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FREQUENCIES OF FUNCTIONAL CASPASE 12 GENOTYPES AMONG NORTH-AFRICANS

© 2011 A. D. Kempińska-Podhorodecka[1], O. M. Knap[2], K. Kobus[1], A. Ciechanowicz[3]

[1] Medical Biology Laboratory of Pomeranian Medical University, 70-111 Szczecin, Poland
e-mail: agnieszkakempinska@poczta.onet.pl

[2] Independent Laboratory of Disaster Medicine of Pomeranian Medical University, Poland

[3] Department of Laboratory Diagnostics and Molecular Medicine of Pomeranian Medical University, Poland, Medical Biology

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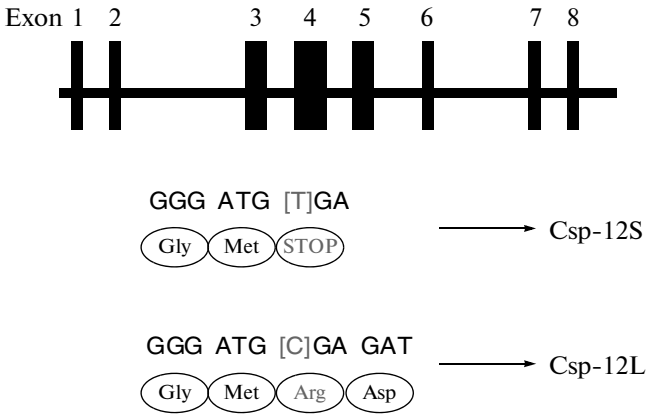
Caspase 12(Csp-12) is a cysteine protease that plays a role in regulation of cytokine maturation. It is present either in a functional full-length variant (Csp-12L) that predisposes to a lower immune response or in an inactive, common version (Csp-12S) that contains a stop codon that results in a truncated form. Genomic DNA from unrelated North Africans, residents of 4th Nile Cataract Region in Sudan, was analyzed. One hundred umbilical blood samples of Polish newborns served as a reference group from the Caucasian population. The analysis of stop-codon polymorphism performed on the 212 human samples from Northern Sudan identified 6.6% individuals with heterozygous genotypes while not one homozygous Csp-12L was found. All examined Polish individuals were homozygous Csp-12S.

Caspases are proteases that modulate apoptosis and the cytokine maturation process [1, 2]. A Thymidine-Cytosine substitution at position 125 (Arg125X) in exon 3 of Csp-12 changes the codon from a premature stop codon to an arginine residue, thus leading to the synthesis of a functional form of caspase-12 (figure). Activated full-length Csp-12 blocks Cspl and the nuclear factor kappa-light-chain-enhancer of activated B cells resulting in decreased production of pro-inflammatory cytokines, thus dampening the immunological response and increasing the risk of severe sepsis development. In contrast, the presence of a premature stop codon results in the synthesis of a truncated non-functional form of caspase-12. The active form Csp-12L has been reported at a frequency of 20% to 30% in African populations, whereas it is absent in Caucasian and Asian populations [3, 4].

The study analyzed ethnically uniform villages, inhabited by the Shagia people in Northern Sudan in the region of the fourth Nile Cataract, 800 km south from Egypt. The population of the Shagia people, who until recently represented a native and isolated tribe, provides a unique opportunity to gain insight into evolutional and migration-related processes at the molecular level. The collected samples were exceptional as the Shagia tribe is being transferred from their previous habitat to prepared settlements where other, ethnically divergent tribes are placed. The second examined tribe, the Manasir, lives approximately 80 km from the described Shagia villages and represents a population with admixture of other populations (Beniamer, Ababda, Foraui, Kesinger tribes).

In the present study frequency analysis of caspase-12 genotypes among representatives of the Shagia and Manasir tribes residing in Norhern Sudan was performed.

Genetic material (buccal swabs) was collected from 122 individuals of the Shagia tribe (68 female and 54 male; median age 20.5 years) and from 90 representatives of Manasirs (46 female and 44 male; median age 42 years) who consented to participate in the study. The authors states their research conforms to the Helsinki Declaration and to local legislation. Patients informed consent was a prerequisite. Institutional ethical clearance from Ethic Committee of Pomeranian Medical University was obtained. Umbilical cord blood samples of 100 healthy newborn children



The human caspase-12 polymorphism. A Cytosine-to-Thymidine substitution in exon 3 (codon125) of Csp-12 generates a premature stop codon, in place of Arg. This mutation leads to the synthesis of a non-functional form of caspase-12 (Csp-12S).

Frequency of caspase-12 genotypes among different population groups

Populations, *n*	Non functional TGA	Functional (T/C) GA	Functional CGA	Refs
	%			
Sub-Saharan Africa, (Senegal), $n = 25$	60.0	36.0	4.0	5
Sub-Saharan Africa (Nigeria), $n = 27$	70.4	25.9	3.7	5
Central African Republic, $n = 36$	55.6	38.9	5.6	5
Central African Republic (Congo), $n = 14$	14.3	50.0	35.7	5
Central African Republic (Kenya), $n = 14$	92.9	7.1	0.0	5
Central African Republic (Namibia), $n = 6$	16.7	50.0	33.3	5
South African, $n = 9$	55.6	33.3	11.1	5
South African, $n = 139$	78.4	20.3	1.3	3
West African (Mali), $n = 97$	58.76	39.18	2.06	4
North African (Algeria), $n = 30$	96.7	3.3	0.0	5
Northeast Africa (Sudan), $n = 212$	93.4	6.6	0.0	This study
North America (Kanada), $n = 32$	100	0.0	0.0	3
European (Denmark), $n = 28$	100	0.0	0.0	3
European (Finland), $n = 19$	100	0.0	0.0	3
European (France), $n = 19$	100	0.0	0.0	3
European (France), $n = 29$	100	0.0	0.0	5
European (Armenia), $n = 1$	100	0.0	0.0	5
European (Undefined), $n = 88$	100	0.0	0.0	5
European (Italy), $n = 41$	100	0.0	0.0	5
European (Scotland), $n = 16$	100	0.0	0.0	5
European (Russia), $n = 39$	100	0.0	0.0	5
European (Poland), $n = 100$	100	0.0	0.0	This study

(57 male and 43 female) were delivered from the Department of Neonatal Diseases at the Pomeranian Medical University.

DNA extraction from buccal swabs was performed using the BuccalAmp Dna Extraction Kit (Epicentre) while isolation of DNA from umbilical cord blood was isolated with the DNeasy Blood & Tissue Kit (Qiagen). Oligonucleotide primers and TaqMan probes for T125C human CASP-12 polymorphism (rs497116) were designed and synthesized by Applied Biosystems. The fluorescence data were analyzed with allelic discrimination 7500 Software v.2.0.2.

In the examined 212 individuals from Northern Sudan, 198 (93.4%) were homozygotes for a functional full-length Csp-12L allele, 14 were heterozygotes (6.6%). No homozygotes for the functional Csp-12L allele were identified. Genotyping analysis showed differences between the examined populations depending on geographical origin. Functional Csp-12L homozygotes were predominant among the members of Shagia and Manasir tribes (91.8% and 95.6%, respectively). Only 10 individuals (8.2%) within the Shagia tribe and 4.4% of Manasir members were heterozygous. In comparison, all Polish newborns were homozygotes for the non-functional Caspase-12S allele (table).

To the best of our knowledge the presented study is unique as the frequency of the functional Caspase 12 in the region of the 4th Nile Cataract in Sudan has never been studied before. The only population investigated previously in the north part of Africa were Algerians [5]. However, the analysis was done on a much smaller group than ours (30 vs 212 individuals; table). The occurrence of the full-length Csp-12 variant among inhabitants of North Sudan (6.6% heterozygotes) is similar to the frequency described in Algeria. Our analysis demonstrates the lack of functional Csp-12L variant among Polish representatives, in agreement with other studies of Caucasian populations from Western Europe and Canada [5]. Individuals with afunctional Csp-12L are more susceptible to bacterial infections and sepsis than those with a non-functional form of Caspase 12. Despite being beneficial the non functional form of Caspase 12 is not found throughout all populations. Possibly an inactive gene could be a disadvantage in smaller populations and thus evolution has abandon such protection. In Sub-Saharan Africa before the population expansion the frequencies of both variants were probably equal 10000 years ago. It is believed that the appearance of Csp-12S was connected with environmental pressure 60–100000 years ago [6]. These results support the

notion that the Arg125X mutation of Csp-12 could be beneficial for human species survival due to lower susceptibility to sepsis.

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