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Analysis of healthy cohorts for single nucleotide polymorphisms in C1q gene cluster

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ABSTRACT

C1q is the first component of the classical pathway of complement activation. The coding region for C1q is localized on chromosome 1p34.1–36.3. Mutations or single nucleotide polymorphisms (SNPs) in C1q gene cluster can cause developing of Systemic lupus erythematosus (SLE) because of C1q deficiency or other unknown reason. We selected five SNPs located in 7.121 kbp region on chromosome 1, which were previously associated with SLE and/or low C1q level, but not causing C1q deficiency and analyzed them in terms of allele frequencies and genotype distribution in comparison with Hispanic, Asian, African and other Caucasian cohorts. These SNPs were: rs587585, rs292001, rs172378, rs294179 and rs631090. One hundred eighty five healthy Bulgarian volunteers were genotyped for the selected five C1q SNPs by quantative real-time PCR methods. International HapMap Project has been used for information about genotype distribution and allele frequencies of the five SNPs in, Hispanics, Asians, Africans and others Caucasian cohorts. Bulgarian healthy volunteers and another pooled Caucasian cohort had similar frequencies of genotypes and alleles of rs587585, rs292001, rs294179 and rs631090 SNPs. Nevertheless, genotype AA of rs172378 was significantly overrepresented in Bulgarians when compared to other healthy Caucasians from USA and UK (60% vs 31%). Genotype distribution of rs172378 in Bulgarians was similar to Greek-Cyriot Caucasians. For all Caucasians the major allele of rs172378 was A. This is the first study analyzing the allele frequencies and genotype distribution of C1q gene cluster SNPs in Bulgarian healthy population.

Key words: Complement, C1q, Lupus nephritis, rs172378, SLE

Introduction

C1q is the first component of the classical pathway of complement activation, and its main functions are to mediate the clearance of cellular debris and of apoptotic cells even in the absence of complement activation via binding to C1q/collectin receptors on phagocytes (Eggleton et al., 2000). C1q has a hexameric structure that looks like a bouquet of tulips under electron microscopy. Its quaternary structure contains an *N*-terminal triple-helical collagen-like region (CLR) and *C*-terminal heterotrimeric globular head domain (gC1q). The gG1q domain is composed of C-terminal halves of the A (ghA), B (ghA) and C (ghA) chains (Kishore & Reid, 1999; Kishore et al., 2004). The coding region for C1q is localized on chromosome 1p34.1–36.3 and consists of three genes, C1qA, C1qB and C1qC (Sellar et al., 1991). Mutations or single nucleotide polymorphisms (SNPs) in C1q gene cluster may be a reason for C1q deficiency (Crispin et al., 2010). Deficiency of C1q induced impaired clearance of apoptotic cells and exposition of nuclear autoantigens to autoreactive B and T cells, thus promoting the onset of autoimmunity. Approximately, 93% of the individuals with C1q deficiency have Systemic lupus erythematosus (SLE) or SLE-like symptoms (Botto et al., 1998; Walport et al., 1998; Pickering et al., 2000; Roumenina et al., 2011). There are some studies that do not support an association between SNPs in C1q gene and susceptibility of SLE and/or low C1q levels (Chew et al., 2008; Cao et al., 2012; Devaraju et al., 2014). We selected five SNPs located in 148.4 kpb region on chromosome 1, containing the C1qC gene, with flanking

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sequences including C1qA upstream and C1qB downstream. The following SNPs: rs587585, rs292001, rs172378, rs294179 and rs631090 were chosen and their allele frequencies and genotype distribution in Bulgarian in comparison to Hispanic, Asian, African and other Caucasian cohorts were analyzed.

Materials and Methods

Subjects

The group of Bulgarian healthy volunteers included 110 (59.46%) women and 75 (40.54%) men with a mean age of 44 (±11.46) years.

The study had the approval of the Ethics Review Board of Medical University - Varna and each patient and healthy volunteer signed a consent form on enrolment.

DNA isolation

Genomic DNA was isolated from whole blood using QIAamp DNA Blood MiniKit, QIAGEN GmbH, Hilden, Germany and was stored at -20°C.

RT PCR Genotyping

Detections of the SNPs: rs587585, rs292001, rs172378, rs294179 and rs631090 were carried out using a validated TaqMan genotyping assay (Applied Biosystems, Foster City, CA). SNP genotyping was performed using an allelic discrimination assay (TaqMan® SNP Genotyping Assays, Applied Biosystems, Foster City, CA) on 7500 Real-Time PCR System and genotypes were read using automated software (Applied Biosystems, Foster City, CA). Reactions were run in 10 µl volumes according to an amplification protocol of 50°C for 2 min, 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds, then 60°C for 1 minute. The information about the genotype distribution of rs587585, rs292001, rs172378, rs294179 and rs631090 in other Caucasians, Hispanics, Asians and Africans cohorts has been obtained by the International HapMap Project - http://hapmap.ncbi.nlm.nih.gov/index.html.en and from results from other screening studies.

Gene frequencies of the polymorphic loci were calculated using the Hardy-Weinberg equilibrium. Calculation of indices of genetic similarity and genetic distance was performed according to Nei (1972). Phylogenetic analysis was done using PAUP, version 4.0 (Swofford, 1998) and visualized with treeview program Mesquite: a modular system for evolutionary analysis, Version 3.02 (Maddison & Maddison, 2015).

Results

Genotype frequencies

Five SNPs in C1q that span the C1qA, B and C gene in 185 healthy volunteers were genotyped with the aim to evaluate their frequency of occurrence. The genotype distributions of investigated SNPs complied with Hardy-Weinberg equilibrium ($p>0.05$). The results about the genotype distribution and allele frequencies of the five SNPs were compared with those from other studies of healthy cohorts (Table 1). The frequency reports from 10 different healthy cohorts, available in the data base International HapMap Project (for rs587585, rs292001, rs294179 and rs631090) and the information from different screening studies about rs172378, rs292001 and rs631090 from the literature (Racila et al., 2003; Chew et al., 2008; Racila et al., 2008; Namjou et al., 2009; Dardiotis et al., 2009; Zakharyan et al., 2011; Cao et al., 2012; Azzato et al., 2013; Goulielmos et al., 2013; Trouw et al., 2013; Zervou et al., 2013; Mosaad et al., 2015) were used. The 10 cohorts from HapMap project were: ASW: African ancestry in Southwest USA; CEU: Utah residents with Northern and Western European ancestry from the CEPH collection; CHB: Han Chinese in Beijing, China; CHD: Chinese in Metropolitan Denver, Colorado; JPT: Japanese in Tokyo, Japan; LWK: Luhya in Webuye, Kenya; MEX: Mexican ancestry in Los Angeles, California; MKK: Maasai in Kinyawa, Kenya; TSI: Tuscan in Italy; YRI: Yoruban in Ibadan, Nigeria. We grouped them in Caucasian (CEU and TSI), Hispanic (MEX), Asian (CHB, CHD and JPT) and African (ASW, LWK, MKK and YRI) healthy cohorts.

The genotype distributions and allele frequencies of four SNPs (rs587585, rs292001, rs294179 and rs631090) were established for our cohort to be representative of Caucasians in comparison with summary data from the above mentioned information sources (Table 1).

Our results confirmed rs587585 genotype and allele distribution typical for a Caucasian cohort (Table 1). Rs587585 had similar distribution of TT, TC and CC genotypes in the Caucasian, Hispanic and Asiatic cohorts (Table 1). The T allele is also the major allele in the African cohort (Table 1).

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Table 1. *Genotype and allele distributions of five SNPs in C1q gene cluster in five different cohorts (Bulgarian, Caucasian, Hispanic, Asian and African).*

Cohorts/SNPs	Genotypes, Allele	Bulgarians	Caucasians	Hispanics	Asians	Africans
rs172378	GG	0.070	0.134	0.344	0.316	0.544
	AG	0.330	0.444	0.483	0.513	0.387
	AA	0.600	0.423	0.172	0.171	0.069
	G	0.230	0.354	0.586	0.573	0.738
	A	0.770	0.646	0.414	0.427	0.262
rs587585	CC	0.030	0.044	0.018	0.013	0.146
	TC	0.180	0.219	0.221	0.258	0.491
	TT	0.790	0.739	0.793	0.729	0.364
	C	0.120	0.152	0.195	0.142	0.392
	T	0.880	0.848	0.805	0.858	0.609
rs292001	AA	0.090	0.120	0.448	0.383	0.736
	GA	0.510	0.517	0.414	0.487	0.241
	GG	0.400	0.364	0.138	0.130	0.024
	A	0.342	0.380	0.655	0.626	0.856
	G	0.658	0.620	0.345	0.374	0.144
rs294179	CC	0.210	0.275	0.293	0.432	0.781
	TC	0.500	0.504	0.517	0.442	0.215
	TT	0.290	0.222	0.190	0.126	0.005
	C	0.465	0.478	0.570	0.631	0.888
	T	0.535	0.522	0.430	0.369	0.112
rs631090	CC	0.010	0.017	0.000	0.565	0.249
	TC	0.130	0.211	0.263	0.399	0.466
	TT	0.860	0.772	0.737	0.041	0.285
	C	0.071	0.076	0.172	0.241	0.482
	T	0.929	0.924	0.828	0.759	0.518

Similar to our results was the rs292001 genotype distribution of pooled Caucasian cohort (CEU, TSI and Armenian – 225 healthy volunteers (Zakharyan et al., 2011), Dutch – 979 healthy volunteers (Trouw et al., 2013), Greek – 333 healthy volunteers (Goulielmos et al., 2013), Turkish – 155 healthy volunteers (Zervou et al., 2013) and Egyptian – 208 healthy volunteers (Mosaad et al., 2015) (Table 1). In Caucasians the A allele was a minor allele, while in the others cohorts it was the major allele (Table 1).

The data received about rs294179 in Bulgarians followed the genotype distribution in Caucasian cohort (Table 1). Results about rs294179 CC, CT and TT genotype distribution were similar in Caucasians and in Hispanics (Table 1). The C allele, major for Asians and Africans, was also major for Hispanics, unlike in the Caucasians where it had an intermediate presence (46% for Bulgarians and 48% for Caucasians) (Table 1). The genotype distribution of rs631090 in our cohort, in the Caucasians (CEU, TSI and Armenian (Zakharyan et al., 2011) cohorts) and in the Hispanic cohort were similar (Table 1). The major T allele in Caucasians, Hispanics and Asians, in Africans had a frequency of 52%.

In the HapMap Project there were neither data about the allele frequencies, nor about the genotype distribution of rs172378 in the cohorts. Our pooled Caucasian cohort included: 62 healthy volunteers from USA (Racila et al., 2003); 67 healthy volunteers from UK (Azzato et al., 2013); 260 healthy volunteers from USA (Racila et al., 2008) and 59 healthy Greek-Cypriot volunteers (Dardiotis et al., 2009).

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When compared to the pooled Caucasian cohort our cohort had a different distribution of the genotypes. The homozygous AA genotype prevailed in the Bulgarian healthy volunteers, while in the pooled Caucasian cohort the heterozygous AG genotype was prevailing (Figure 1A.). Therefore, our cohort was compared with Caucasians separately and we found that genotype distribution in Bulgarian and in Cyprus cohorts was similar (Figure 1A.). Differences between Bulgarians and pooled Caucasians disappeared when comparison on allele frequencies was done. The major allele for rs172378 in Bulgarians, Cypriots and Caucasians (from USA and UK) was A (Figure 1B.). Rs172378 genotypes were almost equally represented in both groups of Hispanics and Asians (Figure 1A.). In Hispanics, Asians and Africans the major allele was G (Figure 1B.).

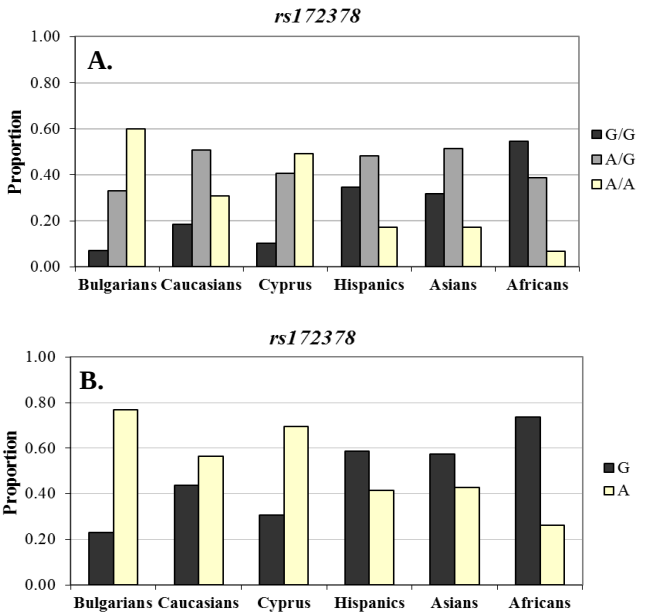

Figure 1. *Genotype (**A.**) and allele (**B.**) distributions of rs172378 in investigated Bulgarian cohort compared with other cohorts – two Caucasian (Caucasian – 322 healthy volunteers from USA and 67 healthy volunteers from UK and Cyprus – 59 Greek-Cypriot healthy volunteers), Hispanic, Asian and African cohorts.*

Genetic distances and phylogenetic tree

Genetic distances between the cohorts analyzed (Table 2, Figure 2), were estimated on the base of five SNPs gene frequencies. Bulgarians, Hispanics and Asians were grouped separately from the other cohorts. Bulgarians clustered together with Caucasians, reflecting the belonging of Bulgarians to the Caucasian race (Figure 2). Conversely, the greatest genetic differences were observed between Bulgarians and the cohorts from Asia and Africa. The last ones clustered together (Figure 2).

Table 2. *Genetic identity (I_{Nei}) above diagonal and genetic distance (D_{Nei}) between cohorts analyzed.*

Cohorts	Bulgarians	Caucasians	Hispanics	Asians	Africans
Bulgarians	0.000	0.990	0.915	0.921	0.725
Caucasians	0.010	0.000	0.954	0.952	0.787
Hispanics	0.089	0.047	0.000	0.997	0.916
Asians	0.082	0.049	0.003	0.000	0.926
Africans	0.322	0.240	0.088	0.077	0.000

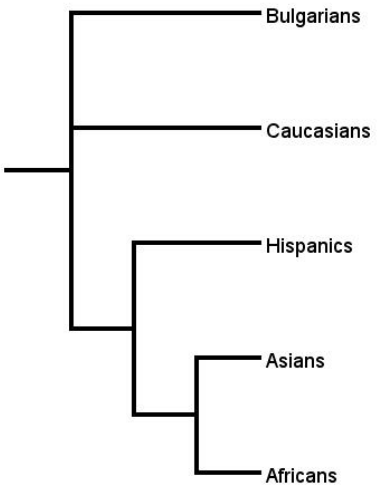

Figure 2. *Nei's genetic distance of five cohorts, visualized in a neighbour-joining dendrogram using PAUP 4.0 and treeview programe Mesquite.*

Discussion

Bulgarian population is heterogenous in origin. The formation of the Bulgarian ethnos began around the turn of the 6th century, from Slavs, Thracians and proto-Bulgarians (who were quite numerous - 32% or perhaps even 60% of the population in early Danubian Bulgaria). There are several studies on the genetic relationships between Bulgarians and the other European populations and non-European population (Horvath et al., 2003; Ivanova et al., 2001; Ivanova et al., 2002; Karachanak et al., 2012; Suslova et al., 2012; Karachanak et al., 2013).

The aim of this study was to investigate the genotype distributions of five SNPs in the C1q gene cluster in the

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Bulgarian population and to compare them with the genotype distributions in different population. Some of these SNPs were previously reported for potential association with SLE and/or with low C1q levels (Racila et al., 2003; Petry & Loos, 2005; Martens et al., 2009; Namjou et al., 2009; Zervou et al., 2013; Mosaad et al., 2015; Radanova et al., 2015). There are several studies suggesting that rs292001 and rs172378 have a very important role in other immune mediated diseases as well (Racila et al., 2006; Racila et al., 2008; Dardiotis et al., 2009; Jin et al., 2012; Azzato et al., 2013; Goulielmos et al., 2013; Trouw et al., 2013). Rs172378 is located in the promoter/regulatory region of C1qA gene at the beginning of the second exon and it is a synonymous polymorphism, which does not cause amino acid substitution, however it may alter the expression levels of C1q.

Our study has found that there was no difference between allele frequencies and genotype distributions of rs587585, rs292001, rs294179 and rs631090 SNPs between the Bulgarian and the pooled Caucasian cohorts, unlike the results about rs172378 genotype distribution. We found that the genotype distribution of rs172378 in our cohort was similar to that in the Greek-Cypriots. This confirms proven propinquity between these two ethnical groups from the other studies (Ivanova et al., 2002; Horvath et al., 2003; Karachanak et al., 2013). According to Horvath et al. (2003) genetic distances between Bulgarians and other southeastern European populations increase in the order: Albanians, Greeks, Slovaks, Croatians, Serbians, Hungarians. Also Ivanova et al. (2002) proved that Bulgarians are more closely related to Macedonians, Greeks, and Romanians than to other European populations and Middle Eastern people living near the Mediterranean. Karachanak et al. (2013) found that Bulgarians were close to Macedonian Greeks, but relatively far from Turks (their southeastern neighbors). They also found that the common in Altaic and Central Asian Turkic-speaking population's haplogroups C-M217, N-M231 and Q-M242 were present in frequency of 1.5% in modern Bulgarians. This shows that shared paternal ancestry between proto-Bulgarians and Altaic and Central Asian Turkic-speaking groups either did not exist or was negligible (Karachanak et al., 2013).

Conclusions

This is the first study analyzing the allele frequencies and genotype distribution of SNPs in the C1q gene cluster in Bulgarian healthy population. Genotype distribution of the SNPs analyzed associate Bulgarian to the Caucasian cohorts with the exception of rs172378 genotypes found to be close to those in the Greek-Cypriots cohorts.

For our Caucasian cohort there are not many screening genetic investigations of healthy volunteers. The research presented gives an opportunity to fill the gaps about genotype distributions in the Bulgarian population.

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