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Genetic Risk Factors for Intracranial Aneurysm in the Kazakh Population

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Abstract

An intracranial aneurysm (IA) is a weak or thin area on a blood vessel in the brain that balloons as it fills with blood. Genetic factors can influence the risk of developing an aneurism. The purpose of this study was to explore the relationship between single nucleotide polymorphisms (SNPs) and IA in Kazakh population. The patients were genotyped for 60 single nucleotide polymorphisms. Genotyping was performed on the QuantStudio 12K Flex (Life Technologies). A linear regression analysis found 13 SNPs' significant association with development and rupture of IA: the rs1800956 polymorphism of the *ENG* gene, rs1756 46 polymorphism of the *JDP2* gene, variant rs1800255 of the *COL3A1*, rs4667622 of the *UBR3*, rs2374513 of the *c12orf75*, rs3742321 polymorphism of the *StAR*, the rs3782356 polymorphism of *MLL2* gene, rs3932338 to 214 kilobases downstream of *PRDM9*, rs7550260 polymorphism of the *ARHGEF*, rs1504749 polymorphism of the *SOX17*, the rs173686 polymorphism of *CSPG2* gene, rs6460071 located on *LIMK1* gene, and the rs4934 polymorphism of *SERPINA3*. A total of 13 SNPs were identified as potential genetic markers for the development and risk of rupture of aneurysms in the Kazakh population. Similar results were obtained after adjusting for the confounding factors of arterial hypertension and age.

Keywords Intracranial aneurysm · Ruptured and unruptured aneurysms · SNP · Genotyping · Risk factors

Introduction

Intracranial aneurysms (IAs) are rare in children and young adults, but the prevalence increases significantly after 30 years of age to 3.2% in the middle-aged population without comorbidities, with equal distribution between the sexes. The incidence of unruptured IAs does not vary significantly by country or by ethnic group, despite differences in the incidence of aneurismal subarachnoid hemorrhage (SAH) among ethnic groups (Vlak et al. 2011). Aneurysmal SAH is a serious complication associated with cerebrovascular pathology that is observed in 0.8–10% of cases (Wiebers et al. 2003) and has an unfavorable outcome, with mortality occurring within 30 days in 45% of all cases (Johnston et al. 1998).

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Although there are data on the frequency of SAH in Almaty, Kazahkstan's largest city, there have been no previous studies on the epidemiology of cerebral aneurysms in the Kazakh population. In 2005, the incidence of SAH was five cases per 100,000 people, although this was determined based solely on inpatient data (Makhambetov 2007). About 83% of people in Kazakhstan who experience ruptured aneurysms are of working age (mean age, 45.3 years), which places a significant economic burden on society (Akshulakov et al. 2016).

Preventive treatment must be considered for patients with unruptured aneurysms who are at risk of rupture. Previous studies have shown that the sex and hormonal background of the patient, alcohol abuse, and presence of arterial hypertension (AH) are general risk factors for the development of aneurysmal SAH. In addition, environmental and genetic factors play important roles in the pathogenesis and rupture of IAs. There have been many studies on genetic markers for the risk of brain aneurysm (Tromp et al. 2014; Bourcier et al. 2015), which vary according to ethnicity and may not be generalizable to different populations. We analyzed available published data on SNP of association with IA and stratification for population ethnicity. For example, a genome-wide association study (GWAS) of IAs that included cohorts from Europe and Japan found 13 single nucleotide polymorphisms (SNPs) that were associated with cerebral aneurysms (Yasuno et al. 2010), while a meta-analysis of over 116,000 individuals from 61 studies reported 19 SNPs, highlighting the importance of genetics in IA development (Alg et al. 2013). The GWAS identified two loci in the genome—namely, endothelin receptor type A (4q31.22) and cyclin-dependent kinase inhibitor 2B antisense (9p21.3)—that were associated with IA in the Japanese population (Low et al. 2012).

The purpose of the current study was to find associations of genetic variation in candidate genes in patients diagnosed with IA in the Kazakh population. We investigated risk factors for sporadic intracranial aneurysm.

Materials and Methods

Study Population

Cases were enrolled at the Department of Vascular and Functional Neurosurgery of the National Center of Neurosurgery in Astana, Kazakhstan. A total of 728 Kazakh patients were examined; there were 196 cases of ruptured and 138 cases of unruptured aneurysms. The control group comprised 394 healthy subjects with no personal or family history of IA, SAH, or other neurological disorders (arteriovenous malformations of the brain, cavernous angiomas, brain tumors, craniocerebral trauma, patients with connective tissue diseases (Marfan syndrome, Ellers-Danlo syndrome, etc.). A total of 728 individuals living in different regions of Kazakhstan during 2015–2017 and belonging only to the Kazakh ethnicity participated in this study, according to self-reported information; participants who self-identified as being of Russian, Western European, East Asian, or Middle Eastern origin were excluded. All individuals included in the present study were unrelated. The demographic and clinical characteristics of the patients and controls are summarized in Table 1.

In all cases, IA was diagnosed based on computed tomography (CT) or magnetic resonance (MR) angiography data and was confirmed at surgery, when applicable. Ruptured IA cases were defined based on symptoms of acute SAH observed by CT or MR imagining. Unruptured IA cases were identified by CT or else by MR or conventional angiography in the absence of clinical or radiological signs of SAH. All patients age younger than 18 years and patients with arteriovenous malformations, non-saccular fusiform and infectious aneurysms, or traumatic and unknown origin of SAH were excluded.

The research protocol complied with the Declaration of Helsinki and was approved by the Human Research Ethic Committee of the National Center for Neurosurgery. All study participants completed a questionnaire and provided informed consent, approved by the ethics committee. In the case of physical or mental incapacity, consent was obtained from family members.

Selection of Candidate Gene Polymorphisms for Development and Rupture IA

We analyzed available published data on SNP of association with IA and stratification for population ethnicity. The panel of 60 SNPs used in this study (Table 2) was selected based on published data.

Genotyping

Genomic DNA was isolated from 9 ml of EDTA-anticoagulated whole venous blood by a standard salt-out method (Miller et al. 1988). DNA concentration was determined by measuring the absorbance at 260 nm on a Nanodrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Genotyping of the extended panel of polymorphisms of candidate genes was performed on the QuantStudio 12K Flex (Life Technologies). The reaction mixture consisting of the DNA sample combined with 2× TaqMan Open Array Real-Time PCR Master Mix (Life Technologies, Carlsbad, CA, USA) was loaded into custom-designed Open Array plates using a QuantStudio 12K Flex AccuFill system. The Open Arrays were covered with immersion fluid from QuantStudio 12K Flex Open Array accessories kit and loaded into the QuantStudio 12K Flex instrument for amplification. Samples were subjected to a standard thermal cycling protocol provided by Life Technologies. Data analysis was performed using the software package TaqMan Genotyper Software v.1.3.

Table 1 Anthropometric and biochemical characteristics of the study population

Factors	Study group			*P* value
	Ruptured aneurysms	Unruptured aneurysms	Control group	
Patients	196 (58.7%)	138 (41.371%)	394 (100%)	
Male	83 (42%)	35 (25%)	197 (50%)	
Female	113 (58%)	103 (75%)	197 (50%)	0.151
Age (years)	49.7 ± 11.2	54.1 ± 11.1	52.4 ± 13.2	0.037
< 40	36 (18%)	15 (11%)	71 (18%)	
40–59	123 (62%)	79 (57%)	196 (50%)	
≥ 60	37 (20%)	44 (32%)	127 (32%)	
Arterial hypertension	134 (68.3%)	82 (59.4%)	171 (43.1%)	0.331
Stage 1 hypertension	17 (8.6%)	6 (4.3%)	11 (2.8%)	
Stage 2 hypertension	20 (10.2%)	29 (21%)	48 (12.2%)	
Stage 3 hypertension	97 (49.5%)	47 (34%)	112 (28.4%)	
Smoking	57 (29%)	35 (25.3%)	131 (33.2%)	0.352
Number of aneurysms	268 (59.3%)	184 (40.7%)		
Multiple	47 (24%)	29 (21%)		0.409
Size (mm)				
< 5	133 (49.6%)	55 (29.9%)		0.001
5.0–6.9	47 (17.5%)	34 (18.5%)		0.816
7.0–9.9	37 (13.8%)	29 (15.7%)		0.593
10.0–19.9	45 (16.8%)	45 (24.5%)		0.073
≥ 20	6 (2.2%)	21 (11.4%)		0.001
Localization				
Internal carotid artery	78 (29.1%)	98 (53.3%)		0.001
Middle cerebral artery	105 (39.2%)	49 (26.6%)		0.024
Anterior cerebral and anterior communicating arteries	72 (26.8%)	23 (12.5%)		0.001
Posterior circulation arteries	13 (4.8%)	14 (7.6%)		0.238
Size				
Depth	6.97 ± 5.74	10.42 ± 9.82		0.001
Width	5.23 ± 4.36	7.92 ± 7.57		0.001
Neck	3.39 ± 2.14	4.69 ± 3.15		0.001

Statistical Analysis

Stepwise regression analyses were performed to estimate the effect of confounding factors (patient age, sex, hypertension, smoking, and history of cardiovascular disease and diabetes mellitus) on IA risk. Genotype and allele frequencies were tested for deviation from Hardy-Weinberg equilibrium (HWE). Linear regression analysis was applied to detect associations of polymorphic loci in additive genetic model adjusting for age and hypertension. Differences at $P < 0.001$ were considered as statistically significant.

The Bonferroni correction based on 304 independent tests was used to assess the significance level of the association. The adjusted significance level was $P = 0.0003$; $P < 0.001$ was considered suggestive of an association. Data were analyzed with R (https://www.r-project.org/) and PLINK 1.07 (http://zzz.bwh.harvard.edu/plink/) software packages.

Linkage disequilibrium (LD) was estimated using Haploview v.4.2 (https://www.broadinstitute.org/haploview/haploview). A HW *P* value cutoff of 0.001 was used for block generation. We excluded SNPs with a minor allele frequency (MAF) of < 0.001. The confidence interval default algorithm was used for block generation (Barrett et al. 2005).

Significant SNPs were further annotated using RegulomeDB (http://www.regulomedb.org/), which harbors information for known and predicted regulatory elements (Boyle et al. 2012) and was also used to annotate functional variations in individual genomes.

Results

Basic demographic data for cases and controls are presented in Table 1. Among our patients with aneurysms, there were more

Table 2 Description of 60 SNPs included in the study

Gene	Polymorphism	Locus
Cyclin-dependent kinase inhibitor 2 B antisense RNA (CDKN2B-AS1)	rs1333040	9p21.3
Cyclin-dependent kinase inhibitor 2 B antisense RNA (CDKN2B-AS1)	rs10757278	9p21.3
Cyclin-dependent kinase inhibitor 2 B antisense RNA (CDKN2B-AS1)	rs2891168	9p21.3
Cyclin-dependent kinase inhibitor 2 B antisense RNA (CDKN2B-AS1)	rs2383207	9p21.3
Cyclin-dependent kinase inhibitor 2 B antisense RNA (CDKN2B-AS1)	rs4977574	9p21.3
Cyclin-dependent kinase inhibitor 2 B antisense RNA (CDKN2B-AS1)	rs6475606	9p21.3
Cyclin-dependent kinase inhibitor 2 B antisense RNA (CDKN2B-AS2)	rs10733376	9p21.3
Putative signal peptidase complex catalytic subunit (SEC11B)	rs9298506	8q11.23
Sex-determining region Y-box 17 (SOX17)	rs10958409	8q11.23
Boule homolog, RNA-binding protein (BOLL)	rs700651	2q33.1
Boule homolog, RNA-binding protein (BOLL)	rs1429412	2q33.1
Endothelin receptor type A (ENDRA)	rs6841581	4q31.23
Endothelin receptor type A (ENDRA)	rs6842241	4q31.23
Sex-determining region Y-box 17 (SOX17)	rs1504749	8q11.23
StAR-related lipid transfer domain containing 13 (STARD13, KL)	rs1980781	13q13.1-q13.2
Fibrillin 2 (FBN2)	rs331079	5q23.3
StAR-related lipid transfer domain containing 13 (STARD13, KL)	rs9315204	13q13.1-q13.2
StAR-related lipid transfer domain containing 13 (STARD13, KL)	rs3742321	13q13.1-q13.2
FYVE, RhoGEF, and PH domain containing 6 (FGD6)	rs6538595	12q22
Ribosome-binding protein 1 (RRBP1)	rs1132274	20p12.1
Collagen, type IV, alpha 1 (COL4A1)	rs3783107	13q34
Ribosome-binding protein 1 (RRBP1)	rs11661542	20p12.1
RB-binding protein 8, endonuclease (RBBP8)	rs4800418	18q11.2
Collagen, type III, alpha 1 (COL3A1)	rs1800255	2q32.2
Cholinergic receptor nicotinic alpha 1 subunit (CHRNA1)	rs2621215	2q31.1
Collagen, type I, alpha 2 (COL1A2)	rs42524	7q21.3
Versican (VCAN)	rs173686	5q14.2-q14.3
Versican (VCAN)	rs251124	5q14.2-q14.3
Transmembrane protein 195 (TMEM 195)	rs4628172	7p21.2
Nitric oxide synthase 3 (NOS3)	rs2070744	7q36
Heparan sulfate proteoglycan 2 (HSPG2)	rs3767137	1p36.12
Thrombomodulin (THBD)	rs41348347	20p11.2
Tumor necrosis factor α (TNFα)	rs361525	6p21.3
Interleukin 6 (IL6)	rs1800796	7p21
ADP ribosylation factor guanine nucleotide exchange factor 11 (ARHGEF11)	rs7550260	1q23.1
ADAM metallopeptidase with thrombospondin type 1 motif 15 (ADAMTS15)	rs185269810	11q24.3
BTB domain containing 16 (BTBD16)	rs911774	10q26.13
Chromosome 9 open reading frame 75 (C12orf75 [168 kb])	rs11112585	9p21.2
Chromosome 9 open reading frame 75 (C12orf75 [242 kb])	rs2374513	9p21.2
MicroRNA let-7a-1 (MIRLET7A1)	rs13293512	9q22.32
Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)	rs3769801	6q23.2
Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)	rs1897472	6q23.2
Filamin A interacting protein 1 (FILIP1)	rs150956085	6q14.1
Matrix metallopeptidase 2 (MMP2)	rs243847	16q12.2
LIM domain kinase 1 (LIMK1)	rs6460071	7q11.23
Serpin family A member 3 (SERPINA3)	rs4934	14q32.1
Ubiquitin protein ligase E3 component n-recognin 3 (UBR3)	rs4667622	2q31.1
Sodium voltage-gated channel alpha subunit 11 (SCN11A)	rs6599001	3p22.2
PR domain containing 9 (PRDM9)	rs3932338	5p14.2

Table 2 (continued)

Gene	Polymorphism	Locus
5-Hydroxytryptamine receptor 1B (HTR1B)	rs10943471	6q14.1
5′-Nucleotidase, cytosolic II (CNNM2)	rs12413409	10q24.32
5′-Nucleotidase, cytosolic II (CNNM2)	rs12411886	10q24.32
Transcobalamin 2 (TCN2)	rs1801198	22q12.2
Histone deacetylase 9 (HDAC9)	rs10230207	7p21.1
Myeloid/lymphoid or mixed-lineage leukemia 2 (MLL2)	rs3782356	Chr. 5
Jun dimerization protein 2 (JDP2)	rs175646	14q24.3
Kallikrein-related peptidase 8 (KLK8)	rs1722561	19q13.41
Endoglin (ENG)	rs1800956	9q34.11
Zinc finger protein 222 (ZNF222)	rs117318348	19q13.31
Transmembrane protein 195 (TMEM 195)	rs7781293	7p21.2

women than men (58 vs. 42% in the ruptured aneurysm group and 75 vs. 25% in the unruptured aneurysm group). Patients with ruptured aneurysm presented with SAH at a younger age than those with unruptured aneurysms (mean age = 49.7 ± 11.2 years, range 18–88 years vs. 54.1 ± 11.1 years, range 18–88 years).

The 334 patients had a total of 452 aneurysms (268 ruptured and 184 unruptured). Multiple aneurysms were seen in 22.7% of patients. Most of the ruptured aneurysms were in middle cerebral artery (MCA; 39.2%), and most of the unruptured aneurysms were in the internal carotid artery (ICA; 53.3%). The majority of aneurysms were < 15 mm. Among ruptured cases, the median size was 6.97 ± 5.74 mm; for unruptured cases, the median size was 10.42 ± 9.82 mm. The impact of morphological prognostic factors on aneurysm rupture was evaluated with the χ^2 and Student's *t* tests. Female sex and age > 60 years, size < 5 mm and ≥ 10 mm, and localization of IA on the ICA, MCA, anterior cerebral artery, and anterior communicating artery influenced the probability of IA rupture ($P \leq 0.20$).

Correlation analysis between the depths of arteries of different locations (middle cerebral artery, internal carotid artery, anterior cerebral artery, posterior cerebral circulation) and age did not reveal statistically significant values (*r*, *P* value). The correlation coefficient does not significantly differ from zero, i.e., the relationship between the parameters is not observed.

Poisson regression analysis showed that the number of aneurysms depends on hypertension ($P = 9.11e-06$) and age ($P = 0.0233$), with the age playing a minor effect.

Anthropometric and biochemical characteristics were examined as potential confounding factors before evaluating the association between genotype distribution and IA status. The distributions of the measured traits met the criteria for normality and were included in the analysis without transformation. A correlation matrix was constructed to verify that all phenotypes were independent of each other and could be used as independent parameters (Table 3) and also to exclude parameters that did not significantly affect IA development. The matrix revealed that the phenotypes did not interact and could be used as independent parameters. This allowed us to exclude predictors that did not have statistical significance. Of the tested parameters, only age and presence of hypertension were statistically significant predictors ($P < 0.001$). The final statistical model included both of these parameters as adjustment factors that could affect the association between genotype and IA status.

Next, we investigated the association between the occurrence of aneurysms (phenotype) and genetic variability, taking into account the effects of age and hypertension. All data were filtered by analyzing the genotyping results. Samples that yielded an ambiguous result (i.e., low signal) and those that lacked one of the phenotypic parameters were excluded from the analysis, as were markers (SNPs) that did not conform to HWE. Of the 60 SNPs that were genotyped, 38 SNPs were in HWE. The data were filtered using a computer program and SNPs that reached a significance level of $P < 0.001$ were reported.

Genetic analyses were carried out using additive genetic model. The results of the linear regression analysis are shown in Table 4. Three comparing groups were included in the analysis: control group, the patient group with ruptured aneurysm, and the patient group with unruptured aneurysms. The results from linear regression revealed that 13 SNPs were associated with IA, and linear regression analysis after adjusting for age and hypertension.

The allele and genotype frequencies of the remaining 13 SNPs are summarized in Table 5.

Using Haploview v.4.2 software, we obtained LD statistical results for aneurysm samples (ruptured and unruptured) (Fig. 1). For block generation, we used the confidence interval default algorithm and selected SNPs that conformed to HWE and ignored those with MAF < 0.001. Consequently, haplotype blocks were not defined. Tag-SNP analysis was also carried out using the aggressive tagging strategy (r^2 threshold, 0.8; logarithm [base 10] of odds threshold, 3.0; and minimum distance between tags, 0 kb). As a result, tag-SNPs were not defined.

Table 3 Pairwise correlation matrix of measured variables

	trait_c	trait_b	age	gender	rebl	hyp	cvd	athero	diabet	ms	kidney	ophtalm	ear	ml_aneu
trait_c	1.000													
trait_b	0.908	1.000												
age	− 0.109	− 0.070	1.000											
gender	0.098	0.155	0.045	1.000										
reble	0.105	0.072	− 0.017	− 0.056	1.000									
hyp	0.204	0.195	0.361	− 0.050	− 0.050	1.000								
cvd	0.117	0.111	0.261	− 0.042	− 0.046	0.530	1.000							
athero	− 0.016	− 0.016	0.109	− 0.081	− 0.023	0.111	0.168	1.000						
diabet	− 0.051	− 0.058	0.125	− 0.126	0.056	0.124	0.182	0.208	1.000					
ms	0.065	0.055	0.009	− 0.043	0.035	0.115	0.195	0.190	0.179	1.000				
kidney	0.108	0.120	0.141	0.059	0.037	0.179	0.268	0.132	0.124	0.142	1.000			
ophtalm	0.063	0.102	0.047	0.006	− 0.013	0.125	0.048	0.105	0.091	0.055	0.035	1.000		
ear	− 0.036	− 0.036	0.020	− 0.054	− 0.014	− 0.021	− 0.048	− 0.016	− 0.024	− 0.018	− 0.029	0.064	1.000	
ml_aneu	0.368	0.380	− 0.006	0.098	− 0.018	0.111	0.099	0.004	− 0.004	0.018	0.057	0.084	− 0.036	1.000

athero atherosclerosis; *cvd* cardiovascular disease; *ear* ear disease; *hyp* hypertension; *ms* metabolic syndrome; *kidney* kidney disease; *mult aneu* multiple aneurysms; *ophtalm* eye disease; *reble* rebleeding

Discussion

This is a replication study which needs to define the role of ethnic variation in association study with specific reference to intracranial aneurysm. In the present study, we investigated genetic variants previously reported to be associated with IA development and/or age and AH in a Kazakh cohort. Kazakhs are Turkic-speaking people that live in several Central Asian countries including Kazakhstan, Uzbekistan, and Kyrgyzstan as well as in Russia, Mongolia, and China. Although genetic data are scarce, it is supposed that the Kazakh population was formed from the admixture of the European and Asian populations (Comas et al. 1998).

The present study focuses on 60 SNPs in 44 candidate genes that were previously reported as genetic risk factors for IA. Dysplasia of connective tissue or other defects in the vascular wall contributes to the development of IAs. These can arise as a result of mutations in genes associated with endothelial function and vascular remodeling, connective tissue and extracellular matrix (ECM) formation, and inflammation, among other processes.

The results from linear regression revealed that ENG (rs1800956) SNP was associated with IA in the Kazakh population. Endoglin (ENG) is a type I membrane glycoprotein and the part of the TGF beta receptor complex that involved in vascular remodeling. Joo SP et al. were showed that the rs1800956 of endoglin may play an important role in the pathogenesis of IAs in the Korean population (Joo et al. 2008). Polymorphism, rs1800956 in exon 8 of endoglin leads to an aspartic acid to histidine replacement, has been reported to have an effect on IA susceptibility in Chinese Han population but not in Japanese population (Xin Hu, 2015). Xin Hu et al. carried out a meta-analysis to evaluate the potential association of endoglin polymorphisms on IA risk. They found that rs1800956 was significantly related to IA occurrence (Hu et al. 2015).

The results of our study revealed a reliable association between the rs175646 polymorphism of the Jun dimerization protein 2 gene and the risk of aneurysm development and rupture in the additive model ($\beta = 0.479$, $P = 2.75E{-}21$), taking into account the predisposing factors of age and AH. Jun dimerization protein 2 (JUNDM2) is a protein that in humans is encoded by the JDP2 gene. The Jun dimerization protein is a member of the AP-1 family of transcription factors. The protein JDP2 has 163 amino acids, belongs to the family of basic leucine zipper (bZIP), and shows high homology with the ATF3 bZIP domain (Aronheim et al. 1997). The protein JDP2 was involved in a variety of transcriptional responses associated with AP-1 such as UV-induced apoptosis, cell differentiation, tumorigenesis, and antitumogeneris; can also function as a repressor by recruiting histone deacetylase 3/HDAC3 to the promoter region of JUN; and may control transcription via direct regulation of the modification of histones and the assembly of chromatin. Vascular remodeling via apoptotic mechanisms is an important factor in vascular diseases. c-Jun amino-terminal kinase (JNK) is a member of the mitogen-activated protein kinase family and initiates apoptosis mainly via phosphorylation of the c-Jun transcription factor (Takagi et al. 2002). A JDP2 single nucleotide polymorphism was studied in Japanese, Korean, and Dutch cohorts, as an increased risk of intracranial aneurysms. Krischek et al. were showed the SNP of the Jun dimerization protein 2 gene, located on 14q24, that are associated with intracranial

Table 4 Results of linear regression analysis

Gene	SNP	Not adjusted		Adjusted		*n*	a11	a12	a22
		beta	*P*	beta	*P*				
ENG	rs1800956	0.39	1.26243E−21	0.38	3.69259E−22	617	244	196	177
JDP2	rs175646	0.479	2.74754E−21	0.488	8.74124E−24	550	231	230	89
COL3A1	rs1800255	0.471	6.57893E−15	0.455	7.19567E−15	570	361	177	32
UBR3	rs4667622	0.544	1.11563E−14	0.508	1.31544E−13	565	400	153	12
C12orf75 (242 kb)	rs2374513	0.318	2.15815E−09	0.303	3.70438E−09	608	279	272	57
STARD13, KL	rs3742321	0.288	1.94445E−07	0.302	2.16331E−08	427	164	184	79
PRDM9	rs3932338	0.293	3.57319E−07	0.282	3.5069E−07	553	270	236	47
MLL2	rs3782356	0.226	4.17232E−07	0.23	8.46602E−08	586	285	182	119
ARHGEF11	rs7550260	0.265	4.88958E−07	0.281	2.73076E−08	608	322	236	50
SOX17	rs1504749	0.289	1.47165E−06	0.286	7.45635E−07	656	480	146	30
VCAN (CSPG2)	rs173686	0.285	1.76742E−06	0.316	3.42134E−08	584	398	153	33
LIMK1	rs6460071	0.217	5.57745E−06	0.224	1.37586E−06	544	317	145	82
SERPINA3	rs4934	0.241	1.99338E−05	0.254	3.13953E−06	647	419	194	34
ENPP1	rs3769801	0.261	0.000120749	0.291	7.58854E−06	380	149	195	36
KLK8	rs1722561	0.243	0.000200688	0.288	4.63813E−06	638	469	151	18
(CDKN2B-AS2	rs10733376	0.223	0.000311511	0.239	5.84244E−05	603	354	225	24
CDKN2B-AS1	rs6475606	0.215	0.000312243	0.229	7.58131E−05	560	300	225	35
FGD6	rs6538595	0.205	0.000345749	0.214	0.000130222	520	268	211	41
MIRLET7A1	rs13293512	0.213	0.000509998	0.204	0.000649543	504	277	189	38
BTBD16)	rs911774	0.157	0.000928624	0.174	0.000140712	635	351	199	85
IL6	rs1800796	0.22	0.001004144	0.21	0.001092267	406	134	225	47
NOS3	rs2070744	0.132	0.00460441	0.108	0.016910962	566	215	221	130
C12orf75	rs11112585	0.152	0.008267853	0.141	0.011631234	582	417	124	41
CNNM2	rs12413409	0.118	0.008614071	0.112	0.010438434	555	253	170	132
CHRNA1	rs2621215	− 0.212	0.009818993	− 0.189	0.016581243	462	350	101	11
SOX17	rs10958409	0.139	0.010742741	0.173	0.000849728	527	240	227	60
THBD	rs41348347	0.133	0.023049339	0.154	0.006930993	526	317	168	41
STARD13, KL	rs1980781	− 0.102	0.109645336	− 0.135	0.029200512	552	306	228	18
RRBP1	rs1132274	0.093	0.123544282	0.082	0.16229746	548	348	169	31
COL1A2	rs42524	0.084	0.130648189	0.092	0.086491105	380	151	139	90
CDKN2B-AS1	rs4977574	0.06	0.394970571	0.076	0.26436905	544	409	116	19
CDKN2B-AS1	rs2891168	− 0.039	0.465973596	− 0.01	0.846148617	561	270	234	57
BOLL	rs700651	0.038	0.507898118	0.08	0.150591707	524	268	212	44
MMP2	rs243847	0.027	0.618007988	0.07	0.183605879	526	140	278	108
CNNM2	rs12411886	0.047	0.633044867	0.054	0.572936201	588	503	84	1
CDKN2B-AS1	rs1333040	− 0.017	0.747533184	− 0.034	0.515207475	440	165	179	96
VCAN	rs251124	0.014	0.807915636	0.039	0.486940062	503	125	286	92
STARD13, KL	rs9315204	− 0,012	0.819959155	0.018	0.729792221	487	231	185	71

aneurysms in the Japanese population. There was no difference in allelic or genotypic frequencies in the Dutch population (Krischek et al. 2010).

A statistically significant association between the risk of IA development and rupture and the effects of age and AH was observed for the rs1800255 polymorphism of the *COL3A1* gene ($\beta = 0.471$, $P = 6.58\text{E}{-15}$) in the additive model. Collagen types I and III constitute 80–90% of the total arterial collagen and along with other ECM proteins confer strength and elasticity to the vessel wall, including those of intracranial arteries, which likely contributes to IA pathogenesis. A *COL3A1* gene polymorphism resulting in an Ala698Thr substitution that ensures a low thermal stability of the peptide has been linked to sporadic (non-familial) IA (Chen et al. 2012). However, this association did not depend on the presence of hemorrhagic stroke or hypertension. These results support the

Table 5 Allele frequency and genotype distribution in the Kazakh population

No.	Gene name	rs	Total number of samples	Allele	na	Allele freq	Genotype	nb	Genotype freq
1	ENG	rs1800956	617	C	684	0.55	CC	244	0.39
				G	550	0.45	GC	196	0.32
							GG	177	0.29
2	JDP2	rs175646	550	C	692	0.63	CC	231	0.42
				T	408	0.37	CT	230	0.42
							TT	89	0.16
3	UBR3	rs4667622	565	A	953	0.84	AA	400	0.71
				G	177	0.16	AG	153	0.27
							GG	12	0.02
4	*C12orf75 (242 kb)*	rs2374513	608	C	830	0.68	CC	279	0.46
				T	386	0.32	CT	272	0.45
							TT	57	0.09
5	MLL2	rs3782356	586	C	752	0.64	CC	285	0.49
				T	420	0.36	CT	182	0.31
							TT	119	0.20
6	COL3A1	rs1800255	570	C	899	0.79	CC	361	0.63
				A	241	0.21	CA	177	0.31
							AA	32	0.06
7	PRDM9	rs3932338	553	G	776	0.70	GG	270	0.49
				A	330	0.30	GA	236	0.43
							AA	47	0.08
8	VCAN (CSPG2)	rs173686	584	G	949	0.81	GG	398	0.68
				A	219	0.19	GA	153	0.26
							AA	33	0.06
9	LIMK1	rs6460071	544	G	779	0.72	GG	317	0.58
				A	309	0.28	GA	145	0.27
							AA	82	0.15
10	STARD13, KL	rs3742321	427	T	512	0.60	TT	164	0.38
				C	342	0.40	CT	184	0.43
							CC	79	0.19
11	SOX17	rs1504749	656	A	1106	0.84	AA	480	0.73
				C	206	0.16	CA	146	0.22
							CC	30	0.05
12	SERPINA3	rs4934	647	G	1032	0.80	GG	419	0.65
				A	262	0.20	GA	194	0.30
							AA	34	0.05
13	ARHGEF11	rs7550260	608	C	880	0.72	CC	322	0.53
				A	336	0.28	CA	236	0.39
							AA	50	0.08

view that functional variants of *COL3A1* are a genetic risk factor for IA in the Chinese population. This indicates that the *COL3A1* gene is a strong marker for the risk of aneurysm rupture in the Kazakh population, as was observed in the Chinese population (Christopher et al. 1995; Meng et al. 2017), what was expected that the Kazakh population is a mixture of European and Asian populations.

Another gene that has been implicated in IA pathogenesis is ubiquitin protein ligase E3 component n-recognin (*UBR3*) that is supposed to act via an epigenetic mechanism. rs4667622 is

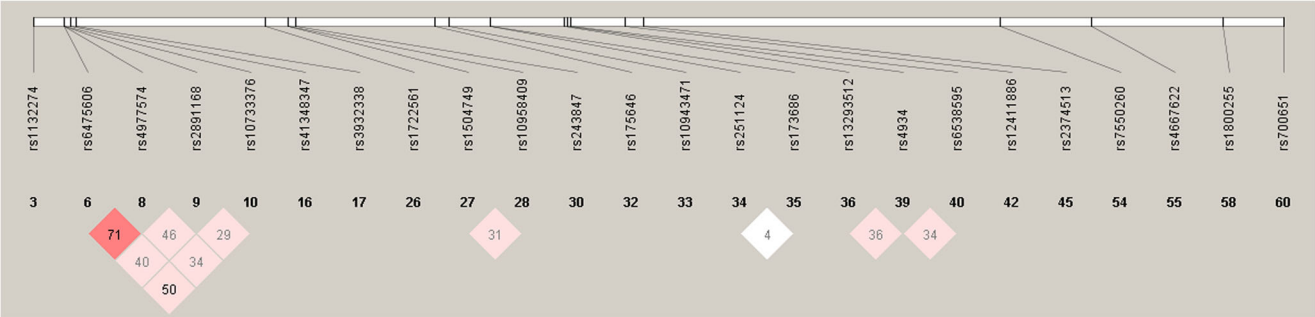

Fig. 1 LD SNP plot. LD is displayed according to standard color schemes, with dark red for very strong LD (logarithm [base 10] of odds LOD > 2, D′ = 1), light red (LOD > 2, D′ < 1) and blue (LOD < 2, D′ = 1) for intermediate LD, and white (LOD < 2, D′ < 1) for no LD

located 63 kilobases downstream of *UBR3* and 30 kilobases upstream of *MYO3B*. The association between the rs4667622 polymorphism of the *UBR3* gene and IA risk was first reported in a GWAS study of the Portuguese population (Abrantes et al. 2015). We identified a similar relationship in the additive model in the Kazakh population ($\beta = 0.544$, $P = 1.12E{-}14$). UBR3 (formerly referred to as ZNF650) has been associated to neurological phenotypes, namely ischemic stroke and temporal brain volume and therefore its role in IA warrants further investigation.

rs2374513 is located in the region near *c12orf75* on chromosome 12q. In the study by Varinder S. Alg in 2013, the association of rs2374513 with intracranial aneurysm was shown in the European population. This polymorphism is with unknown function (Alg et al. 2013). Our results suggest that rs2374513 is significantly associated with intracranial aneurysm in the Kazakh population ($\beta = 0.318$, $P = 2.16E{-}09$). It is known that the Kazakh anthropological type, differentiated by features of Caucasoid and Mongoloid races, occupies an intermediate position (Kuranov et al. 2014).

Steroidogenic acute regulatory protein (StAR) plays an important role in the pathogenesis of aneurysms. It is linked to the reorganization and proliferation of vascular epithelial cells and increases the risk of aneurysm rupture. Consistent with findings in the Japanese population (Yasuno et al. 2010), our results demonstrate a reliable association between the rs3742321 polymorphism of the StAR-related lipid transfer domain containing (*STARD*) *13* gene and the risk of IA in the additive model in the Kazakh population ($\beta = 0.288$, $P = 1.94E{-}07$).

rs3932338 SNP mapped to 214 kilobases downstream of *PRDM9* was also highly associated with the risk of aneurysm in Kazakh population. The *PRDM9* gene encodes a protein with a highly variable tandem-repeat zinc finger (ZF) DNA-binding domain that plays a key role in determining sequence-specific hotspots of meiotic recombination genome-wide (Schwartz et al. 2014). Abrantes P. et al. described the first IA GWAS performed in a southern European population, rs3932338 SNP associated with IA in the Portugal population (Abrantes et al. 2015).

Histone-lysine *N*-methyltransferase 2D (KMT2D), also known as MLL2 in humans and Mll4 in mice, is a major mammalian histone H3 lysine 4 (H3K4) mono-methyltransferase (Akshulakov et al. 2016). It is part of a family of six Set1-like H3K4 methyltransferases that also contains KMT2A (or MLL1), KMT2B (or MLL2), KMT2C (or MLL3), KMT2F (or SET1A), and KMT2G (or SET1B). KMT2D is a large protein over 5500 amino acids in size and is widely expressed in adult tissues. Junxia Yan et al. selected 10 variants from 9 genes, including MLL2, to form 78 candidate variants by considering commonness in families, known disease genes, or ontology association with angiogenesis. However, in Junxia's study, SNP (rs3782356) was not associated with IA (Yan et al. 2015). Our results were demonstrated association between the rs3782356 polymorphism of MLL2 gene and the risk of aneurysm development.

GWAS studies on the association of specific genes with IA in Asian and European populations have revealed new potential loci (Ruigrok and Rinkel 2010; Akiyama et al. 2010). These genes are known to encode proteins that play an important role in gene transcription, protein translation, cell cycle regulation, and apoptosis. Additionally, a strong association between the rs7550260 polymorphism of the Rho guanine nucleotide exchange factor (*ARHGEF*) *11* gene and risk of IA in the Kazakh population was confirmed in additive model ($\beta = 0.265$, $P = 4.89E{-}07$), in agreement with an earlier study (Sathyan et al. 2014).

The SOX17 gene is mainly expressed in endothelial cells. The transcription factor Sox17 is an essential player in vascular development through the regulation of angiogenesis and arterial differentiation. Genome-wide association studies (GWASs) showed similar results of SOX17 in developing IA in Caucasian cohorts; some conflicting findings were reported in a Japanese cohort. The results could imply that SOX17 variants affect IA formation differently in diverse ethnic populations (Alg et al. 2013). Our results suggest that polymorphism SOX17 (*rs1504749*) is significantly associated with IA ($\beta = 0.289$, 1.47E6) in the Kazakh population.

The Versican gene (also known as chondroitin sulfate proteoglycan [*CSPG*]*2*) also predicts the risk of developing aneurysms and their later rupture. Some studies have shown that a decreased density of smooth muscle cells results in decreased production of *CSPG2*, which in turn leads to weakness of the vascular wall. CSPG2 plays an important role in cell adhesion by connecting the cell to the ECM through interaction with hyaluronan, type I

collagen, tenascin-R, fibulin-1 and fibulin-2, fibrillin-1, fibronectin, P- and L-selectins, and chemokines and by regulating cell proliferation, migration, and angiogenesis. T allele carriers showed increased risk of IA, and the CT genotype has been defined as a risk factor for the occurrence and rupture of aneurysms in a southern Indian population (Alg et al. 2013). The rs173686 polymorphism has also been linked to IA in the European population. However, there was no confirmed association in a study of Han Chinese (Sun et al. 2007). In the Kazakh population, we observed an association between the rs173686 polymorphism of *CSPG2* gene and risk of IA ($\beta = 0.285$, 1.77E−6). The heterogeneity of the study results can be explained by the localization of this gene near exon 7, which is distinguished by a high degree of polymorphism that can have variable effects including among different ethnic groups (Sun et al. 2007; Ruigrok et al. 2009). Thus, caution must be exercised to generalize results obtained in one population to others.

LIM domain kinase 1 is an enzyme that in humans is encoded by the *LIMK1* gene. The LIMK1 protein helps control the organization of actin filaments, which are long, thin fibers that make up a significant part of the cytoskeleton. Actin filaments are necessary for several normal cellular functions, such as cell division, cell movement (motility), maintenance of cell shape, transport of proteins and other molecules within cells, and chemical signaling between cells. Akagawa et al. illustrated that SNPs in *ELN* and *LIMK1* at chromosome 7q11 might exert the synergistic effect on development of IA by affecting the stability and synthesis of vascular walls by sharing elastin signaling pathway (Akagawa et al. 2006). The study of Siew-Kee Low revealed a SNP, rs6460071 located on LIMK1 gene and was significantly associated with increased risk of IA in the Japanese population, but did not find associated with ELN (Low et al. 2011). Our results demonstrate that SNP rs6460071 on LIMK1gene associated with IA in the Kazakh population ($\beta = 0.217$, $P = 5.57E{-}6$).

The pathogenesis of cerebral aneurysms is multifactorial and includes inflammation of blood vessels. The serpin family A member (*SERPINA*)*3* gene encodes an acute-phase protein that inhibits the activity of some serine proteases. An alanine-to-threonine loss-of-function mutation in the *SERPINA3* gene increased proteinase activity, leading to the disintegration of matrix proteins and increasing the risk of aneurysm occurrence and rupture. The rs4934 polymorphism of *SERPINA3* was found to be associated with aneurysmal SAH in European populations, but its relationship to the risk of aneurysm development and rupture has not been confirmed in Asians (Slowik et al. 2005; Krischek et al. 2007; Liu et al. 2010). The data obtained in the present study of sporadic IA cases in the Kazakh population showed an association with the rs4934 polymorphism in the dominant model (OR = 1.03, $P = 5.50829E{-}09$). Thus, this polymorphism is a genetic marker for the risk of IA in the Kazakh population, despite the lack of such an association in other Asians.

Linear regression analysis showed that the age (p-0.000830), hypertension (p-7.75e−12), and SNPs rs1800956 ($p < 2e{-}16$), rs1800255 (p-2.42e−10) are statistically significant predictors explaining 33.97% of the variability of aneurysm development.

We constructed haplotypes using possible pairwise combinations of all SNPs between patients and controls. However, the analyzed SNPs did not show strong LD. In addition, we generated haplotype blocks for aneurysm samples (ruptured and unruptured). Haplotype association with aneurismal SAH was not found for all haplotypes. These results are coherent with the other linkage-mapping studies in the Asian and European populations (Onda et al. 2001).

Conclusion

Thirteen SNPs were identified as potential genetic markers for the development and risk of aneurysms rupture in the Kazakh population. Similar results were obtained after adjusting for the confounding factors of arterial hypertension and age. Presence of such SNPs (hetero and homozygous alleles) matches with frequent development of aneurysms. In addition, homozygous of these SNPs often have complications as ruptured aneurysms. It should be noted that factors such as hypertension are age in conjunction with polymorphisms in genes (rs1800956 and rs1800255) cause the development of aneurysms.

In conclusion, the results of the present study reveal polymorphisms that can be used as genetic markers of the risk of IA in the Kazakh population.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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