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Original Article

Polymorphism of *TNIP1* was associated with atherosclerotic ischemic stroke in southern Han Chinese but unrelated with telomere

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Abstract: Objective: To evaluate the association between atherosclerotic ischemic stroke (AIS) and single-nucleotide polymorphisms (SNP) in gene *TERT*, *TNIP1*, *OBFC1* in southern Chinese Han population. Methods: Sequenom MassARRY system was used to genotype 12 SNPs (rs10069690, rs2242652, rs2853677, rs2853676 in *TERT*; rs7708392, rs10036748, rs960709 in *TNIP1*; rs9325507, rs3814220, rs12765878, rs11191865, rs9420907 in *OBFC1*) in both atherosclerotic ischemic stroke patients (n=400) and healthy controls (n=399). Association analyses were performed in SNPstats platform in five genetic models (dominant, recessive, additive, codominant, overdominant). Analysis of allele frequencies and linkage disequilibrium were also conducted. Odd ratio (OR) and 95% confidence interval (95% CI) were adjusted for confounding factors (age, gender, past medical history, smoke, alcohol, blood lipid). Results: SNP rs7708392 was significantly associated with an increased risk of AIS after adjustment for above confounding factors in our population (heterozygous model P=0.04, OR=1.62, 95% CI 1.01-2.61 and overdominant model P=0.037, OR=1.64, 95% CI 1.03-2.62). None of the rest SNPs was observed to associate with AIS susceptibility in allele or any genetic model. No significant difference was found between the common haplotype in *OBFC1* and *TNIP1* and the risk of AIS. And there were no statistical significance between telomere length, serum lipid levels, hypertension, diabetes mellitus and rs7708392 genotype in the control group. Conclusion: *TNIP1* rs7708392 polymorphism was first found to be associated with the occurrence of AIS, but the association may be independent of telomere, hypertension and diabetes mellitus. Further study should be conducted to confirm the association and to explore the role of this variant in the pathogenesis of AIS.

Keywords: SNP, stroke, cerebral infarction, *TNIP1*, *TERT*, *OBFC1*

Introduction

Stroke is the second most common cause of death and leading cause of adult disability worldwide [1]. In China, the annual stroke mortality rate has become the first leading cause of death and adult disability over heart disease [2]. Ischemic stroke (IS) accounts for about 62.4%-69.6% of all stroke cases [3]. Modifiable risk factors including hypertension, metabolic disturbances, smoking, and obesity are the most common of stroke. However, the genetic risk factors involved in stroke remains elusive.

Telomeres consist of DNA-protein complexes located at the end of the chromosomes, protecting and maintaining genetic integrity and stability. Evidences suggested that shorter telomere length was associated with an increased risk of age-related disease [4, 5], such as cardiovascular disease and ischemic stroke [6-10]. Telomere length shortening was considered to be an indicator of the cumulative burden of inflammation and oxidative stress [11]. Loss of protein A20, which binds with the protein (ABIN-1) encoded by the gene TNF α-induced protein 3-interacting protein 1 (*TNIP1*), resulted in inflammation and autoimmune responses with elevation of IL-6 [12, 13]. However, present studies mostly focused on the associations between *TNIP1* gene polymorphisms and systemic lupus erythematosus [13, 14]. An in vivo

study indicated that ABIN-1 involved in the regulation of chronic inflammation and cardiovascular disease [15]. Telomerase reverse transcriptase protein (*TERT*) was considered as rate limiting catalytic subunit of telomerase [16]. Cumulative studies confirmed that polymorphisms of gene *TERT* were associated with telomere-related diseases including cancers, myocardial infarction, and IS [4, 17-19]. Oligonucleotide/oligosaccharide binding fold containing 1 (*OBFC1*) codes for oligosaccharide-binding fold-containing protein 1 and is part of CST complex, which is bind to the telomeric 3' overhang and plays an important role in telomere maintenance [30].

Up to now, there were only few studies conducted on the correlation between SNPs (rs10069690, rs2242652, rs2853677, rs2853676, rs10036748, rs960709, rs9325507, rs3814220, rs12765878, rs11191865, rs7708392 and rs9420907) and atherosclerotic ischemic stroke (AIS). Thus, this case-control study was designed to assess if these variants conferred risk to AIS in southern Han Chinese, and the possible relation with telomere.

Materials and methods

Study population and sample collection

From February 2015 to March 2016, atherosclerotic ischemic stroke patients were recruited from the Department of Neurology of Affiliated Haikou Hospital of Xiangya Medical College of Central South University in Haikou city, Hainan province, China. The diagnostic criteria were defined as a sudden focal or global disturbance of cerebral function caused by vascular occlusion over 24 hours or longer, and further confirmed with computed tomography (CT) or magnetic resonance imaging (MRI). Newly diagnosed and only LAA (large vessel atherosclerosis) cases classified on TOAST [21] (Trial of Org 10172 in Acute Stroke Treatment) were included. Patients who had the following conditions were excluded: cardioembolism, brain trauma, tumors, transient ischemic attack, or cerebrovascular malformation; and inflammatory disease, collagenosis, or severe heart, liver, renal diseases. At the same time, the controls were enrolled from the health checkup center in the same hospital. The exclusion criteria included subjects diagnosed with any history of cerebrovascular and cardiovascular disease.

The case-control study protocol was approved by the Clinical Research Ethics of Haikou Municipal Hospital. Written informed consent was obtained from all the subjects or families participating in the present study.

A 3-5 ml sample of peripheral venous blood was collected from each participant, and temporarily stored at -20°C in the hospital central lab. Then the further study was completed in Northwest University (Xi'an city, Shaanxi province, China).

DNA isolation and genotyping assay

Genomic DNA was taken with the GoldMag-Mini Purification Kit (GoldMag Co. Ltd. Xian city, China) according to manufacturer's protocols. DNA concentrations were qualified with the NanoDrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA). Genotype were performed on the Sequenom MassARRAY RS1000 [22]. The results were managed and analyzed by Sequenom Typer 4.0 Software (Sequenom, Inc.).

Telomere length measurement

Real-time quantitative PCR (RT-PCR)-based method was used to calculate the relative telomere length (RTL) in a LightCycler®480 QPCR System (Roche, Basel, Switzerland). RTL was the ratio between the copy number of telomere repeats (T) and a single-copy gene copy number (S).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were shown as counts. Hardy-Weinberg equilibrium (HWE) in control group was tested by χ^2 test. Kruskal-Wallis H test was used to assess the difference of telomere length among genotype of rs7708392. Independent sample t test and Chi-square (χ^2) tests were used to test for the differences of measurement data and enumeration data between groups. The odds ratio (OR) and 95% confidence interval (CI) were calculated on SNPStats platform in five genomic models including dominant, co-dominant, additive, recessive, and overdominant model. A two-sided $P<0.05$ was considered to be statistically significant. Data analyses were done by Microsoft Excel,

Table 1. Characteristics and clinical features

Characteristic	Case	Control	*P*
Age (years)	66.8 ± 11.6	48.7 ± 11.1	<0.001
Gender (male/female)	34.3	38.3	0.23
Cigarette smoking (%)	32.8	13.8	<0.001
Alcohol (%)	17.3	10.5	0.006
DM (%)	23	5.3	<0.001
Hypertension (%)	69.3	7.8	<0.001
BMI (kg/m^2)	24.7 ± 3.8	23.8 ± 2.8	<0.001
TC (mmol/l)	4.91 ± 1.2	5.18 ± 0.9	<0.001
TG (mmol/l)	1.34 ± 0.9	1.49 ± 0.5	0.004
LDL-C (mmol/l)	2.92 ± 1.0	3.12 ± 0.7	0.001
HDL-C (mmol/l)	1.28 ± 0.3	1.38 ± 0.5	0.001

BMI, body mass index; DM, diabetes mellitus; TC, total cholesterol; TG, total triglyceride; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol.

SPSS23.0 (SPSS Inc., Chicago, IL) and SNPStats platform. Linkage disequilibrium and haplotype construction were analyzed on the haploView software.

Results

Patient characteristics and clinical features

A total of 400 atherosclerotic ischemic stroke patients and 399 healthy controls were included in this present case-control study. The distribution of demographic and clinical data were presented in **Table 1**. We observed differences in age, smoking, alcohol, history of diabetes mellitus (DM), history of hypertension, body mass index (BMI), total cholesterol (TC), total triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) between the case and control group. Blood lipid in cases is lower than that in controls. No significant difference was presented in gender.

The SNPs and the risk of AIS

The detailed information about all SNPs included in this study was shown in **Table 2**. There was no significant difference from HWE in genotype frequencies in the control group for all SNPs. All the SNPs were not associated with AIS in allele model. CC genotype was not observed for rs9420907 in both case and control group. None of the following SNPs: rs10069690, rs2242652, rs2853677, rs2853676, rs10036748, rs960709, rs9325507, rs3814220, rs12765878, rs11191865, and rs9420907 were significantly different in any model after adjustment for the confounding factors between the AIS patients and the controls. **Table 3** presented the association of rs7708392 with the risk of AIS in genetic models after adjustment for gender, age, smoking, alcohol, diabetes history, hypertension history, BMI, TC, TG, HDL-C, and LDL-C. A statistically significant difference was found in heterozygous (P= 0.04, OR=1.62, 95% CI 1.01-2.61) and overdominant model (P=0.037, OR=1.64, 95% CI 1.03-2.62).

Haplotypes and the risk of AIS

For further investigation of the correlation between SNPs and risk of AIS, linkage disequilibrium and haplotype analysis were conducted for the SNPs within the same gene. There was strong linkage disequilibrium among rs10036748, rs7708392, rs960709 within *TNIP* and rs9325507, rs3814220, rs12765878, rs11191865 within *OBFC1.* The common haplotype was shown in **Table 4**. However, none of the haplotypes were associated with AIS susceptibility.

The rs7708392 genotype and telomere, serum lipid levels

The association between rs7708392 genotype and telomere, serum lipid levels in control group was presented in **Table 5**. There was no statistical difference for relative telomere length among these three genotypes. No difference was found for each lipid level, hypertension, and diabetes mellitus among them.

Discussion

We performed this case-control study to assess the correlation between some polymorphisms in *TERT*, *TNIP1* and *OBFC1* and the risk of AIS in southern Chinese Han population. The results suggested that rs7708932 within *TNIP1* was associated with an increased risk of ischemic stroke. None of the rest SNPs had a significant difference with AIS susceptibility. The haplotype analysis showed that none of the common haplotype in *TNIP1* and *OBFC1* was associated with AIS risk.

Atherosclerosis, which originated from endothelial dysfunction, is a major cause of isch-

Table 2. Candidate SNPs in this study

SNP	Position	Band	Alleles A/B	Gene	MAF (%) Case	MAF (%) Control	ORs	95% CIs	*P*	HWE *P*
rs10069690	1279790	5p15.33	T/C	TERT	0.14	0.15	0.88	0.67-1.17	0.39	1
rs2242652	1280028	5p15.33	A/G	TERT	0.15	0.16	0.88	0.67-1.15	0.36	0.1
rs2853677	1287194	5p15.33	G/A	TERT	0.38	0.41	0.89	0.73-1.09	0.24	0.54
rs2853676	1288547	5p15.33	T/C	TERT	0.15	0.17	0.89	0.68-1.17	0.41	0.47
rs7708392	150457485	5q33.1	G/C	TNIP1	0.25	0.23	1.09	0.87-1.38	0.44	0.33
rs10036748	150458146	5q33.1	C/T	TNIP1	0.25	0.23	1.13	0.90-1.42	0.30	1
rs960709	150461049	5q33.1	A/G	TNIP1	0.25	0.23	1.09	0.87-1.37	0.46	0.78
rs9325507	105645622	10q24.33	T/C	OBFC1	0.35	0.37	0.93	0.75-1.13	0.41	0.59
rs3814220	105647300	10q24.33	G/A	OBFC1	0.35	0.37	0.91	0.74-1.12	0.42	0.52
rs12765878	105669622	10q24.33	C/T	OBFC1	0.35	0.37	0.93	0.75-1.13	0.45	0.52
rs11191865	105672842	10q24.33	A/G	OBFC1	0.35	0.37	0.92	0.75-1.13	0.44	0.52
rs9420907	105676465	10q24.33	C/A	OBFC1	0.02	0.01	2.42	0.85-6.89	0.09	1

A/B minor/major allele, SNP single nucleotide polymorphism, HWE Hardy-Weinberg equilibrium, MAF minor allele frequency, OR odd ratio, CI confidence interval.

Table 3. Association between rs7708392 and the risk of atherosclerotic ischemic stroke in genetic models

Model	Genotype	Control	Case	OR (95% CI)	*P*#
Codominant	C/C	236	224	1	
	G/C	135	152	1.62 (1.01-2.61)	0.04
	G/G	25	24	0.87 (0.34-2.25)	0.83
Dominant	C/C	236	224	1	
	G/C-G/G	160	176	1.48 (0.94-2.32)	0.09
Recessive	C/C-G/C	371	376	1	
	G/G	25	24	0.73 (0.29-1.84)	0.5
Overdominant	C/C-G/G	261	248	1	
	G/C	135	152	1.64 (1.03-2.62)	0.037
Log-additive	---	---	---	1.22 (0.85-1.76)	0.28

OR odd ratio, CI confidence interval. #adjusted for gender, age, smoking, alcohol, diabetes history, hypertension history, body mass index, total cholesterol, total triglyceride, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol.

Table 4. Haplotype frequencies and the risk of AIS

Gene	Haplotype	Case Freq	Control Freq	OR (95% CI)	*p*
TNIP1	T-C-G	0.75	0.76	1	
	C-G-A	0.25	0.22	1.25 (0.86-1.81)	0.25
OBFC1	G-T-A-C-A	0.63	0.62	1	
	A-C-G-T-A	0.35	0.37	0.90 (0.65-1.24)	0.52
	G-T-A-C-C	0.02	0.006	1.64 (0.24-11.05)	0.61

AIS atherosclerotic ischemic stroke, Freq frequency, OR odd ratio, CI confidence interval. *P* adjusted for gender, age, smoking, alcohol, diabetes history, hypertension history, body mass index, total cholesterol, total triglyceride, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol.

emic stroke, especially in the carotid and intracranial arteries. Evidence manifested the association among vascular function, inflammation factors and atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus [23, 24]. *TINP1*, a gene which codes for TNFAIP3-interacting protein-1 (ABIN-1), is a regulatory molecule that stops signal way by several receptors, including TNF-alpha, TLR and PPAR [25]. Previous studies had confirmed the variants in *TINP1* gene were associated with an increased risk of systemic lupus erythematosus in European, Chinese and Japanese population [26]. Naveed Akbar, et al reported that ABIN-1 was associated with cardiovascular disease in mice [15]. However, up to now, there was no report on the association between *TINP1* polymorphisms and risk of AIS. Therefore, we conducted the disease association between three variants rs10036748, rs7708392, rs960709 and the risk of IS. The results showed that rs7708392 was associated with an increased risk of IS in heterozygous and overdominant model. For exploration of the possible reason, we also performed the association analysis between rs7708392 genotype and hypertension, blood lipid levels and diabetes mellitus in the control group. However, none of them showed a significant difference among them. Although the difference disappeared after Bonferroni correction, this polymorphism

Table 5. Genotype of rs7708392 and telomere, hypertension, diabetes mellitus and serum lipid in controls

Genotype	n	Telomere (M)	HBP (%)	DM (%)	HDL	LDL	TG	TC
CC	236	1.08	17.8	6.4	5.22 ± 0.89	3.13 ± 0.74	1.49 ± 0.52	5.22 ± 0.89
GC	135	1.12	13.3	6.9	1.38 ± 0.53	3.11 ± 0.71	1.52 ± 0.60	5.18 ± 0.81
GG	24	1.15	20	12	1.31 ± 0.54	3.10 ± 0.64	1.42 ± 0.46	4.94 ± 0.77
p		0.56	0.47	0.56	0.76	0.94	0.68	0.3

M median, HBP hypertension, DM diabetes mellitus, TC total cholesterol, TG triglyceride, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol.

was still a potential target in developing atherosclerosis and further ischemic stroke, which deserved further investigation in multiracial and larger sample studies.

Telomerase prolongs telomere sequence during DNA replication by adding the short telomere repeats (TTAGGG) to maintain chromosomal integrity and stability. *TERT* is a rate-limiting catalytic component of this enzyme. Therefore, mutations in the *TERT* gene may change the telomerase enzyme activity, shorten telomere length and further induce the development of some disease [27, 28]. The variants rs10069690 and rs2242652 were found to increase the risk of lung cancer, but not in rs2853676 [27]. And rs2736100 was associated with coronary artery disease in European population [4]. We performed the study on the association between rs2853676, rs2853677, rs10069690 and rs2242652 and risk of AIS. However, our results demonstrated that no statistical difference was found between them after adjustment for confounders in any model.

Oligonucleotide/oligosaccharide binding fold containing 1 (*OBFC1*) codes for oligosaccharide-binding fold-containing protein 1. Some study suggested that *OBFC1* could bind to telomeric single-stranded DNA in vitro, and overexpression of *OBFC1* mutant resulted in elon-gated telomeres [29]. GWAS meta-analysis showed that many SNPs including rs9325507, rs3814220, rs12765878 and rs9420907 were associated with leukocyte telomere length and further confirmed in replication [30]. Some previous study manifested that mutations in *OBFC1* were associated with an increased risk in ischemic heart disease [20]. For ischemic stroke, five polymorphisms including rs9325507, rs3814220, rs12765878, rs11191865 and rs9420907 were selected to test the association with the risk of AIS. Our results indicated that no CC genotype was observed in rs9420907, and no significant difference was found in allele or genotype or any genetic model.

The results from our study should be interpreted with caution in light of several limitations. Firstly, the statistic difference existed in age between cases and controls. The present study had a disproportionate number of subjects under the age of 40 (20.1% in controls and only 2% in cases). Secondly, there were significantly higher blood lipid levels in controls compared to the case group. This might be due to the use of lipid-lowering drugs or more attention was given on physical activity and healthy life style in the case group.

We concluded that variants within the *TERT* and *OBFC1* genes probably played no major role in the determination of AIS. SNP (rs7708392) within the *TNIP1* gene was associated with an increased risk of AIS, which maybe unlikely to be caused by telomere shortening, hypertension, diabetes and serum lipid. Haplotype analysis showed no significant difference between the case and the control within *TNIP1* and *OBFC1*.

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Disclosure of conflict of interest

None.

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References

[1] Johnston SC, Mendis S and Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. Lancet Neurol 2009; 8: 345-354.

[2] Liu L, Wang D, Wong KS and Wang Y. Stroke and stroke care in China: huge burden, significant workload, and a national priority. Stroke 2011; 42: 3651-3654.

[3] Jia Q, Liu LP and Wang YJ. Stroke in China. Clin Exp Pharmacol Physiol 2010; 37: 259-264.

[4] Codd V, Nelson CP, Albrecht E, Mangino M, Deelen J, Buxton JL, Hottenga JJ, Fischer K, Esko T, Surakka I, Broer L, Nyholt DR, Mateo Leach I, Salo P, Hägg S, Matthews MK, Palmen J, Norata GD, O'Reilly PF, Saleheen D, Amin N, Balmforth AJ, Beekman M, de Boer RA, Böhringer S, Braund PS, Burton PR, de Craen AJ, Denniff M, Dong Y, Douroudis K, Dubinina E, Eriksson JG, Garlaschelli K, Guo D, Hartikainen AL, Henders AK, Houwing-Duistermaat JJ, Kananen L, Karssen LC, Kettunen J, Klopp N, Lagou V, van Leeuwen EM, Madden PA, Mägi R, Magnusson PK, Männistö S, McCarthy MI, Medland SE, Mihailov E, Montgomery GW, Oostra BA, Palotie A, Peters A, Pollard H, Pouta A, Prokopenko I, Ripatti S, Salomaa V, Suchiman HE, Valdes AM, Verweij N, Viñuela A, Wang X, Wichmann HE, Widen E, Willemsen G, Wright MJ, Xia K, Xiao X, van Veldhuisen DJ, Catapano AL, Tobin MD, Hall AS, Blakemore AI, van Gilst WH, Zhu H; CARDIoGRAM consortium, Erdmann J, Reilly MP, Kathiresan S, Schunkert H, Talmud PJ, Pedersen NL, Perola M, Ouwehand W, Kaprio J, Martin NG, van Duijn CM, Hovatta I, Gieger C, Metspalu A, Boomsma DI, Jarvelin MR, Slagboom PE, Thompson JR, Spector TD, van der Harst P, Samani NJ. Identification of seven loci affecting mean telomere length and their association with disease. Nat Genet 2013; 45: 422-427, 427e421-422.

[5] Vulliamy T, Marrone A, Szydlo R, Walne A, Mason PJ and Dokal I. Disease anticipation is associated with progressive telomere shortening in families with dyskeratosis congenita due to mutations in TERC. Nat Genet 2004; 36: 447-449.

[6] D'Mello MJ, Ross SA, Briel M, Anand SS, Gerstein H and Pare G. Association between shortened leukocyte telomere length and cardiometabolic outcomes: systematic review and meta-analysis. Circ Cardiovasc Genet 2015; 8: 82-90.

[7] Allende M, Molina E, Gonzalez-Porras JR, Toledo E, Lecumberri R and Hermida J. Short leukocyte telomere length is associated with cardioembolic stroke risk in patients with atrial fibrillation. Stroke 2016; 47: 863-865.

[8] Ding H, Chen C, Shaffer JR, Liu L, Xu Y, Wang X, Hui R and Wang DW. Telomere length and risk of stroke in Chinese. Stroke 2012; 43: 658-663.

[9] Fitzpatrick AL, Kronmal RA, Kimura M, Gardner JP, Psaty BM, Jenny NS, Tracy RP, Hardikar S and Aviv A. Leukocyte telomere length and mortality in the Cardiovascular Health Study. J Gerontol A Biol Sci Med Sci 2011; 66: 421-429.

[10] Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A and Willeit P. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 2014; 349: g4227.

[11] Jurk D, Wilson C, Passos JF, Oakley F, Correia-Melo C, Greaves L, Saretzki G, Fox C, Lawless C, Anderson R, Hewitt G, Pender SL, Fullard N, Nelson G, Mann J, van de Sluis B, Mann DA, von Zglinicki T. Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. Nat Commun 2014; 5: 4172.

[12] Chu Y, Vahl JC, Kumar D, Heger K, Bertossi A, Wójtowicz E, Soberon V, Schenten D, Mack B and Reutelshöfer M. B cells lacking the tumor suppressor TNFAIP3/A20 display impaired differentiation and hyperactivation and cause inflammation and autoimmunity in aged mice. Blood 2011; 117: 2227-2236.

[13] Zhang DM, Cheng LQ, Zhai ZF, Feng L, Zhong BY, You Y, Zhang N, Song ZQ, Yang XC, Chen FR and Hao F. Single-nucleotide polymorphism and haplotypes of TNIP1 associated with systemic lupus erythematosus in a Chinese Han population. J Rheumatol 2013; 40: 1535-1544.

[14] Alarcon-Riquelme ME, Ziegler JT, Molineros J, Howard TD, Moreno-Estrada A, Sanchez-Rodriguez E, Ainsworth HC, Ortiz-Tello P, Comeau ME, Rasmussen A, Kelly JA, Adler A, Acevedo-Vazquez EM, Cucho-Venegas JM, Garcia-De la Torre I, Cardiel MH, Miranda P, Catoggio LJ, Maradiaga-Cecena M, Gaffney PM, Vyse TJ, Criswell LA, Tsao BP, Sivils KL, Bae SC, James JA, Kimberly RP, Kaufman KM, Harley JB, Esquivel-Valerio JA, Moctezuma JF, Garcia MA, Berbotto GA, Babini AM, Scherbarth H, Toloza S, Baca V, Nath SK, Aguilar Salinas C, Orozco L, Tusie-Luna T, Zidovetzki R, Pons-Estel BA, Langefeld CD and Jacob CO. Genome-wide association study in an Amerindian ancestry population reveals novel systemic lupus erythematosus risk loci and the role of European admixture. Arthritis Rheumatol 2016; 68: 932-943.

[15] Akbar N, Nanda S, Belch J, Cohen P and Khan F. An important role for A20-binding inhibitor of nuclear factor-kB-1 (ABIN1) in inflammation-

mediated endothelial dysfunction: an in vivo study in ABIN1 (D485N) mice. Arthritis Res Ther 2015; 17: 22.

[16] Sarek G, Marzec P, Margalef P and Boulton SJ. Molecular basis of telomere dysfunction in human genetic diseases. Nat Struct Mol Biol 2015; 22: 867-874.

[17] Zee RY, Ridker PM and Chasman DI. Genetic variants in eleven telomere-associated genes and the risk of incident cardio/cerebrovascular disease: the Women's Genome Health Study. Clin Chim Acta 2011; 412: 199-202.

[18] Karami S, Han Y, Pande M, Cheng I, Rudd J, Pierce BL, Nutter EL, Schumacher FR, Kote-Jarai Z, Lindstrom S, Witte JS, Fang S, Han J, Kraft P, Hunter D, Song F, Hung RJ, McKay J, Gruber SB, Chanock SJ, Risch A, Shen H, Haiman CA, Boardman L, Ulrich CM, Casey G, Peters U, Amin Al Olama A, Berchuck A, Berndt SI, Bezieau S, Brennan P, Brenner H, Brinton L, Caporaso N, Chan AT, Chang-Claude J, Christiani DC, Cunningham JM, Easton D, Eeles RA, Eisen T, Gala M, Gallinger SJ, Gayther SA, Goode EL, Grönberg H, Henderson BE, Houlston R, Joshi AD, Küry S, Landi MT, Le Marchand L, Muir K, Newcomb PA, Permuth-Wey J, Pharoah P, Phelan C, Potter JD, Ramus SJ, Risch H, Schildkraut J, Slattery ML, Song H, Wentzensen N, White E, Wiklund F, Zanke BW, Sellers TA, Zheng W, Chatterjee N, Amos CI, Doherty JA; GECCO and the GAME-ON Network: CORECT, DRIVE, ELLIPSE, FOCI, and TRICL. Telomere structure and maintenance gene variants and risk of five cancer types. Int J Cancer 2016; 139: 2655-2670.

[19] Walsh KM, Codd V, Smirnov IV, Rice T, Decker PA, Hansen HM, Kollmeyer T, Kosel ML, Molinaro AM, McCoy LS, Bracci PM, Cabriga BS, Pekmezci M, Zheng S, Wiemels JL, Pico AR, Tihan T, Berger MS, Chang SM, Prados MD, Lachance DH, O'Neill BP, Sicotte H, Eckel-Passow JE; ENGAGE Consortium Telomere Group, van der Harst P, Wiencke JK, Samani NJ, Jenkins RB, Wrensch MR. Variants near TERT and TERC influencing telomere length are associated with high-grade glioma risk. Nat Genet 2014; 46: 731-735.

[20] Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL and Marsh EE. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke 1993; 24: 35-41.

[21] Gabriel S, Ziaugra L and Tabbaa D. SNP genotyping using the Sequenom MassARRAY iPLEX platform. Curr Protoc Hum Genet 2009; Chapter 2: Unit 2.12.

[22] Full LE, Ruisanchez C and Monaco C. The inextricable link between atherosclerosis and prototypical inflammatory diseases rheumatoid arthritis and systemic lupus erythematosus. Arthritis Res Ther 2009; 11: 217.

[23] Barbulescu AL, Vreju F, Cojocaru-Gofita IR, Musetescu AE and Ciurea PL. Impaired arterial stiffness in systemic lupus ertythematosus-correlations with inflammation markers. Curr Health Sci J 2012; 38: 61-65.

[24] Yap WH, Yeoh E, Tay A, Brenner S and Venkatesh B. STAT4 is a target of the hematopoietic zinc-finger transcription factor Ikaros in T cells. FEBS Lett 2005; 579: 4470-4478.

[25] Wang C, Ahlford A, Jarvinen TM, Nordmark G, Eloranta ML, Gunnarsson I, Svenungsson E, Padyukov L, Sturfelt G, Jonsen A, Bengtsson AA, Truedsson L, Eriksson C, Rantapaa-Dahlqvist S, Sjowall C, Julkunen H, Criswell LA, Graham RR, Behrens TW, Kere J, Ronnblom L, Syvanen AC and Sandling JK. Genes identified in Asian SLE GWASs are also associated with SLE in Caucasian populations. Eur J Hum Genet 2013; 21: 994-999.

[26] Gao L, Thakur A, Liang Y, Zhang S, Wang T, Chen T, Meng J, Wang L, Wu F, Jin T, Li X, Liu JJ, Chen C and Chen M. Polymorphisms in the TERT gene are associated with lung cancer risk in the Chinese Han population. Eur J Cancer Prev 2014; 23: 497-501.

[27] Wu D, Yu H, Sun J, Qi J, Liu Q, Li R, Zheng SL, Xu J and Kang J. Association of genetic polymorphisms in the telomerase reverse transcriptase gene with prostate cancer aggressiveness. Mol Med Rep 2015; 12: 489-497.

[28] Wan M, Qin J, Songyang Z and Liu D. OB fold-containing protein 1 (OBFC1), a human homolog of yeast Stn1, associates with TPP1 and is implicated in telomere length regulation. J Biol Chem 2009; 284: 26725-26731.

[29] Levy D, Neuhausen SL, Hunt SC, Kimura M, Hwang SJ, Chen W, Bis JC, Fitzpatrick AL, Smith E, Johnson AD, Gardner JP, Srinivasan SR, Schork N, Rotter JI, Herbig U, Psaty BM, Sastrasinh M, Murray SS, Vasan RS, Province MA, Glazer NL, Lu X, Cao X, Kronmal R, Mangino M, Soranzo N, Spector TD, Berenson GS and Aviv A. Genome-wide association identifies OBFC1 as a locus involved in human leukocyte telomere biology. Proc Natl Acad Sci U S A 2010; 107: 9293-9298.

[30] Scheller Madrid A, Rode L, Nordestgaard BG and Bojesen SE. Short telomere length and ischemic heart disease: observational and genetic studies in 290 022 individuals. Clin Chem 2016; 62: 1140-9.