

doi: 10.3325/cmj.2011.52.351

Prevalence of 845G>A *HFE* mutation in Slavic populations: an east-west linear gradient in South Slavs

Aim To compare A allele frequencies of the 845G>A mutation of 10 Slavic populations in central, eastern, and southern Europe between each other and with other European populations.

Methods The 845G>A mutation from the DNA of 400 Polish neonates collected in 2005-2006 was analyzed by polymerase chain reaction-restriction fragment length polymorphism. The data were compared with reports from other countries.

Results We identified 381 GG homozygotes, 18 GA heterozygotes, and 1 AA homozygote. The 845A allele frequency was 2.5%, which makes the summary figure for Poland from this and previous studies 3.5%. The average prevalence for Poland and other West Slavic countries was 3.6%, similar to Russia (inhabited by the East Slavs, 3.5%). The average prevalence in South Slavic countries was 2.2%, gradually decreasing from 3.6% in Slovenia to 0% in Bulgaria, with a longitudinal linear gradient (adjusted $R^2 = 0.976$, $P < 0.001$).

Conclusions The West and East Slavs, together with Finland, Estonia, Germany, Austria, Hungary, Slovenia, and Croatia, form a group with 845A allele frequencies between 3% and 4%. In the South Slavs, there is a gradual decline in the prevalence of 845A allele from northwest to southeast, with a surprisingly exact east-west linear gradient.

Grażyna Adler^{1*}, Jeremy S Clark^{2*}, Beata Łoniewska³, Andrzej Ciechanowicz²

¹Department of Medical Biology, Pomeranian Medical University, Szczecin, Poland

²Department of Clinical and Molecular Biochemistry, Pomeranian Medical University, Szczecin, Poland

³Department of Neonatal Diseases, Pomeranian Medical University, Szczecin, Poland

*Contributed equally to the study.

Received: April 7, 2011

Accepted: May 23, 2011

Correspondence to:

Grażyna Adler
Pomeranian Medical University
Department of Medical Biology
Powst. Wlkp.72
PL 70-111 Szczecin, Poland
gra2@op.pl

In 1996, two major *HFE* gene mutations (845G>A and 187C>G) responsible for an inherited form of hemochromatosis were identified (1). Hereditary hemochromatosis is a common autosomal recessive disorder characterized by increased iron absorption. It has significant clinical consequences such as liver cirrhosis, diabetes mellitus, arthropathy, cardiomyopathy, and endocrine dysfunction (2). A total of 60% to 96% of patients with hemochromatosis in Europe have the mutation 845G>A in exon 4. This causes cysteine to tyrosine substitution at position 282 (C282Y) of the polypeptide chain, resulting in destabilization of one of the bridging sulfide molecules disrupting *HFE* binding to β 2-macroglobulin (1,3). The *HFE* polypeptide chain loses its ability to bind to transferrin receptor, and this results in a 200-300% increase in iron absorption from food. The severity of symptoms in homozygotes is variable and depends on the race, age, sex, and diet (2,4,5). Merryweather-Clarke et al (6) reported the highest prevalence of 845A *HFE* in northwestern Europe (5.2 to 10.1%), ie, Sweden, Norway, UK, and Ireland. In Finland, Hungary, Poland, Russia, Austria, Germany, Czech Republic, and Slovakia the prevalence was between 3.2 and 4%. In southern Europe (Greece, Romania, Italy, and Spain), the prevalence is very low (6-18) and in Turkey it is almost non-existent (7). According to more recent data, France (6.1%) can now be added to the northwestern group (19,20). As the major comparison of the prevalence between European countries by Merryweather-Clarke et al (6) included few data on Slavic populations, we further assessed the 845A *HFE* frequency in the Polish population and compared it with other Slavic populations and previously published results, as well as determined its distribution across the entire Europe.

MATERIALS AND METHODS

The study sample comprised 400 consecutively born neonates (187 female and 312 male) delivered at the Neonatology Department, Pomeranian Medical University, Szczecin, Poland in 2005-2006. All neonates were of Polish origin, with Polish grandparents, and informed consent was obtained from all parents. The Ethical Committee of the Pomeranian Medical University approved the protocol of the study (BN-001/57/05). Genomic DNA from neonates was extracted from 100 μ L of umbilical cord blood using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). For identification of the 845G>A *HFE* mutation, we used polymerase chain reaction (PCR)-restriction fragment length polymorphism. About 20 ng of genomic DNA was used with a PCR mixture (10 μ L) contain-

ing 10 \times buffer (pH 8.3, 1.5 mM MgCl₂), 0.2 mM each of the deoxynucleotide triphosphates, 0.5 U Polymerase Taq (MBI Fermentas, Vilnius, Lithuania), and 4 pmol each of the forward and reverse primers. 5'- CCT CAT CCT TCC TCT TTC CT-3' was used as a forward primer and 5'- TCC TCA GGC ACT CCT CTC AA-3' as a reverse primer (TIB MOL BIOL, Poznan, Poland). PCRs were performed in a Mastercycler Gradient thermal cycler (Eppendorf, Hamburg, Germany), with the following temperature profiles: initial denaturation at 94°C for 5 minutes, 37 cycles of 20 seconds at 94°C, 40 seconds at 54°C, and 40 seconds at 72°C; with a final extension step at 72°C for 8 minutes. Amplification was followed by digestion of the 367 bp product using the *Rsa*I restriction enzyme (5'-GTAC-3') (MBI Fermentas) for 3.5 hours at 37°C. PCR digestion products were separated on 3% agarose gels, stained with ethidium bromide, and recorded using a DS-34 Polaroid Instant Camera (Polaroid, Dreieich, Germany) under UV light (Transilluminator 4000, Stratagene, La Jolla, CA, USA). The *Rsa*I digestion yields fragments of 225 and 142 bp for G845 homozygotes; 225, 142, 113, and 29 bp for heterozygotes; or 225, 113, and 29 bp for 845A homozygotes. Genotypes of GA and AA patients were also confirmed by DNA sequencing (3100-Avant Genetic Analyzer, Applied Biosystems Hitachi, Foster City, CA, USA).

Statistical analysis

Geographical coordinates (longitude) used in the analysis were derived from Google maps (Google Inc, Mountain View, CA, USA), except in cases of South Slavic countries, where additional sources were used for Serbia and Montenegro (http://www.mapcrow.info/cgi-bin/cities_distance_airpt.cgi?city3=9173706%2C00&city4=135261%2C00) and other South Slavic countries (<http://universimedia.pagesperso-orange.fr/geo/loc.htm>). Graphical materials were developed using Designworks software (GSP Ltd, London, UK) and Microsoft Office (Microsoft, Redmond, WA, USA). Linear regression analysis was performed using STATISTICA, version 8.0 (StatSoft, Inc, Tulsa, OK, USA, www.statsoft.com), with the significance level set at $P < 0.05$.

RESULTS

The frequency of the 845A allele in 400 Polish neonates was 2.5%. The 845G>A genotype distribution was 381 GG homozygotes, 18 GA heterozygotes, and 1 AA homozygote. The 845G>A genotype distribution conformed to the expected Hardy-Weinberg equilibrium. The frequen-

TABLE 1. Allele frequencies for 845G>A HFE in Slavic countries

Population	Reference	Number of participants		Frequency of 845A allele (%)	
		per study	sum per country	per study	per country*
West Slavs					
Poland	Present study	400 (neonates)		2.5	3.5
	Raszeja-Wyszomirska J et al, 2008 (21)	1517 (healthy adults)	2788	4.0	
	Moczulski DA et al, 2001 (22)	871 (healthy adults)		3.1	
Czech Republic	Cimbuřová M et al, 2005 (14)	481 (neonates)	620	3.4	3.8
	Zdárský E et al, 1998 (10)	139 (healthy adults)		5.0	
Slovakia	Gabrikova D et al, 2011 (23)	359 (general population)	359	4.0	4.0
South Slavs					
Slovenia	Cukajti M et al, 2007 (24)	1282 (blood donors)		3.6	3.6
	Hruškovičová H et al, 2005 (25)	115 (healthy adults)	1779	3.0	
	Zorc M et al, 2004 (26)	182 (adults)		4.1	
	Ristić S et al, 2003 (27)	200 (blood donors)		3.3	
Croatia	Starčević- Čizmarević N et al, 2006 (28)	350 (healthy adults)	550	3.4	3.4
	Ristić S et al, 2003 (27)	200 (healthy adults)		3.3	
Bosnia and Herzegovina	Terzić R et al, 2006 (29)	200 (blood donors)	400	2.0	2.2
	Hercegovac A et al, 2008 (30)	200 (healthy adults)		2.3	
Serbia and Montenegro	Šarić M et al, 2006 (31)	318 (healthy adults)	318	1.6	1.6
Macedonia	Arsov T et al, 2005 (32)	100 (healthy adults)	100	1.0	1.0
Bulgaria	Ivanova A et al, 1999 (33)	100 (healthy adults)	100	0.0	0.0
East Slavs					
Russia (European part)	Kondrashova V et al, 2006 (34)	260 (healthy women)	1100	3.3	3.5
	Pothekina E S et al, 2005 (35)	840 (blood donors)		3.5	
Belarus	no data				
Ukraine	no data				

*Weighted average.

cy of 845A HFE in 10 Slavic countries varied from 2.5% to 5.0% (Table 1).

The average prevalence of 845A allele in the countries inhabited by the West Slavs was 3.6% and varied from 3.5% in Poland (including our study) through 3.8% in the Czech Republic to 4.0% in Slovakia (10,14,21-23) (Figure 1). This places the West Slavs to a group with allele frequencies between 3% and 4%, together with East Slavic Russia (3.5%) and Finland, Estonia, Germany, Austria, Hungary, Slovenia, and Croatia.

The average prevalence of the 845A allele in South Slavic countries was 2.2%. The highest prevalence was observed in Slovenia (3.6%) (24-26), after which a gradual northwest-southeast decrease was observed: 3.4% in Croatia, 2.2% in Bosnia and Herzegovina, 1.6% in Serbia and Montenegro, 1.0% in Macedonia, and 0% in Bulgaria (27-30,32,33). When allele frequency was plotted against geographical longitude, a surprisingly exact east-west lin-

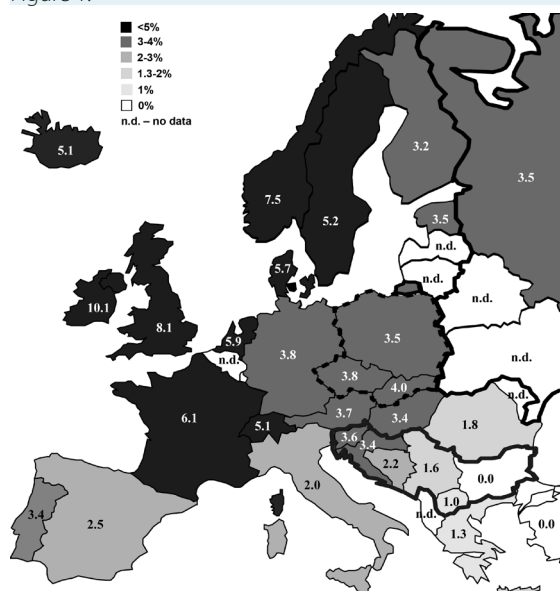
ear gradient was obtained (adjusted $R^2=0.976$, $P<0.001$; Figure 2).

DISCUSSION

Our study showed that the distribution of 845A HFE among Slavic countries was bi-modal. The West and East Slavs had a similar prevalence as other central and eastern European populations, with values ranging between 3% and 4%. The South Slavs exhibited a linear decreasing west-to-east trend, with a prevalence varying from 3.6% to 0%.

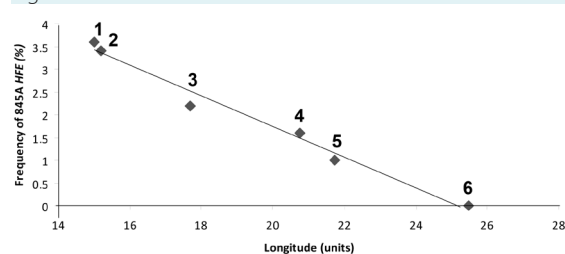
Population migrations in Europe have led to the distribution of ethnic groups and cultures, and consequently to genetic mixing (68). Migrations, together with other factors, have also determined the prevalence of genetic diseases, such as hemochromatosis (68). Initially, the mutation 845G>A HFE was described in populations of northwestern European origin and has spread to territories inhabited by the Celts (68). On the other

Figure 1.



Allele frequencies for the 845G>A *HFE* mutation. Global averages for countries inhabited by the West Slavs – dashed line, South Slavs – lower solid thick line, and East Slavs – upper solid thick line (references as in Table 1). Global averages for other countries – Austria (36), Denmark (37), Estonia (38,39), Finland (7,40-42), France (19,20), Greece (7), Germany (7-9), Hungary (43), Iceland (7,44), both (45), Ireland (6,7,46-48), Italy (7,12,13,15,16,49-52), Netherlands (53,54), Norway (7,55,56), Portugal (57), Romania (18), Spain (7,11,17,58-61), Sweden (40), Switzerland (62), Turkey (7), UK (6,7,63-67). n.d. – no data.

Figure 2.



Linear trend in the frequency of 845A *HFE* with increase in longitude. 1 – Slovenia; 2 – Croatia; 3 – Bosnia and Herzegovina; 4 – Serbia and Montenegro; 5 – Macedonia; 6 – Bulgaria. Adjusted $R^2=0.976$, $P<0.001$

hand, the 845G>A mutation might have originated from the Germanic Iron Age population in southern Scandinavia and spread with the Vikings (37,68). In either case, this would result in lower 845A allele prevalence in the areas where their expansion was limited: central Europe, the Balkans, and Mediterranean countries.

Our study, together with the study by Merryweather-Clarke et al (6), suggests that a group of countries in central and east Europe have similar prevalence of the mutation. To our knowledge, this is the first comprehensive comparison of the 845A *HFE* mutation prevalence between all West and South Slavic populations.

Among the South Slavs, there was a linear gradual decrease in the prevalence of allele 845A *HFE*. This linearity suggests a possible stability and demic diffusion of the genes from the northwest into a block (the South Slavs) in which there are no conditions for the maintenance of a high frequency of the mutation (either because of genetic background or environmental reasons). An alternative explanation is that there is a gradient of conditions to which South Slavic populations have been exposed, forming a gradient of positive selection and heterozygous advantage. A third possibility, perhaps supported by Y-chromosome haplotypes, is that the medieval expansion of the Slavs (beginning during the 5th and 6th century) resulted in a gradient of ancestors carrying this allele (69).

It would be interesting to see if such a gradient is found with mutations in other genes and to compare this with genetic distance data both among the Southern Slavs and the surrounding populations. Additionally, a spatial frequency distribution map constructed using intra-country regions would be of benefit – especially as a gradient similar to the one described here (but across one country) has been found in Portugal (57). It would also be interesting to fill in the gaps for the East Slavic populations, including those in Belarus, Ukraine, and the West Slavic group in Germany (the Sorbs).

The research is part of the author's habilitation thesis titled: Carrier State In Some Pathogenic Mutations And Predisposition To Longevity (ISSN 1427-4930, ISBN 978-83-61517-37-5).

Funding This study was funded entirely by the Pomeranian Medical University, Szczecin, Poland.

Ethical approval received from the Ethical Committee of the Pomeranian Medical University (BN-001/57/05).

Declaration of authorship GA gave the idea for the study and primarily conducted the research. JSC was involved in the analysis, gave the ideas, and participated in writing of the manuscript. BL was involved in the selection of Polish origin newborns and collection of cord blood samples. AC was involved in the analysis, gave the ideas, and participated in writing of the manuscript.

Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

References

- 1 Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet.* 1996;13:399-408. [Medline:8696333](#) [doi:10.1038/ng0896-399](#)
- 2 Hanson EH, Imperatore G, Burke W. HFE gene and hereditary haemochromatosis a HuGE review. *Am J Epidemiol.* 2001;154:193-206. [Medline:11479183](#) [doi:10.1093/aje/154.3.193](#)
- 3 Bacon BR, Powel LW, Adams PC, Kresina TF, Hoofnagle JH. Molecular medicine and haemochromatosis: at the crossroads. *Gastroenterology.* 1999;116:193-207. [Medline:9869618](#) [doi:10.1016/S0016-5085\(99\)70244-1](#)
- 4 Dooley JS, Walker AP. Genetic haemochromatosis: detection, management and population screening. *Genet Test.* 2000;4:97-101. [Medline:10953946](#) [doi:10.1089/10906570050114777](#)
- 5 Trinder D, Macey DJ, Olynyk JK. The new iron age. *Int J Mol Med.* 2000;6:607-12. [Medline:11078817](#)
- 6 Merryweather-Clarke AT, Pointon JJ, Jouanolle AM, Rochette J, Robson KJH. Geography of HFE C282Y and H63D mutations. *Genet Test.* 2000;4:183-98. [Medline:10953959](#) [doi:10.1089/10906570050114902](#)
- 7 Merryweather-Clarke AT, Pointon JJ, Shearman JD, Robson KJ. Global prevalence of putative haemochromatosis mutations. *J Med Genet.* 1997;34:275-8. [Medline:9138148](#) [doi:10.1136/jmg.34.4.275](#)
- 8 Gottschalk R, Seidl C, Loffler T, Seifried E, Hoelzer D, Kaltwasser JP. HFE codon 63/282 (H63D/C282Y) dimorphism in German patients with genetic haemochromatosis. *Tissue Antigens.* 1998;51:270-5. [Medline:9550327](#) [doi:10.1111/j.1399-0039.1998.tb03101.x](#)
- 9 Nielsen P, Carpinteiro S, Fischer R, Cabeda JM, Porto G, Gabbe EE. Prevalence of the C282Y and H63D mutations in the HFE gene in patients with hereditary haemochromatosis and in control subjects from Northern Germany. *Br J Haematol.* 1998;103:842-5. [Medline:9858243](#) [doi:10.1046/j.1365-2141.1998.01037.x](#)
- 10 Zdarsky E, Horak J, Stritesky J, Heirler F. Haemochromatosis. Determination of the C282Y mutation frequency in the population on the Czech Republic and sensitivity of haemochromatosis detection using Guthrie Cards [in Czech]. *Cas Lek Cesk.* 1999;138:497-9. [Medline:10566227](#)
- 11 Alvarez S, Mesa MS, Bandrés F, Arroyo E. C282Y and H63D mutation frequencies in a population from central Spain. *Dis Markers.* 2001;17:111-4. [Medline:11673657](#)
- 12 Cassanelli S, Pignatti E, Montosi G, Garuti C, Mariano M, Campioli D, et al. Frequency and biochemical expression of C282Y/H63D haemochromatosis (HFE) gene mutations in the healthy adult population in Italy. *J Hepatol.* 2001;34:523-8. [Medline:11394651](#) [doi:10.1016/S0168-8278\(01\)00035-6](#)
- 13 Lio D, Balistreri CR, Colonna-Romano G, Motta M, Franceschi C, Malaguarnera M, et al. Association between the MHC class I gene HFE polymorphisms and longevity: a study in Sicilian population. *Genes Immun.* 2002;3:20-4. [Medline:11857056](#) [doi:10.1038/sj.gene.6363823](#)
- 14 Cimburova M, Putova I, Provaznikova H, Pinterova D, Horak J. S65C and other mutations in the haemochromatosis gene in the Czech population. *Folia Biol (Praha).* 2005;51:172-6. [Medline:16419611](#)
- 15 Melis MA, Cau M, Congiu R, Ruvoletto L, Cao A, Galanello R. Frequency of haemochromatosis C282Y and H63D mutations in Sardinia. *Genet Test.* 2002;6:327-9. [Medline:12537659](#) [doi:10.1089/10906570260471886](#)
- 16 Mariani R, Salvioni A, Corengia C, Erba N, Lanzafame C, De Micheli V, et al. Prevalence of HFE mutations in upper Northern Italy: study of 1132 unrelated blood donors. *Dig Liver Dis.* 2003;35:479-81. [Medline:12870733](#) [doi:10.1016/S1590-8658\(03\)00220-2](#)
- 17 Ropero P, Briceno O, Mateo M, Polo M, Mora A, Gonzalez FA, et al. Frequency of the C282Y and H63D mutations of the haemochromatosis gene (HFE) in a cohort of 1,000 neonates in Madrid (Spain). *Ann Hematol.* 2006;85:323-6. [Medline:16520984](#) [doi:10.1007/s00277-006-0094-4](#)
- 18 Voicu PM, Cojocariu C, Petrescu-Danila E, Covic M, Stanciu C, Rusu M. Prevalence of HFE (haemochromatosis) gene mutations C282Y and H63D in a Romanian population. *Blood Cells Mol Dis.* 2009;42:14-5. [Medline:18842428](#) [doi:10.1016/j.bcmd.2008.08.004](#)
- 19 Mura C, Ragueneas O, Ferec C. HFE mutation analysis in 711 probands: evidence for S65C implication in mild form of haemochromatosis. *Blood.* 1999;93:2502-5. [Medline:10194428](#)
- 20 Coppin H, Bensaid M, Fruchon S, Borot N, Blanche H, Roth MP. Longevity and carrying the C282Y mutation for haemochromatosis on the HFE gene: case control study of 492 French centenarians. *BMJ.* 2003;327:132-3. [Medline:12869454](#) [doi:10.1136/bmj.327.7407.132](#)
- 21 Raszeja-Wyszomirska J, Kurzawski G, Suchy J, Zawada I, Lubinski J, Milkiewicz P. Frequency of mutations related to hereditary haemochromatosis in northwestern Poland. *J Appl Genet.* 2008;49:105-7. [Medline:18263976](#) [doi:10.1007/BF03195255](#)
- 22 Moczulski DK, Grzeszczak W, Gawlik B. Frequency of the haemochromatosis C282Y and H63D mutations in a Polish population of Slavic origin. *Med Sci Monit.* 2001;7:441-3. [Medline:11386022](#)
- 23 Gabrikova D, Boronova I, Bernasovsky I, Behulova R, Macekova S, Bozikova A, et al. Haemochromatosis gene mutations in the general population in Slovakia. *Central European Journal of Medicine.* 2011;6:148-51. [doi:10.2478/s11536-010-0067-9](#)
- 24 Cukjati M, Vaupotič T, Ruprecht R, Curin-Šerbec V. Prevalence of H63D, S65C and C282Y hereditary haemochromatosis gene mutations in Slovenian population by an improved high-throughput genotyping assay. *BMC Med Genet.* 2007;8:69. [Medline:18036208](#) [doi:10.1186/1471-2350-8-69](#)
- 25 Hruskovicova H, Milanez T, Kobal J, Potisk KP, Petrovic D, Peterlin B. Haemochromatosis-causing mutations C282Y and H63D are not risk factors for atherothrombotic cerebral infarction. *Med Sci*

- Monit. 2005;11:BR248-52. [Medline:15990686](#)
- 26 Zorc M, Hruskovicova H, Petrovic MG, Milcia M, Peterlin B, Petrovic D. Haemochromatosis-causing mutations C282Y and H63D are not risk factors for coronary artery disease in Caucasians with type 2 diabetes. *Folia Biol (Praha)*. 2004;50:69-70. [Medline:15222129](#)
- 27 Ristic S, Makuc J, Starcevic N, Logar N, Brajenovic-Milic B, Stepec S, et al. Haemochromatosis gene mutations in the Croatian and Slovenian populations. *Clin Genet*. 2003;64:444-6. [Medline:14616770](#) [doi:10.1034/j.1399-0004.2003.00169.x](#)
- 28 Starcevic-Cizmarevic N, Stepec S, Ristic S, Milic S, Brajenovic-Milic B, Stimac D, et al. Haemochromatosis gene mutations in patients with alcoholic cirrhosis. *Clin Genet*. 2006;70:257-9. [Medline:16922731](#) [doi:10.1111/j.1399-0004.2006.00672.x](#)
- 29 Terzic R, Sehic A, Teran N, Terzic I, Peterlin B. Frequency of HFE gene mutations C282Y and H63D in Bosnia and Herzegovina. *Coll Antropol*. 2006;30:555-7. [Medline:17058523](#)
- 30 Hercegovic A, Teran N, Trezic R, Peterlin B. Molecular and genetic analysis of HFE gene in the Bosnian- Herzegovinian population [in Bosnian]. *Glasnik Antropološkog društva Srbije*. 2008;43:82-6.
- 31 Saric M, Zamurovic Lj, Keckarevic-Markovic M, Keckarevic D, Stevanovic M, Savic-Pavicevic D, et al. Frequency of haemochromatosis gene mutations in the population of Serbia and Montenegro. *Clin Genet*. 2006;70:170-2. [Medline:16879202](#) [doi:10.1111/j.1399-0004.2006.00655.x](#)
- 32 Arsov T, Petlichkovski A, Strezova A, Jurhar-Pavlova M, Trajkov D, Spiroski M. Prevalence of the hereditary haemochromatosis mutations (C282Y, H63D and S65C) in the Republic of Macedonia. *Balkan Journal of Medical Genetics*. 2002;5:11-4.
- 33 Ivanova A, von Arsen N, Adjarov D, Oellerich M, Wieland E. C282Y and H63D mutations in the HFE gene are not associated with porphyria cutanea tarda in Bulgaria. *Hepatology*. 1999;30:1531-2. [Medline:10610354](#) [doi:10.1002/hep.510300626](#)
- 34 Kondrashova TV, Neriishi K, Ban S, Ivanova TI, Krikunova LI, Shentereva NI, et al. Frequency of hemochromatosis gene (HFE) mutations in Russian healthy women and patients with estrogen-dependent cancers. *Biochim Biophys Acta*. 2006;1762:59-65. [Medline:16216474](#)
- 35 Potekhina ES, Lavrov AV, Samokhodskaya LM, Efimenko AY, Balatskiy AV, Baev AA, et al. Unique genetic profile of hereditary haemochromatosis in Russians: high frequency of C282Y mutation in population, but not in patients. *Blood Cells Mol Dis*. 2005;35:182-8. [Medline:16055358](#) [doi:10.1016/j.bcmd.2005.06.012](#)
- 36 Datz C, Lalloz MR, Vogel W, Graziadei I, Hackl F, Vautier G, et al. Predominance of the HLA-H Cys282Tyr mutation in Austrian patients with genetic haemochromatosis. *J Hepatol*. 1997;27:773-9. [Medline:9382962](#) [doi:10.1016/S0168-8278\(97\)80312-1](#)
- 37 Milman N, Steig T, Koefoed P, Pedersen P, Fenger K, Nilsen FC. Frequency of the haemochromatosis HFE mutations C282Y, H63D and S65C in blood donors in the Faroe Island. *Ann Hematol*. 2005;84:146-9. [Medline:15042317](#) [doi:10.1007/s00277-004-0865-8](#)
- 38 Barton JC, Acton RT, Prasthofer EF, Rivers CA. Hemochromatosis in a Lithuanian with HFE C282Y homozygosity and C282Y allele frequencies in the Baltic Sea region. *Eur J Haematol*. 2001;67:263-4. [Medline:11860450](#) [doi:10.1034/j.1600-0609.2001.00579.x](#)
- 39 Parlist P, Mikelsaar AV, Tasa G, Beckman L. The frequency of C282Y and H63D mutations in Hemochromatosis gene in native Estonians. *Eur J Epidemiol*. 2001;17:213-6. [Medline:11680538](#) [doi:10.1023/A:1017951314164](#)
- 40 Beckman LE, Saha N, Spitsyn V, Van Landeghen G, Beckman L. Ethnic differences in the HFE codon 282 (Cys/Tyr) polymorphism. *Hum Hered*. 1997;47:263-7. [Medline:9358014](#) [doi:10.1159/000154422](#)
- 41 Tuomainen TP, Kontula K, Nyyssonen K, Lakka TA, Helio T, Salonen JT. Increased risk of acute myocardial infarction in carriers of the haemochromatosis gene Cys282Tyr mutation: a prospective cohort study in men in eastern Finland. *Circulation*. 1999;100:1274-9. [Medline:10491370](#)
- 42 Pastinen T, Perola M, Ignatius J, Sabbati C, Tainola P, Levander M, et al. Dissecting a population genome for targeted screening of disease mutations. *Hum Mol Genet*. 2001;10:2961-72. [Medline:11751678](#) [doi:10.1093/hmg/10.26.2961](#)
- 43 Andrikovics H, Kalmar L, Bors A, Fandl B, Petri I, Kalász L, et al. Genotype screening for hereditary haemochromatosis among voluntary blood donors in Hungary. *Blood Cells Mol Dis*. 2001;27:334-41. [Medline:11358395](#) [doi:10.1006/bcmd.2001.0384](#)
- 44 Merryweather-Clarke AT, Simonsen H, Shearman JD, Pointon JJ, Norgaard-Pedersen B, Robson KJ. A retrospective anonymous pilot study in screening newborns for HFE mutations in Scandinavian populations. *Hum Mutat*. 1999;13:154-9. [Medline:10094552](#) [doi:10.1002/\(SICI\)1098-1004\(1999\)13:2<154::AID-HUMU8>3.0.CO;2-E](#)
- 45 Milman N, Pedersen P. Evidence that the Cys282Tyr mutation of the HFE gene originated from a population in Southern Scandinavia and spread with the Vikings. *Clin Genet*. 2003;64:36-47. [Medline:12791037](#) [doi:10.1034/j.1399-0004.2003.00083.x](#)
- 46 Murphy S, Curran MD, Mc Dougall N, Callender ME, O'Brien CJ, Middleton D. High incidence of the Cys282Tyr mutation in the HFE gene in the Irish population-implication for haemochromatosis. *Tissue Antigens*. 1998;52:484-8. [Medline:9864039](#) [doi:10.1111/j.1399-0039.1998.tb03076.x](#)
- 47 Ryan E, O'Keane C, Crowe J. Haemochromatosis in Ireland and HFE. *Blood Cells Mol Dis*. 1998;24:428-32. [Medline:9851896](#) [doi:10.1006/bcmd.1998.0211](#)
- 48 Byrnes V, Ryan E, Barrett S, Kenny P, Mayne P, Crowe J. Genetic haemochromatosis, a Celtic disease: is it now time for population screening? *Genet Test*. 2001;5:127-30. [Medline:11551098](#) [doi:10.1089/109065701753145583](#)
- 49 Carella M, D'Ambrosio L, Totaro A, Grifa A, Valentino MA, Piperno A, et al. Mutation analysis of the HLA-H gene in Italian haemochromatosis patients. *Am J Hum Genet*. 1997;60:828-32.

- Medline:9106528
- 50 Piperno A, Sampietro M, Pietrangelo A, Arosio C, Lupica L, Montosi G, et al. Heterogeneity of haemochromatosis in Italy. *Gastroenterology*. 1998;114:996-1002. Medline:9558289 doi:10.1016/S0016-5085(98)70319-1
- 51 Borgna-Pignatti C, Solinas A, Bombieri C, Micciolo R, Gamberini MR, De Stefano P, et al. The haemochromatosis mutations do not modify the clinical picture of thalassaemia major in patients regularly transfused and chelated. *Br J Haematol*. 1998;103:813-6. Medline:9858237 doi:10.1046/j.1365-2141.1998.01067.x
- 52 Longo F, Zecchina G, Sbaiz L, Fischer R, Piga A, Camaschella C. The influence of haemochromatosis mutations on iron overload of thalassaemia major. *Haematologica*. 1999;84:799-803. Medline:10477452
- 53 van der A DL, Peeters PH, Grobbee DE, Roest M, Marx JJ, Voorbij HM, et al. HFE mutations and risk of coronary heart disease in middle-aged women. *Eur J Clin Invest*. 2006;36:682-90. Medline:16968463 doi:10.1111/j.1365-2362.2006.01711.x
- 54 Cobbaert CM, Boer JMA, van der A DL, Jansen EHJM, Koeken A, de Baar E, et al. Significance of HFE and FPNI (N144H) gene mutations in the development of cardiovascular disease: results from the Dutch Prospective Monitoring on Cardiovascular Disease Risk Factors. *Clin Chem*. 2005;51 suppl:A121.
- 55 Porto G, de Sousa M. Variation of hemochromatosis prevalence and genotype in national groups. In: Barton, Edwards CQ, editors. *Hemochromatosis. Genetics, pathophysiology, diagnosis and treatment*. Edinburgh (UK): Cambridge University Press; 2000. p. 51-62.
- 56 Distant S, Berg JP, Lande K, Haug E, Bell H. High prevalence of the haemochromatosis-associated Cys282Tyr HFE gene mutation in a healthy Norwegian population in the city of Oslo, and its phenotypic expression. *Scand J Gastroenterol*. 1999;34:529-34. Medline:10423072 doi:10.1080/003655299750026290
- 57 Cardoso CS, Oliveira P, Porto G, Oberkanins C, Mascarenhas M, Rodrigues P, et al. Comparative study of the two more frequent HFE mutations (C282Y and H63D): significant different allelic frequencies between the North and South of Portugal. *Eur J Hum Genet*. 2001;9:843-8. Medline:11781701 doi:10.1038/sj.ejhg.5200723
- 58 Baiget M, Barcelo MJ, Gimferrer E. Frequency of the HFE C282Y and H63D mutations in distinct ethnic groups living in Spain. *J Med Genet*. 1998;35:701. Medline:9719385 doi:10.1136/jmg.35.8.701
- 59 Fabrega E, Castro B, Sanchez-Castro L, Benito A, Fernandez-Luna JL, Pons-Romero F. The prevalence of the Cys282Tyr mutation in the haemochromatosis gene in Cantabria in patients diagnosed with hereditary haemochromatosis [in Spanish]. *Med Clin (Barc)*. 1999;112:451-3. Medline:10320958
- 60 Moreno L, Vallcorba P, Boixeda D, Cabello P, Bermejo F, San Roman C. The usefulness of the detection of Cys282Tyr and His63Asp mutations in the diagnosis of hereditary haemochromatosis. *Rev Clin Esp*. 1999;199:632-6. Medline:10589245
- 61 Sánchez M, Bruguera M, Bosch J, Rodés J, Ballesta F, Oliva R. Prevalence of the Cys282Tyr and His63Asp HFE gene mutations in Spanish patients with hereditary haemochromatosis and in controls. *J Hepatol*. 1998;29:725-8. Medline:9833909 doi:10.1016/S0168-8278(98)80252-3
- 62 Claeys D, Walting M, Julmy F, Wuillemin WA, Meyer BJ. Haemochromatosis mutations and ferritin in myocardial infarction: a case-control study. *Eur J Clin Invest*. 2002;32 Suppl 1:3-8. Medline:11886425 doi:10.1046/j.1365-2362.2002.0320s1003.x
- 63 Miedzybrodzka Z, Loughlin S, Baty D, Terron A, Kelly K, Dean J, et al. Haemochromatosis mutations in North-East Scotland. *Br J Haematol*. 1999;106:385-7. Medline:10460595 doi:10.1046/j.1365-2141.1999.01554.x
- 64 Willis G, Jennings BA, Goodman E, Fellows IW, Wimperis JZ. A high prevalence of HLA-H 845A mutations in haemochromatosis patients and the normal population in eastern England. *Blood Cells Mol Dis*. 1997;23:288-91. Medline:9410472 doi:10.1006/bcmd.1997.0145
- 65 Grove J, Daly AK, Burt AD, Guzail M, James OF, Bassendine MF, et al. Heterozygotes for HFE mutations have no increased risk of advanced alcoholic liver disease. *Gut*. 1998;43:262-6. Medline:10189855 doi:10.1136/gut.43.2.262
- 66 Mullighan CG, Bunce M, Fanning GC, Marshall SE, Welsh KI. A rapid method of haplotyping HFE mutations and linkage disequilibrium in a Caucasoid population. *Gut*. 1998;42:566-9. Medline:9616322 doi:10.1136/gut.42.4.566
- 67 A simple genetic test identifies 90% of UK patients with haemochromatosis. The UK Haemochromatosis Consortium. *Gut*. 1997;41:841-4. Medline:9462220 doi:10.1136/gut.41.6.841
- 68 Simon M, Alexandre JL, Fauchet R, Genetet B, Bourel M. The genetics of haemochromatosis. *Prog Med Genet*. 1980;4:135-68. Medline:7003653
- 69 Rebała K, Mikulich AI, Tsybovsky IS, Sivakova D, Dzupinkova Z, Szczerkowska-Dobosz A, et al. Y-STR variation among Slavs: evidence for the Slavic homeland in the middle Dnieper basin. *J Hum Genet*. 2007;52:406-14. Medline:17364156 doi:10.1007/s10038-007-0125-6