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Original scientific paper

A Pentanucleotide Repeat Polymorphism (TTTTA) in the Apolipoprotein (a) Gene – Its Distribution and Its Association with the Risk of Cardiovascular Disease

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A B S T R A C T

Apolipoprotein (a) is a component of lipoprotein (a). Several studies have shown the association between risk of coronary heart diseases and the size of apo(a) isoforms, although this issue is still controversial. Recent researches focused the attention on the pentanucleotide (TTTTA), highlighting a statistical correlation between low Lp(a) levels and high repeat numbers. In the present paper we studied the distribution of the apo(a) pentanucleotide polymorphism among populations from Corsica, and we then compared it with other populations from Europe, Africa and Asia. The results stressed out the usefulness of these markers in population genetics analysis. We later investigated the possible association of the apo(a) pentanucleotide polymorphism with serum lipid levels in two samples from Corsica (France): one comprises patients or individuals with high risk of future coronary heart disease and the other is a control sample. No significant differences between the two groups have been found, but the analysis of variance showed a significant association between different genotypes and cholesterol and LDL serum levels.

Key words: *apoA, pentanucleotide repeat polymorphism, cardiovascular disease*

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Introduction

In previous studies different authors had highlighted an association between VNTR and restriction sites of the Apolipoprotein genes (ApoE, ApoC, ApoB) and lipid levels and thus with the risk in determining cardiovascular disease[1–4], but sometimes controversial results were obtained[5]. In a previous work[6], we analyzed Apolipoprotein E and C, besides the VNTR ApoB, the restriction sites XbaI and EcoRI and the locus ins/del, located in the ApoB gene. These studies underlined a significant association only in the control sample between HDL levels and ApoCII and ApoB XbaI genotypes, and moreover between LDL levels and ApoE and ApoB XbaI genotypes.

In the present study we investigated the distribution of the pentanucleotide apo(a) in three samples from the general population of Corsica and the possible association of the pentanucleotide repeat polymorphism (TTTTA) of apo(a) with serum lipid levels in the Corsican sample of Corte.

Apolipoprotein (a) is a component of lipoprotein (a) and it is molecularly homologous to plasminogen. It is well known that the level of Lp (a) is an independent risk factor for cardiovascular disease, and it is genetically determined. Numerous studies have shown the association between risk of coronary heart disease and the size of apo(a) isoforms, although this issue is still controversial. Recent researches concentrated on the pentanucleotide (TTTTA), located 1.3 kb upstream of the first exon in the apo(a) gene (chromosome 6, 6q26–q27). These studies highlighted a statistical correlation between low Lp(a) levels and high repeat numbers[7–9].

The aims of this study are essentially two: a) to analyze the distribution of apo(a) frequencies in order to verify their usefulness as markers in population genetic studies, and b) to estimate if different apo(a) genotypes or alleles could influence the plasma lipid levels.

Materials and Methods

Three Corsican samples (France) from Bonifacio (southern Corsica, n = 48), Corte (central Corsica, n = 99) and Balagna (northern Corsica, n = 50) have been analyzed (Figure 1).

Corsica is the 3rd island in the western Mediterranean Basin. The density at the present day is 28.8 inhabitants per km^2. Corsica has experienced a high degree of isolation as suggested by its geomorphologic characteristics, its small villages (often less than 400 inhabitants), the uni-

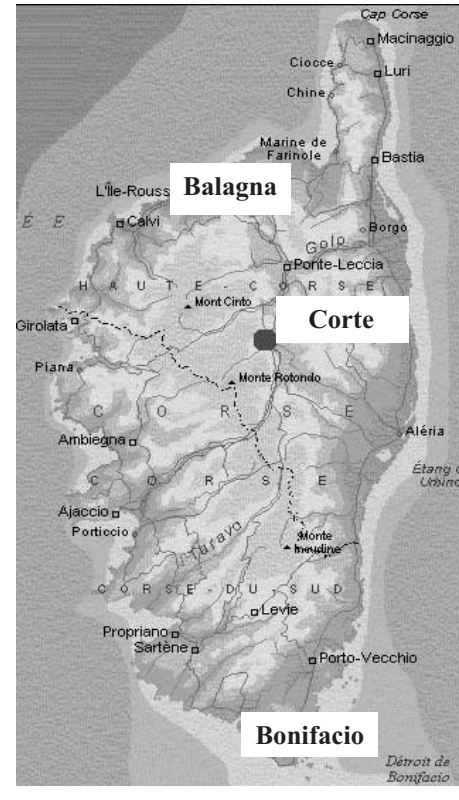

Fig. 1. Geographical position of the analyzed Corsican populations.

queness of its gene frequencies for some polymorphism and a strong genetic heterogeneity with respect to other Mediterranean populations[10,11].

The sample of Corte is divided into two groups. Both of them comprehend unrelated individuals, born and lived in the same area for at least three generations. The first group is formed by 52 individuals (22 males and 30 females) affected by cardiovascular diseases (myocardial infarction or hypertension) or with high risk for those diseases, with an average age of 58 years. The risk factor has been determinated considering triglycerides levels, total cholesterol/HDL ratio, ApoA/ApoB ratio, as they have been proved to be the best indicators as risk factors for cardiovascular diseases[12,13]. The second group is a control sample, constituted by 47 healthy individuals (21 males and 26 females) that do not show any risk factor for cardiovascular disease, with an average age of 56 years. We use only this group for the first purpose of the present work.

Blood samples were collected at University of Corsica (Corte). Lipid levels of the patients group from Corte were determinated with the standard techniques at an analysis laboratory of Corte, by one of us (M. Memmi). Cholesterol and triglycerides levels were determinated using enzymatic methods, HDL cholesterol was measured in the supernatant after precipitation of other lipoproteins with $MgCl_2$, ApoA and ApoB were quantified by immunoturbidimetry. VLDL was measured with density-gradient ultracentrifugation, LDL cholesterol was subsequently calculated using the formula of Friedewald et al.[14], the diagnosis and the risk factor were determinated by medical doctors from Corte following the standard procedures. Then, all the blood samples were taken to the Department of Experimental Biology of Cagliari University, where they were analyzed.

DNA was extracted from whole blood by the phenol-chloroform standard technique, and then it was amplified using the following primers:

5' – GAA TTC ATT TGC GGA AAG ATT G – 3'

5' – CTT CAA CCG GGG TGA GAG TCT C – 3'

The amplified fragments were then separated through a poliacrylamide gel and colored with Ethidium bromide.

Genepop program (version 2.1) was used to calculate the allele frequencies, the Hardy-Weinberg equilibrium and the heterozygosity values. The deviation from Hardy-Weinberg equilibrium was tested by Markov chain, carried out in accordance with Guo and Thompson[15]. Genepop Program was also used to estimate the differentiation among the samples, using the exact Fisher test, with the Markov chain method.

The healthy Corsican sample was compared with our personal data and others obtained from literature to verify the usefulness of this marker in population analysis. The comparison was made by studying the genetic distances, using Nei method[16]. A dendrogram was built from the matrix of the distances using the UPGMA method. Both these analysis were elaborated using Phylip 3.5c program[17].

Besides, the spatial autocorrelation coefficient (I of Moran) was calculated, using the program SAAP (version 4.3). This analysis shows a possible association between genetic and geographic distances. The significant of each correlation was tested using Bonferroni test[18].

Possible associations between genotypes and lipid levels have been estimated with variance analysis (ANOVA), using Statistica program. The relative risk and the odds ratio were calculate through the Epi Info 6 program (version 6.04b)

Results

Table 1 shows the allele frequencies, the product lengths and the p-value for the Hardy-Weinberg equilibrium of pentanucleotide apo(a) in the three Corsican samples. All the samples except Balagna meet the Hardy-Weinberg equilibrium. We totally found 6 alleles. The allele frequencies distribution is bimodal for all the samples, with pick on alleles 8 and 10 for the samples from Corte and Balagna, Bonifacio shows the pick on alleles 6 and 8.

A certain degree of internal variability was detected in Corsica, in fact, the comparison Balagna-Bonifacio, carried on with the Fisher test, shows significant value (p=0.047). Corsican allele frequencies were compared with data from the other two Mediterranean islands: Sardinia and Sicily. The Sardinian samples came from Southern Sardinia, Nuoro area (central) and Gallura area (northern), the Sicilian samples were from Trapani and Palermo areas.

Variability among the islands was tested with Fisher's test. Results showed significant values, demonstrating a strong heterogeneity between Sardinia and Sicily (p=0.008) and between Sicily and Corsica (p= 0.003), whereas Sardinia and Corsica did not appear statistically heterogeneous (p= 0.09).

Corsican samples were compared with several other samples from different country[19–21], calculating the genetic distances.

In Table 2 Nei distances are showed. The greatest distance is between Japan and Balagna (0.0647) whereas the minor one is between Southern Sardinia and Nuoro (0.0001). The tree obtained from the distances matrix with UPGMA method (Figure 2) shows three principal clusters. China and Japan populations constitute the first cluster, and a second one is formed by Morocco and Southern Africa. The third cluster, split into two branches, groups all the European populations. In one branch we find the populations from Northern Iberian Peninsula and Central-northern Europe, on the other populations from the islands of Corsica, Sicily, Sardinia and Central-northern Spain are located. Some populations occupy abnormal positions: Corsican population from Balagna is located on an isolated branch, out of the Euro-Mediterranean populations cluster, and the Sicilian population of Alia is associated with the Iberian Peninsula and Continental Europe. This comes as a surprise, since it should be on a different cluster, where the other Sicilian population of Trapani is located.

Spatial autocorrelation analysis showed significant values for alleles 7, 10

TABLE 1
ALLELE FREQUENCIES, PRODUCT LENGHTS AND HARDY-WEINBERG EQUILIBRIUM OF THE PENTANUCLEOTIDE APO(A) IN 4 EXAMINED SAMPLES FROM CORSICA

	Product lengths (bp)	Allele frequencies			
		Corte (patients)	Corte (healthy)	Bonifacio	Balagna
6	86	0.010	0	0.010	0
7	91	0.020	0	0	0
8	96	0.776	0.777	0.719	0.680
9	101	0.082	0.064	0.115	0.080
10	106	0.112	0.149	0.104	0.230
11	111	0	0.011	0.052	0.010
HW (p-value)		0.532	1	0.117	0.005

TABLE 2
MATRIX OF GENETIC DISTANCES CALCULATED USING NEI METHOD. (NUMBERS IN BOLD INDICATE THE LOWEST AND THE HIGHEST VALUES OF GENETIC DISTANCES)

	S. Sard.	Nuoro	Gallura	Alia	Trapani	Bonif.	Corte	Balag.	Catal.	C. Spain	Alpuj.	Tenerife	Basq.	Tyrol	Danm.	France	Nether.	Moroc.	S. Africa	China
Nuorese	**0.0001**																			
Gallura	0.0044	0.0039																		
Alia	0.0206	0.0218	0.0215																	
Trapani	0.0078	0.0079	0.0077	0.0052																
Bonifacio	0.0017	0.0022	0.0067	0.0182	0.0062															
Corte	0.0037	0.0028	0.0020	0.0196	0.0052	0.0056														
Balagna	0.0199	0.0189	0.0158	0.0102	0.0047	0.0191	0.0097													
Catalonia	0.0068	0.0073	0.0122	0.0057	0.0022	0.0066	0.0079	0.0086												
C. Spain	0.0005	0.0009	0.0074	0.0214	0.0097	0.0021	0.0066	0.0239	0.0070											
Alpujarra	0.0004	0.0003	0.0027	0.0190	0.0057	0.0017	0.0018	0.0157	0.0063	0.0016										
Tenerife	0.0032	0.0033	0.0037	0.0115	0.0016	0.0021	0.0023	0.0094	0.0041	0.0050	0.0017									
Basques	0.0064	0.0068	0.0118	0.0062	0.0022	0.0062	0.0075	0.0087	0.0001	0.0066	0.0058	0.0039								
Tyrol	0.0102	0.0117	0.0218	0.0098	0.0087	0.0081	0.0179	0.0216	0.0034	0.0081	0.0115	0.0099	0.0034							
Danmark	0.0118	0.0122	0.0168	0.0042	0.0029	0.0110	0.0111	0.0065	0.0007	0.0123	0.0107	0.0068	0.0009	0.0050						
France	0.0002	0.0004	0.0048	0.0218	0.0089	0.0019	0.0047	0.0222	0.0078	0.0004	0.0008	0.0040	0.0073	0.0106	0.0132					
Netherland	0.0138	0.0150	0.0238	0.0060	0.0074	0.0122	0.0184	0.0159	0.0022	0.0123	0.0143	0.0111	0.0024	0.0013	0.0021	0.0146				
Morocco	0.0146	0.0158	0.0157	0.0298	0.0162	0.0076	0.0180	0.0329	0.0226	0.0159	0.0135	0.0103	0.0222	0.0228	0.0280	0.0147	0.0297			
S. Africa	0.0096	0.0105	0.0093	0.0356	0.0230	0.0116	0.0171	0.0443	0.0253	0.0098	0.0108	0.0151	0.0248	0.0269	0.0338	0.0081	0.0345	0.0172		
China	0.0172	0.0195	0.0364	0.0455	0.0375	0.0194	0.0367	0.0645	0.0268	0.0124	0.0228	0.0304	0.0264	0.0163	0.0347	0.0156	0.0250	0.0371	0.0222	
Japan	0.0182	0.0204	0.0383	0.0452	0.0379	0.0196	0.0379	**0.0647**	0.0265	0.0129	0.0238	0.0312	0.0261	0.0153	0.0342	0.0166	0.0239	0.0382	0.0240	0.0008

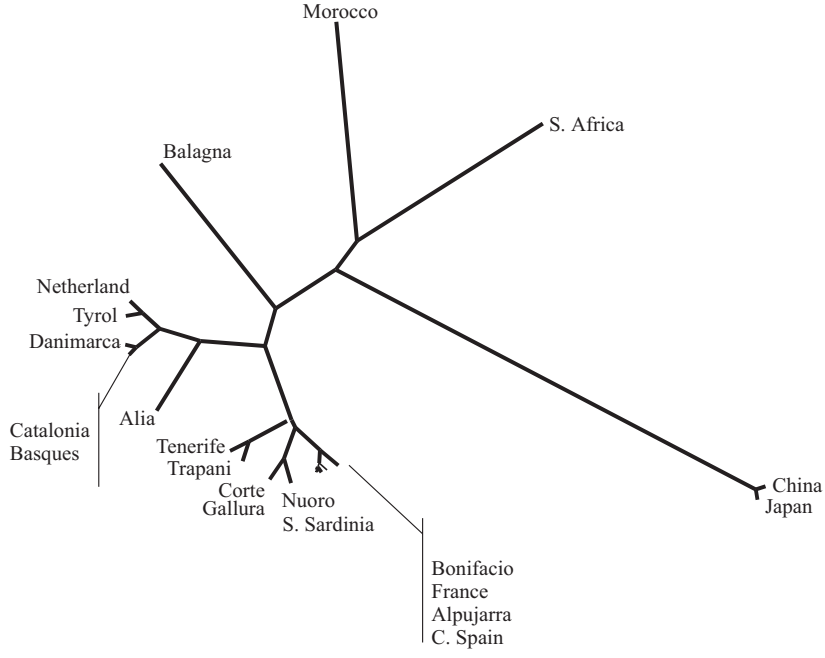

Fig. 2. Genetic tree drawn through UPGMA method.

and 11 (Table 3). In Figure 3 correlograms of those alleles are showed. The correlogram of allele 7 describes a regional patchy, whereas the correlograms of alleles 10, 11 and the one obtained by the average values of the all alleles explain a long distance differentiation.

As far as the second purpose of the present study is concerned, the sample formed by individuals affected or with high risk for cardiovascular diseases was compared with the control sample of Corte. Few differences in the allele frequencies distribution have been found. The patient group shows a major number of alleles and alleles with shorter size (Table 1). However, the two samples are not statistically different.

TABLE 3
I OF MORAN VALUES AND ITS SIGNIFICANCE

	552	977	1186	1659	2888	8388	13550	p
Apo(a)*7	–0.03	0.04	0.06	0.05	0.03	–0.42**	–0.08	0.009**
Apo(a)*8	0.02	–0.05	–0.22	–0.04	–0.05	0.02	–0.02	0.696
Apo(a)*9	0.03	–0.01	–0.30*	0.02	–0.04	–0.03	–0.01	0.214
Apo(a)*10	0.26*	–0.14	–0.05	0.05	–0.05	0.12	–0.54**	0.001**
Apo(a)*11	–0.20	0.19	0.05	0.01	0.11	0.36*	–0.16	0.039*
Average	0.02	0.00	–0.09	0.02	0.00	–0.13	–0.16	

* $p<0.05$; ** $p<0.01$

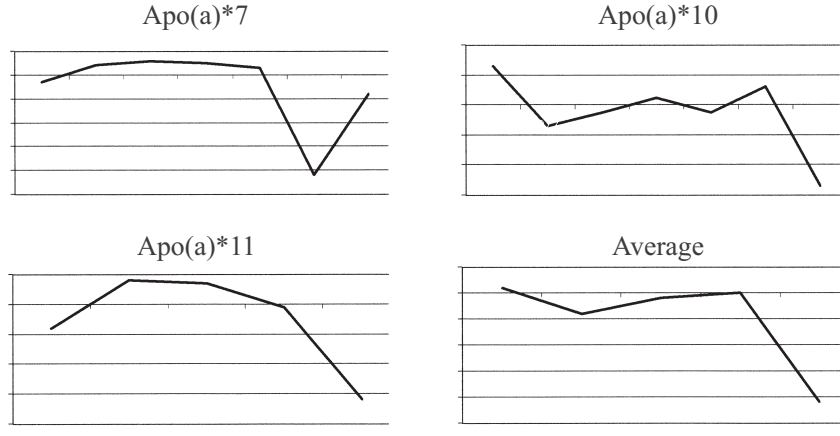

Fig. 3. Correlograms of the alleles with I of Moran significant values.

Odds ratio (OR) and relative risk (RR) were calculated for each genotype, to establish if a certain genotype could represent a risk factor for cardiovascular disease, but neither OR or RR values resulted significant. On the contrary, when allele frequencies are considered, different results came out. Alleles 6 and 7 have a relative risk of 2.01 and 2.02 respectively, both with a p value <0.05. It was not possible calculating the RR for allele 11 since it is absent in the patients group, but odds ratio resulted zero and the p value was 0.0009. These results, however, are not final and must be interpreted cautiously, because of the low number of individuals carrying these alleles. Before analyzing the effect of genotype on plasma lipid levels, we verified if the lipid levels in the two samples were statistically different. Through Statistica package t-test was applied to the average values of the lipids (total cholesterol, triglycerides, HDL, LDL, VLDL, ApoA and ApoB). In each case, except for HDL, the average values are greater in the patients than in the control sample. The p value appeared significant in all cases except in HDL, confirming the differences between the two samples.

Table 4 shows the average values of plasma lipids in the different genotypes both in patients, in the control group and in the total sample. Variance analysis has been applied to test if the observed differences were statistically significant. We only found significant correlation between genotypes and total cholesterol levels in the patients group, and between genotypes and LDL in the control group. Considering the total sample, only the value related to total cholesterol appeared significant.

But since some genotype are presented only by one or two individuals, we preferred excluding those genotypes, so only the three common Apo(a) genotypes 8–8, 8–9 and 8–10 are included in the analysis, as suggested by Bo[21]. In this case just total cholesterol and LDL levels presented significant association with apo(a) genotypes in the control sample. Precisely 8–10 genotype presented the lowest values and 8–9 genotype the greatest values of total cholesterol and LDL.

Discussion

Pentanucleotide (TTTTA) in the apo(a) gene has not been employed yet in re-

TABLE 4
AVERAGE VALUES FOR LIPIDS IN THE TOTAL, CONTROL AND PATIENTS SAMPLES FOR EACH GENOTYPE (LIPID VALUES ARE EXPRESSED IN MG/DL)

Total Genotype	N	Chole-sterol	HDL	LDL	Trigly-cerides	VLDL	ApoA	ApoB
6–7	1	267.0	55.0	180.0	160.0	32.0	172.0	154.0
7–8	2	278.0	55.5	170.5	261.0	52.0	177.5	153.5
8–8	56	237.7	47.7	155.7	168.5	33.7	147.6	128.9
8–9	13	244.6	49.0	156.5	185.7	39.1	156.6	125.6
8–10	20	225.2	52.3	144.0	145.0	29.1	139.6	118.9
8–11	1	189.0	46.0	123.0	102.0	20.0	112.0	74.0
9–10	1	395.0	64.0	297.0	172.0	34.0	194.0	173.0
10–10	2	203.5	39.5	145.0	95.0	19.0	147.0	104.5
Control Genotype	N	Chole-sterol	HDL	LDL	Trigly-cerides	VLDL	ApoA	ApoB
8–8	28	208.8	49.6	137.9	103.3	20.8	140.1	100.6
8–9	6	218.0	48.0	145.8	99.8	24.2	147.2	94.3
8–10	10	180.6	52.7	108.3	97.7	19.6	125.4	91.4
8–11	1	189.0	46.0	123.0	102.0	20.0	112.0	74.0
10–10	2	203.5	39.5	145.0	95.0	19.0	147.0	104.5
Patients Genotype	N	Chole-sterol	HDL	LDL	Trigly-cerides	VLDL	ApoA	ApoB
6–7	1	267.0	55.0	180.0	160.0	32.0	172.0	154.0
7–8	2	278.0	55.5	170.5	261.0	52.0	177.5	153.5
8–8	28	266.5	45.9	173.6	233.7	46.6	155.1	157.2
8–9	7	267.4	50.0	165.6	259.3	51.8	164.7	152.4
8–10	10	269.8	52.0	179.8	192.4	38.6	153.9	146.4
9–10	1	395.0	64.0	297.0	172.0	34.0	194.0	173.0

search on population genetics before now. In this work the variability of the common pentanucleotide repeat polymorphism in three samples from Northern, Central and Southern Corsica (France) is showed. This polymorphism probably evolved by duplication or by slippage mutation during DNA replication, as suggested for other repetition sequences in the human genome[22].

Differentiation test between the islands stressed out a strong heterogeneity between Sicily and Sardinia and between Sicily and Corsica, whereas Sardinia and Corsica did not appear differentiated. This result is confirmed by historical and archaeological data that indicate close relationship between the two islands that during the Quaternary formed a single block. This result has been also confirmed by other papers on classical and DNA markers[10,23,24].

Genetic tree highlighted that apo(a) pentanucleotide can discriminate populations belonging to different continents. In fact, Asian and African populations appear clearly differentiated from the European ones. Moreover, the populations

from the three Mediterranean islands appear always part of a single cluster. The peculiar position of Balagna population, stressed out by several statistical analysis, does not surprise, because a previous paper had underlined the genetic differentiation of this population in respect both of the other Corsicans and Euro-Mediterranean populations[24]. The genetic differentiation could be explained with the isolation of Balagna population: this, in turn, is probably due to the geographic location of Balagna, whose isolation is demonstrated, in fact, by its very low rate of exogamic marriages[25]. The Sicilian populations from Alia and Trapani did not resulted associated, and this bears witness to their genetic differentiation. This differentiation can be a consequence of genetic drift that acted on genetic structure of Alia population, and that was furthermore favored by isolation and bottleneck events due to cholera epidemics[26].

The general allele frequencies distribution of pentanucleotide apo(a) seems to be influenced by geographical phenomenon, as spatial autocorrelation analysis showed.

As far the possible associations between genotypes and plasma lipid levels, our data give controversial results. In fact, we did not found a statistical differentiation between the patients and the control group, neither for genotype or allele frequencies, and also the relative risk test did not point out any genotype as factor predisposing to cardiovascular disease. Genotype distribution appears quite similar in the healthy individuals and the ones affected by cardiovascular diseases. With further analysis applied on allele frequencies, as suggested by other author[7,8], allele 6 and 7 appear as possible risk factor, and allele 11 could represent a protection factor for those pathologies. This is confirmed by the absence of the shortest alleles in our control group and the absence of the allele 11 in patients group we analyzed. This result is in accordance with other papers that demonstrated an association between higher numbers of repeats and lower Lp(a) levels, and so with low risk of contracting cardiovascular diseases[9,27,28].

Finally, variance analysis stressed out, in the control sample, an association between total cholesterol and LDL low levels and HDL high levels and 8–10 genotype, as though it represented a protection factor. This association assumes a great importance. LDL has been calculated according with Friedwald[14] and following this method, Lp(a) levels are included in LDL values, so this relation could be interpreted also as an association between Lp(a) levels and (TTTTA) apo(a) genotypes.

Therefore our research lead to the conclusion that if, on one hand, a certain degree of association between plasma lipid levels and genotypes is undoubted, we did not claim certainly that a particular apo(a) genotype can represent a risk factor in determining cardiovascular disease, as other authors suggested[21,28]. The negative effects of alleles with a low number of tandem repeats, pointed out by previous works, seem been confirmed in this study. However, the relationship between apo(a) genotypes and cardiovascular disease could be further clarified by a research relying on more samples.

In conclusion, pentanucleotide apo(a) turned out to be extremely useful for the analysis of micro and macro geographical variability, as suggested by other authors[9,29], but we can not be sure that it could have a direct influence in determining cardiovascular disease. The controversial results obtained on this subject by different authors and confirmed in the present paper could be due to the presence of genetic differences between populations, as De Knijff had suggested to explain analogous controversy on ApoE gene[30], and they could be clarified through

the haplotype analysis of Apolipoprotein loci, that we are carrying on.

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PENTANUKLEOTIDNI PONAVLJAJUĆI POLIMORFIZAM (TTTTA) U APOLIPOPROTEIN (A) GENU: RASPROSTRANJENOST I POVEZANOST S RIZIKOM OBOLIJEVANJA OD KARDIOVASKULARNIH BOLESTI

S A Ž E T A K

Apolipoprotein (a) je komponenta lipoproteina (a). Nekoliko studija je pokazalo povezanost između rizika obolijevanja od koronarne bolesti srca i veličine apo(a) izoforma, premda je ovaj nalaz još predmetom kontroverzi. U žarištu pažnje novijih istraživanja je pentanukleotid (TTTTA), koji pojašnjava statistički značajnu korelaciju između niske razine Lp(a) i velikog broja ponavljajućih jedinica. U ovom radu istražuje se raspodjela polimorfizama apo(a) pentanukleotida među populacijama iz Korzike, te je potom ona uspoređena s drugim populacijama iz Europe, Afrike i Azije. Rezultati naglašavaju korisnost ovog biljega u populacijsko-genetičkim analizama. Potom je istraživana moguća povezanost polimorfizma apo(a) pentanukleotida s razinom serumskih lipida u dva uzorka iz Korzike (Francuska): jedan su sačinjavali bolesnici i osobe s visokim rizikom od razvoja koronarne bolesti srca, a drugi uzorak je bio kontrolna skupina. Dvije skupine nisu se značajno razlikovale no analiza varijance pokazala je značajnu povezanost između različitih genotipova i razine kolesterola i LDL u serumu.