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.

**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
grazyna.adler2@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 B2-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 μL 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 μL) containing 10× buffer (pH 8.3, 1.5 mM MgCl2), 0.2 mM each of the deoxynucleoside triphosphates, 0.5 U Polymerase Taq (MBI Fermentas, Vilnius, Lithuania), and 4 pmol each of the forward and reverse primers. 5′- CAT CCA TCC TTC CT-3′ was used as a forward primer and 5′- TCC TCA GCC 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 Rsal 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 Rsal 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://universalmedia.pagesperso-orange.fr/geo/loc.html). 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.
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 in-
habited by the West Slavs was 3.6% and varied from 3.5% in
Poland (including our study) to 4.0% in the Czech
Republic (10,14,21-23) (Figure 1). This places the West Slavs to a group with allele frequencies be-
tween 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 Slav-
ic countries was 2.2%. The highest prevalence was ob-
served 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 Europe-
an 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 distri-
bution of ethnic groups and cultures, and consequently
to genetic mixing (68). Migrations, together with other
factors, have also determined the prevalence of genet-
ic 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

| 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) | 4.0                         |           |
|            | Moczulski DA et al, 2001 (22) | 871 (healthy adults) | 3.1                         |           |
| Czech Republic | Cimburová M et al, 2005 (14) | 481 (neonates) | 3.4                         | 3.8       |
|            | Zdársky E et al, 1998 (10) | 139 (healthy adults) | 5.0                         |           |
| Slovakia   | Gabrišková D et al, 2011 (23) | 359 (general population) | 4.0                      | 4.0       |
| South Slavs |           |                        |                            |           |             |
| Slovenia   | Cukajić 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-Cizmarević N et al, 2006 (28) | 350 (healthy adults) | 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) | 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) | 1.6                         | 1.6       |
| Macedonia  | Arsov T et al, 2005 (32) | 100 (healthy adults) | 1.0                         | 1.0       |
| Bulgaria   | Ivanova A et al, 1999 (33) | 100 (healthy adults) | 0.0                         | 0.0       |
| East Slavs | Russia (European part) | Kondrashova V et al, 2006 (34) | 260 (healthy women) | 3.3       | 3.5       |
|            | Pothenkina E S et al, 2005 (35) | 840 (blood donors) | 3.5                         |           |
| Belarus    | no data |                        |                            |           |
| Ukraine    | no data |                        |                            |           |

*Weighted average.
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.cmj.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, Grinke 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, Olynk JK. The new iron age. Int J Mol Med. 2000b;6:607-12. Medline:1078817

6 Merryweather-Clarke AT, Pointon JJ, Jouanolle AM, rochette RN, 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

7 Merryweather-Clarke AT, Pointon JJ, Shearman JD, robson KJ. Geography of hFe C282Y and h63d mutation prevalences in the healthy adult population in the Czech republic and sensitivity of haemochromatosis C282Y and H63D mutations in a Polish population. Folia Biol (Praha). 2005;51:270-5. Medline:9550327 doi:10.1111/j.1399-0039.1998.tb03101.x

8 Gottschalk R, Seidl C, loffler T, Seifried E, hoelzer D, Kaltwasser JP. Prevalence of the C282Y mutation in the healthy adult population in Italy. J Hepatol. 2001;34:275-8. Medline:9138148 doi:10.1016/j.jhep.1998.08.004

9 Nielsen P, Carpinteiro S, Fischer R, Cabeda JM, Porto G, Gabbe EE. Frequency and biochemical expression of C282Y/h63d mutation in patients with hereditary haemochromatosis. tissue Antigens. 1998;51:270-5. Medline:9550327 doi:10.1111/j.1399-0039.1998.tb03101.x

10 Melis MA, Cau M, Conigui 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

11 Alvarez S, Mesa MS, Bandrés F, Arroyo E. C282Y and h63d mutation frequencies in a population from central Spain. dis Markers. 1999;138:497-9. Medline:10566227

12 Zdarsky E, Horak J, Stritesky J, Heifler 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

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 Mura C, Raguenes O, Ferec C. HFE mutation analysis in 711 probands: evidence for S65C implication in mild from of haemochromatosis. Blood. 1999;93:2502-5. Medline:10194428

16 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

17 Rasperova M, Gruzskova-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 Immun. 2011;6:148-51. doi:10.2478/s11536-010-0067-9

18 Gabrikova D, Boronova I, Bernasovsky I, Behulova R, Macekova J, Milkiewicz P. Frequency of mutations related to hereditary haemochromatosis C282Y and H63D mutations in a Polish population. Central European Journal of Medicine. 2011;6:148-51. doi:10.2478/s11536-010-0067-9

19 Melis MA, Cau M, Conigui 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

20 Gabrišková I, Boronová I, Bernasovská I, Behulová R, Maceková J, Milkiewicz P. Frequency of mutations related to hereditary haemochromatosis in northern Poland. J Appl Genet. 2008;49:105-7. Medline:18263976 doi:10.1007/BF03195255

21 Močulszki DK, Grzeszczak W, Gawklik B. Frequency of the C282Y and H63D mutations in the Slavic population of Sardinia. Genet test. 2002;6:327-9. Medline:12537659 doi:10.1089/10906570260471886

22 Rusu M. Prevalence of hFe (haemochromatosis) gene mutations in the healthy adult population in central Slovakia. Folia Biol (Praha). 2005;51:270-5. Medline:9550327 doi:10.1111/j.1399-0039.1998.tb03101.x

23 Chalupski-Kolaczek A, Kownacki P, Grabowicz A, Novak Z, Gobi A, Motyl J, Dobrzański A. Genetic analysis of the hFe gene 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

24 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

25 Adler et al
Mon. 2005;11:BR248-52. Medline:15990686
26 Zorc M, Hruskovciová H, Petrovic MG, Milca 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. Polia Biol (Prah). 2004;50:69-70. Medline:15222129
27 Ristic S, Makuc J, Starcevic N, Logar N, Braunjevic-Bilic M, 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 E, Braunjevic-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 Hercegovac A, Teran N, Terzic R, Peterlin B. Molecular and genetic analysis of HFE gene in the Bosnian-Herzegovinan population [in Bosnian]. Glasnik Antropolskog 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, Petlichkiovski A, Strezova A, Jurlar-Pavlova M, Trajkov D, Spiroksi 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.30010626
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, Efmenko 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, Lalroz 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, Nielsen FC. Frequency of the haemochromatosis HFE gene 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. Haemochromatosis in a Lithuanian with HFE C282Y homozygosity and C282Y allele frequencies in the Baltic Sea region. Eur J Haematol. 2001;67:263-4. Medline:11804050 doi:10.1046/j.1600-0609.2001.00579.x
39 Parlist P, Mikelseva 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:11605038 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, Nyssonen K, Lakk TA, Helio T, Salonen JT. Increased risk of acute myocardial infarction in carries of the haemochromatosis gene Cys282Tyr mutation: a prospective cohort study in men in istern Finland. Circulation. 1999;100:1274-9. Medline:10491370
42 Pastinen T, Perola M, Ignatius J, Sabatti 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<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:10.1089/1099-0043.15.2<127::AID-HGUM2>3.0.CO;2-E
49 Carella M, D'Ambrosio L, Totoar 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.
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

Borgna-Pignatti C, Solinas A, Bombieri C, Miccioło R, Gamberrini 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

Longo F, Zecchina G, Sbaiz L, Fischer R, Piga A, Camaschella C. The influence of haemochromatosis mutations on iron overload of thalassemia major. Haematologica. 1999;84:799-803. Medline:10477452

van der Adl, Peeters PH, Grobbee DE, Roest M, Marx JJ, Voorbij H, 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

Cobbwaert CM, Boer JMA, van der Adl, 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.

Porto G, de Sousa M. Variation of haemochromatosis prevalence and genotype in national groups. In: Barton, Edwards CQ, editors. Haemochromatosis. Genetics, pathophysiology, diagnosis and treatment. Edinburgh (UK): Cambridge University Press; 2000. p. 51-62.

Distante 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

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

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

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

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

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

Claeys D, Wailing M, Jullny F, Wullermin 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.1365-2362.2002.02020.x

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

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

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

Mullighan CG, Bunce M, Fanning GC, Marshall SE, Welsh KI. A rapid method of haplotyping HFE mutations and linkage disequilibrium in a Caucasian population. Gut. 1998;42:566-9. Medline:9616322 doi:10.1136/gut.42.4.566

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

Simon M, Alexandre JL, Fauchet R, Genetet B, Bourel M. The genetics of haemochromatosis. Prog Med Genet. 1980;4:135-68. Medline:7003653

Rebala K, Mikulich AI, Tsymbovskiy IS, Sivakova D, Dzuhipinka Z, Szczerskowska-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