additive models for genetic effects. Haplotype estimation and inference were determined by expectation-maximization algorithm. Haplotype blocks per gene locus were defined using the software Haploview v4.1 [18]. In addition, the relationship between haplotype blocks and each of the pre-specified endpoints was examined by a referent haplotype-based Cox regression analysis, adjusting for the same potential covariables used in the single SNP analysis. False discovery rate (FDR) analysis was conducted using the QVALUE software [19]. Genotyping call rates, and concordance rates were both >99% per SNP. Furthermore, the gene variants examined in the regression analysis were tested for adherence with the Cox-proportionality assumption. A two-tailed p-value of 0.05 was considered a statistically significant result. All analyses were carried out using SAS/Genetics 9.1 package (SAS Institute Inc., Cary, NC, USA) or R software [20].

Results

Details of the telomere-associated genes evaluated in the present study are shown in Table 1 and Supplementary Data Table 1. The baseline characteristics of the 23,294 initially healthy Caucasian women are shown in Table 2. For ease of presentation, Table 3 presents those SNPs that were found to have a nominal (uncorrected) p-value of less than 0.10 for the Cox regression analysis, in an additive model. None of these associations remained significant after Bonferroni correction of multiple testing. Online Supplementary Tables 2, 3 and 4 present the nominal (uncorrected) association results for all the SNPs tested for total CVD, incident MI, and incident ischemic stroke, respectively. Again, for ease of presentation, only those gene loci that were associated with at least two of the prespecified endpoints in the marker-by-marker approach were included in the haplotype-based analysis. These included *TEP1, TNKS, ACD, and TERT*. As shown in Supplementary Data Table 5, several haplotypes were found to be associated with CVD risk. Again, these were non-significant after correction for multiple testing. All SNPs tested were in agreement of proportionality assumption after correction for multiple testing. However, an apparent excess of nominally significant p-values for ischemic stroke risk was noted, and corresponded to an estimated 28% of SNPs with true associations on the basis of the FDR analysis.

Discussion

To the best of our knowledge, the present study is the first prospective assessment of the relationship of 154 tSNPs in 11 telomere-associated pathway gene loci with CVD risk. Although, none of the polymorphisms tested remained significantly associated with CVD risk after correction for multiple testing, our present findings provide encouragement for further examining the involvement of telomere-pathway genes in CVD. As previously mentioned, we note that the apparent excess of nominally significant p-values for ischemic stroke risk corresponded to an estimated 28% of SNPs with true associations on the basis of the FDR.

The enzyme, encoded by *TERT*, is the catalytic component of telomerase, a ribonucleoprotein polymerase that maintains genomic stability by addition of the telomere

repeat TTAGGG to telomere ends. The study by Matsubara *et al*. showed that a functional promoter polymorphism of *TERT* (rs2735940) was associated with telomere shortening [5], and with CAD in a Japanese sample population [7]. Although, this SNP was not genotyped in the present study, one of our genotyped *TERT* tSNPs (rs2736100), which is about 30 base-pair upstream from it, was found to be significantly associated (uncorrected) with incident MI risk (Table 3), further supporting a role of *TERT* gene locus in the development of CVD. Of note, based on the HapMap information, the linkage disequilibrium patterns between Europeans and Asians/Japanese were virtually identical. Thus, aggressive investigation of cellular model(s) or pathway(s) in relation to TERT and atherosclerosis/ vascular remodelling is warranted.

For *TERC* --the RNA template component of telomerase-- common gene variation near this gene locus has recently been associated with mean telomere length [6], making this gene locus a critical candidate for CVD. However, the present study found no evidence for an association of any of the *TERC* tag-SNPs/haplotypes thereof with CVD risk.

Genetic variants of *TNKS*, *TEP1*, or *ACD* have been widely examined in relation to cancer risk including breast cancer risk [21], breast cancer susceptibility and prognosis [22], and risk of lung cancer [23]. However, as no genetic-epidemiological data are available for *TNKS*, *TEP1* and *ACD* gene variation in relation to atherosclerosis/CVD risk, no cross-reference comparison can be made.

Strengths of the present study are the overall sample size, the biological relevance of the polymorphisms considered, the prospective design and the complete long-term follow-up. We also chose, on an *a priori* basis, to adjust for multiple comparisons, and to present all our data simultaneously rather than focusing on any one specific finding. Nonetheless, some potential limitations of our study require discussion. Limitations include generalizability and potential bias. We examined only Caucasian middle aged and older women distinct socioeconomic status (health professionals) and our findings may not generalizable to other populations with diverse ethnicity or socioeconomic background.

In our study, we had the ability to detect, based on the present sample sizes, assuming 80% power, at an alpha of 0.05, a hazards ratio of greater than 1.10 (total CVD), 1.30 (MI), and 1.30 (ischemic stroke) if the minor allele frequency is 0.50, and of greater than 1.90 (total CVD), 2.80 (MI), and 2.80 (ischemic stroke) if the minor allele frequency is 0.01 assuming a univariable-additive model. Thus, we cannot rule out a low to modest risk of CVD associated with the tSNPs tested.

In conclusion, the present findings warrant further investigation into the involvement of the telomere-associated pathway genes tested in the pathogenesis of CVD, although none of the genetic variants assessed remained significant after correction for multiple testing. More importantly, our present findings require confirmation/replication in future large, prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Telomere-associated candidate genes examined

Gene	Symbol	Chromosome	Number of SNP
Telomerase RNA component	*TERC*	3q26	4
Telomerase reverse transcriptase	*TERT*	5p15.33	20
POT1 protection of telomeres 1 homolog	*POT1*	7q31.33	26
Telomeric repeat binding factor (NIMA-interacting) 1	*TERF1*	8q13	10
Tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase	*TNKS*	8p23.1	21
Tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase 2	*TNKS2*	10q23.3	9
Uncoupling protein 2 (mitochondrial, proton carrier)	*UCP2*	11q13	11
Telomerase-associated protein 1	*TEP1*	14q11.2	37
Adrenocortical dysplasia homolog	*ACD*	16q22.1	4
Telomeric repeat binding factor 2	*TERF2*	16q22.1	9
Telomeric repeat binding factor 2, interacting protein	*TERF2IP*	16q23.1	3

Table 2

Baseline characteristics of white female participants.

Characteristic	N=23,294
Age, years	52 (48, 59)
Body-mass index, kg/m^2	24.89 (22.46, 28.32)
History of diabetes, %	2.52
History of hyperlipidemia ≥240 mg/dL, %	29.76
History of hypertension ≥140/90 mmHg, %	24.61
Smoking status	
current	11.64
past	37.45
never	50.91
Postmenopausal, %	54.45
Current hormone use, %	43.86
Aspirin use, %	49.87
Beta-carotene use, %	49.81
Vitamin E use, %	50.08

Data are median and interquartile range for continuous, and percentages for categorical variables.

Table 3

Cox regression analysis showing genetic variants with p-values <0.10 (ascending order).

Gene	SNP	Chr	Position	MAF	HR	95%CI lower	upper	puncorrected
TotCVD								
TEP1	rs8017603	14	19973745	0.4951	0.889583	0.818307	0.967067	0.006
TEP1	rs1713434	14	19951366	0.4386	0.891394	0.817883	0.971511	0.0088
TNKS	rs6601328	8	9440612	0.1096	1.174958	1.03447	1.334525	0.013
TEP1	rs7140768	14	19966696	0.4287	1.110475	1.021539	1.207154	0.014
TEP1	rs7145318	14	19966903	0.4283	1.110155	1.021259	1.206788	0.014
ACD	rs9972635	16	66240080	0.05534	0.774298	0.631705	0.949079	0.014
TEP1	rs1878705	14	19975354	0.3784	0.911662	0.835735	0.994486	0.037
TNKS	rs11994018	8	9531110	0.1202	1.12395	0.992396	1.272942	0.066
UCP2	rs622064	11	73350221	0.2215	0.910262	0.819365	1.011244	0.080
TERT	rs35033501	5	1306917	0.02486	1.242142	0.968353	1.593339	0.088
TEP1	rs1760897	14	19946092	0.3146	0.924773	0.844075	1.013187	0.093
MI								
TEP1	rs1760898	14	19942720	0.2245	0.770398	0.622786	0.952996	0.016
TEP1	rs8022805	14	19916789	0.05567	0.572957	0.361111	0.909082	0.018
TERT	rs4975605	5	1328527	0.4696	1.215978	1.033112	1.431212	0.019
TERT	rs33961405	5	1330576	0.4877	0.822649	0.698133	0.969374	0.020
TEP1	rs1760897	14	19946092	0.3146	0.808691	0.673295	0.971313	0.023
ACD	rs9972635	16	66240080	0.05626	0.600607	0.385511	0.935716	0.024
TERT	rs34363858	5	1339476	0.01613	0.203405	0.050638	0.817037	0.025
TERT	rs2736100	5	1339515	0.4967	1.199794	1.021203	1.409618	0.027
TEP1	rs2228041	14	19922106	0.0578	0.611007	0.393707	0.948242	0.028
ACD	rs9972635	16	66240080	0.05534	0.609396	0.39127	0.949125	0.028
TERT	rs7447815	5	1293756	0.3938	1.196905	1.015123	1.411241	0.032
TEP1	rs3093926	14	19892891	0.06307	0.669189	0.447248	1.001267	0.051
TNKS	rs11787063	8	9483709	0.2666	0.826178	0.68119	1.002025	0.052
TERF2	rs715162	16	67927758	0.05932	0.683803	0.461551	1.013077	0.058
TERF2	rs7187579	16	67942359	0.1803	1.21057	0.989883	1.480459	0.063

Gene	SNP	Chr	Position	MAF	HR	95%CI lower	upper	puncorrected
TERT	rs33954691	5	1308519	0.1029	1.232049	0.9632	1.575941	0.097
IsStroke								
TERF2IP	rs3784929	16	74234527	0.1139	1.379248	1.73083	1.099083	0.006
TNKS2	rs10881985	10	93617137	0.3035	1.246918	1.473113	1.055456	0.010
TNKS2	rs2066275	10	93554294	0.3036	1.245483	1.471446	1.054219	0.010
TNKS	rs9644704	8	9597578	0.3628	1.237947	1.456212	1.052396	0.010
TNKS	rs7015700	8	9565116	0.1802	1.286949	1.561474	1.060689	0.010
TERF2IP	rs8053257	16	74232188	0.0604	1.464099	1.962009	1.092546	0.011
TNKS	rs6994574	8	9615664	0.3651	1.233861	1.451365	1.048952	0.011
TNKS	rs12155819	8	9610088	0.3641	1.22941	1.445951	1.045298	0.012
TEP1	rs2228041	14	19922106	0.0578	1.457458	1.969814	1.078367	0.014
UCP2	rs622064	11	73350221	0.2215	0.776632	0.959502	0.628615	0.019
TNKS	rs11994018	8	9531110	0.1202	1.304788	1.634687	1.041467	0.021
TNKS	rs6601328	8	9440612	0.1096	1.307125	1.651757	1.0344	0.025
TERT	rs35033501	5	1306917	0.02486	1.613968	2.454539	1.061256	0.025
TEP1	rs2184282	14	19949999	0.1279	1.278122	1.590322	1.02721	0.028
TEP1	rs2104978	14	19906872	0.06524	1.380391	1.843774	1.033466	0.029
TEP1	rs8022805	14	19916789	0.05567	1.409067	1.920826	1.033654	0.030
TNKS	rs4841218	8	9691311	0.3732	1.196219	1.406731	1.017209	0.030
TEP1	rs1713456	14	19919932	0.1813	1.236704	1.503069	1.017543	0.033
TERT	rs2853668	5	1353024	0.2526	0.80919	0.98382	0.665557	0.034
TNKS2	rs1361552	10	93524603	0.4259	1.190833	1.400015	1.012906	0.034
TEP1	rs1713456	14	19919932	0.1812	1.230731	1.496781	1.01197	0.038
TEP1	rs1713434	14	19951366	0.4386	0.843648	0.996433	0.71429	0.045
TNKS	rs6601327	8	9432941	0.3785	1.180241	1.388515	1.003208	0.046
TEP1	rs7145318	14	19966903	0.4283	1.173779	1.377184	1.000417	0.049
TEP1	rs7140768	14	19966696	0.4287	1.166236	1.368283	0.994024	0.059
TNKS	rs6985140	8	9574836	0.07697	1.299513	1.709239	0.988004	0.061
TNKS2	rs2258946	10	93614651	0.1487	0.797235	1.019431	0.623469	0.071
TERT	rs34363858	5	1339476	0.01613	1.580129	2.652757	0.941212	0.083
ACD	rs7187476	16	66257448	0.1548	1.208285	1.500459	0.973004	0.087

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Gene	SNP	Chr	Position	MAF	HR	95%CI lower	upper	puncorrected
TNKS	rs12545912	8	9639108	0.2488	1.169519	1.399183	0.977553	0.087
TEP1	rs3093926	14	19892891	0.06557	1.293974	1.738674	0.963015	0.087
TERF1	rs6994351	8	74069183	0.3952	0.863512	1.023128	0.728797	0.090
UCP2	rs1626521	11	73391986	0.274	0.851841	1.029147	0.705082	0.096

Adjusted for age, BMI, current smoking, treatment assignment, history of diabetes, hypertension and hyperlipidemia, and current hormone use.

MAF=minor allele frequency; Chr.=chromosome; HR=hazard ratio.