

Genetic Background of Primary Iron Overload Syndromes in Japan

メタデータ	言語: eng 出版者: 公開日: 2017-10-05 キーワード (Ja): キーワード (En): 作成者: メールアドレス: 所属:
URL	http://hdl.handle.net/2297/3524

Genetic Background of Primary Iron Overload Syndromes in Japan

Hisao Hayashi, Shinya Wakusawa, Satoshi Motonishi, Ken-ichi Miyamoto,
Hidetoshi Okada, Yasutaka Inagaki and Takaaki Ikeda



INTERNAL MEDICINE

Reprinted from Internal Medicine

Vol. 45, Pages 1107-1111

November 2006

Genetic Background of Primary Iron Overload Syndromes in Japan

Hisao Hayashi¹, Shinya Wakusawa², Satoshi Motonishi³, Ken-ichi Miyamoto³,
Hidetoshi Okada⁴, Yasutaka Inagaki⁵ and Takaaki Ikeda⁶

Abstract

The different prevalences of iron overload syndromes between Caucasians and Asians may be accounted for by the differences in genetic background. The major mutation of hemochromatosis in Celtic ancestry, C 282Y of *HFE*, was reported in a Japanese patient. Five patients of 3 families with the hepatic transferrin receptor gene (*TFR2*)-linked hemochromatosis were found in different areas of Japan, suggesting that *TFR2* is a major gene in Japanese people. Three patients with mutations in the hemojuvelin gene, *HJV*, showed also middle-age-onset hemochromatosis. A heterozygous mutation in the H ferritin gene, *FTH1*, was found in a family of 3 affected patients. Another autosomal dominant *SLC40A1*-linked hyperferritinemia (ferroportin disease) was found in 3 patients of 2 families. Two patients with hemochromatosis were free from any mutations in the genes investigated. In conclusion, the genetic backgrounds of Japanese patients with primary iron overload syndromes were partially clarified, showing some phenotype-genotype correlations.

Key words: ferroportin disease, hemochromatosis

(DOI: 10.2169/internalmedicine.45.1876)

Introduction

Iron is an essential element for human beings, while in excess it induces oxidative stress leading to organ damage and potential carcinogenesis (1). Hemochromatosis has been postulated as a genetic disorder with the impaired regulation of iron homeostasis. In 1996, Feder et al identified C282Y and H63D mutations in the hemochromatosis gene (*HFE*) of Caucasian patients with the classic form of hemochromatosis (2). As the second genetic background responsible for the classic form, a variety of mutations were found in the hepatic transferrin receptor gene (*TFR2*) of patients with non-*HFE* classic hemochromatosis (3). Furthermore, the hemojuvelin gene (*HJV*) (4, 5) and hepcidin gene (human anti-microbial peptide gene; *HAMP*) (6) were cloned in the families with young-adult onset, autosomal recessive, parenchymal iron overload. Genetic dysfunction of the iron ex-

porter, namely ferroportin disease, is caused by heterozygous mutants of *SLC40A1* (7, 8). The hepatic lesion shows reticuloendothelial cell-dominant iron overload, also different in histology from the classic form of hemochromatosis. Another mild iron overload with autosomal dominant inheritance was reported in a Japanese family with a mutation in IRE of H ferritin, heavy chain polypeptide 1 gene (*FTH1*) (9).

The different prevalence of iron overload syndromes between Caucasians and Asians may be accounted for by the differences in genetic background. Here, we reviewed the genetic background and genotype-phenotype correlation in Japanese patients with primary iron overload syndromes.

Primary Iron Overload Syndromes

Based on the genetic backgrounds, hemochromatosis was at one time classified in 4 subgroups (10); i) *HFE* hemo-

¹ Department of Medicine, Aichi Gakuin University School of Pharmacy, Nagoya, ² Department of Medical Technology, Nagoya University School of Health Sciences, Nagoya, ³ Department of Pharmacy, Graduate School of Natural Sciences, Kanazawa University, Kanazawa, ⁴ Molecular Genetics of Cardiovascular Disorders, Graduate School of Medical Science, Kanazawa University, Kanazawa, ⁵ Department of Internal Medicine, Nippon Kokan Hospital, Kawasaki and ⁶ Department of Internal Medicine, Yokosuka Kyousai Hospital, Yokosuka

Received for publication April 28, 2006; Accepted for publication June 20, 2006

Correspondence to Dr. Hisao Hayashi, Department of Medicine, Aichi Gakuin University School of Pharmacy, 1-100 Kusumoto-cho, Chikusa-ku, Nagoya 464-8650

Table 1. Japanese Patients with Primary Iron Overload Syndrome

Patients	Age/Sex	Mutations	Clinical Manifestations			Iron Index		Ref
			Liver	DM	Pig	Ferritin F:3.4-90 M:27-320 (ng/mL)	TF-S 20-50 (%)	
<i>HFE</i> -1	65/F	C282Y homozygous	fibrosis	yes	yes	5660	89.8	15
<i>HFE</i> -2	48/M	A176V heterozygous	cirrhosis	?	?	6487	86.0	16
<i>HJV</i> -1	51/M	Q312X homozygous	cirrhosis	yes	yes	2280	95.5	17
<i>HJV</i> -2	51/F	Q312X homozygous	cirrhosis	yes	yes	4278	95.8	17
<i>HJV</i> -3	48/M	D249H homozygous	cirrhosis	yes	yes	6115	94.8	17
<i>TFR2</i> -1	50/M	AVAQdel homozygous	pre-cirrhosis	no	no	2485	94.5	18
<i>TFR2</i> -2	47/M	AVAQdel homozygous	fibrosis	no	no	4400	90.6	18
<i>TFR2</i> -3	53/F	AVAQdel homozygous	fibrosis	no	no	1470	93.2	18
<i>TFR2</i> -4	41/M	L490R homozygous	cirrhosis	yes	no	2020	93.6	19
<i>TFR2</i> -5	58/M	V561X homozygous	cirrhosis	yes	yes	1982	88.7	19
<i>SLC40A1</i> -1	43/F	A117G heterozygous	chronic hepatitis	yes	yes	9660	92.0	20
<i>SLC40A1</i> -2	43/M	R489S heterozygous	normal	no	no	822	24.8	21
<i>SLC40A1</i> -3	79/M	R489S heterozygous	no biopsy	no	no	2283	62.1	21
<i>FTH1</i> -1	56/F	A49U heterozygous	fibrosis	?	?	1654	58.0	9
<i>FTH1</i> -2	65/M	A49U heterozygous	?	?	?	926	220*	9
<i>FTH1</i> -3	62/F	A49U heterozygous	?	?	?	742	231*	9
<i>FTH1</i> -4	28/F	A49U heterozygous	?	?	?	98	256*	9
Unknown-1	45/M	none	cirrhosis	yes	yes	3000	94.4	35
Unknown-2	47/M	none	fibrosis	yes	yes	3489	94.2	

DM; diabetes mellitus, Pig; skin pigmentation, TF-S; transferrin saturation, Ref; references.

?: no comments on the symptom.

*; the serum level of transferrin (Reference:200-400 mg/dL).

Table 1 summarizes the clinical features and mutations reported in Japanese patients with primary iron overload syndrome, and two patients with the classic form of hemochromatosis who are free from any mutations in the *HFE*, *HJV*, *HAMP*, *TFR2*, *SLC40A1* and *FTH1* genes investigated in this study.

chromatosis, ii) juvenile hemochromatosis by *HJV* (a), and *HAMP* (b), iii) *TFR2* hemochromatosis, iv) *SLC40A1*-linked iron overload. In addition, an autosomal-dominant iron overload with a mutation in *FTH1* has been reported in a Japanese family (9). Recent studies on the homozygotes of C282Y in *HFE* clearly indicate that a large number of patients might be non-hemochromatotic life-long, providing that hemochromatosis is associated with the organ damage due

either to histochemical or biochemical iron overloading (11, 12). Therefore, in this review, we used the terminology of primary iron overload syndromes, which include mild iron overload conditions as a result of the genetic background. Iron overload in aceruloplasminemia should be excluded because the majority of organ damage occurs not in the liver, but in the brain (13, 14). The factors known to cause iron overload, such as alcoholism, viral hepatitis infection, iron supplementation and repeated transfusions might be exacerbating factors of primary iron overload syndromes. Table 1 summarizes the Japanese patients with primary iron overload syndromes reported in the literature (15-21), and 2 patients with the classic form of hemochromatosis with a yet unknown genetic background.

HFE Hemochromatosis

The homozygote of C282Y mutation in *HFE*, a major mutation in Caucasians, was found in a hemochromatosis patient who was a resident of Kyushu, a southwestern island of Japan (15), and a heterozygote of Ala176Val of *HFE* was reported in another patient (16). A population study, however, suggested that C282Y in *HFE* is not prevalent in the Japanese population (22). Over 500 subjects, including apparently healthy volunteers, and patients with chronic hepatitis C (CHC) and hemochromatosis, were all negative for C282Y (23). The estimated amount of iron removed by phlebotomy did not differ between the 5 CHC patients with H63D of *HFE* and 45 H63D-free CHC patients (24).

Juvenile (*HJV* and *HAMP*) Hemochromatosis

Two novel mutations, 745 G>C (D249H) and 934C>T (Q312X) of *HJV*, were reported in 3 patients of 2 Japanese families (17). A missense mutation 745 G>C was homozygous in *HJV* of a patient. A family study confirmed the heterozygosity of 745 G>C in his mother and daughter without any signs of iron overload. Another novel mutation 934C>T of *HJV* was homozygous in 2 siblings of the second family. Different from the previous reports from Europe and North America (5, 25-28), the 3 Japanese patients with *HJV* mutations had the classical form rather than juvenile type hemochromatosis. One patient first manifested diabetic symptoms at the age of 48 years. The proband of another family was admitted first for congestive heart failure and a diabetic condition at the age of 51. His sister, with a 2 year-treatment history of diabetes mellitus, was diagnosed with hemochromatosis at the age of 51 years. As far as we know, there are neither reports on Japanese patients with mutations in *HAMP* nor juvenile hemochromatosis patients with complete gene analysis.

Transferrin Receptor 2 (*TFR2*) Hemochromatosis

An AVAQ594-597 deletion of *TFR2* was found in a

hemochromatosis family living on the main island of Japan (18). Because the AVAQ594-597 deletion was first reported from Italy (3), this indicated it was a universal mutant, occurring in different ethnicities. In addition, 2 unrelated patients were found to be homozygous for the novel mutations of 1469T>G (L490R) and 1665delC (V561X) in *TFR2* (19). All Japanese patients with *TFR2*-hemochromatosis exhibited the middle-age onset triad due to parenchymal iron overload. *TFR2* dysfunction not only plays an important role in Japanese hemochromatosis, but also contributes to the genetic background of non-*HFE*, autosomal-recessive and parenchymal iron overload syndromes around the world (3, 29-31).

Ferroportin Disease

A novel heterozygous A117 G mutation of *SLC40A1* was found in a 43-year-old female patient with the classical form of hemochromatosis (20). She was free from any mutation in *HFE*, *TFR2* and *FTH1*. Her liver specimen showed chronic hepatitis with severe mixed-type iron overload of parenchymal and reticuloendothelial cells, and the transferrin saturation of iron was as high as 92%. Another novel missense mutation 1467A>C (R489S) was heterozygous in *SLC40A1* of the second Japanese family (21). In contrast to the first case, the iron overload was mild, both in a 43-year-old man and his 79-year-old father. The serum ferritin levels of the proband and his father were 822 ng/ml with 24.8% iron saturation and 2283 ng/ml with 62.1% iron saturation, respectively. Their liver function test results were almost within normal limits. The liver biopsy specimen of the proband showed selective iron deposition in the Kupffer cells with otherwise normal structures. This autosomal-dominant disease was found not only in Caucasians (7, 8), but also in Africans and Asians (32-34), suggesting that it is one of the more important iron overload syndromes in the world.

FTH1 Iron Overload

A general iron overload was accidentally found in a 56-year-old Japanese woman (9). Family study disclosed 2 other siblings affected by iron loading. Genetic tests on C282Y and H63D of *HFE*, and Y250X of *TFR2* were performed with negative results. Subsequent study on the IRE of H-ferritin, heavy chain polypeptide 1 gene (*FTH1*), disclosed a heterozygous single A>U conversion at position 49 (A49 U) in the IRE of the H subunit mRNA in 4 members of the family, including an iron load-free, 28-year-old woman, indicating autosomal dominant inheritance of this iron overload syndrome.

Hemochromatosis of Unknown Genetic Background

In this paper, we describe 2 patients with middle-age-onset hemochromatosis. The clinical features of one patient

were reported previously (35). The increased iron parameters of their blood and liver histology, and organ damage secondary to the severe iron overload are compatible with the classic form of hemochromatosis. All coding regions and splice sites of their *HFE*, *HJV*, *HAMP*, *TFR2*, *SLC40A1* and *FTH1* genes were sequenced using the standard methods reported (2, 3, 5, 7-9). However, the 2 patients were free from any mutations in the investigated regions of the genes and their genetic background remains unknown as yet. As reported in other diseases (36, 37), there may be disruptions in the transcriptional and post-transcriptional regulation of the genes or possible candidate genes of primary iron overload syndromes other than those tested for in the study.

Genotype-phenotype Correlation

There is agreement that C282Y/C282Y of *HFE* is the major mutation responsible for middle-age-onset hemochromatosis in Caucasians. However, the spectrum of iron overload of subjects with C282Y homozygosity is widely distributed (11, 12). The phenotypes of patients with *HFE* hemochromatosis are apparently modulated by other genetic factors. Either *HAMP* or *HJV* contributes to the phenotypic heterogeneity of patients with C282Y homozygosity or heterozygosity (38-40). *TFR2* also affects the phenotype of *HFE* traits (41).

The biochemical iron parameters of subjects with C282Y homozygotes revealed the male-dominant gender-specific phenotypic expression of their iron overloading (42, 43). Increasing age, in association with male sex and other genetic factors, plays a role in the serum ferritin levels of C282Y/C282Y individuals (44). Excessive alcohol consumption accentuates the disease expression of *HFE* hemochromatosis (45). The iron homeostasis of individuals with hemochromatosis traits may be affected by chronic gastrointestinal disorders due to bleeding and mal iron absorption. A patient with celiac disease was iron deficient against C282Y homozygosity (46). Excess body mass is commonly associated with the lack of phenotypic expression in C282Y homozygous women (47).

TFR2 hemochromatosis is considered to be an adult-onset syndrome (6). Exceptionally, 2 unrelated French adolescents with mutations in *TFR2* presented a phenotype intermediate between the classic form with middle-age-onset and juvenile hemochromatosis (48). As far as the Japanese were concerned, all patients with *TFR2* hemochromatosis had middle-age-onset hemochromatosis (18, 19), indicating that this gene is a major cause of the classic form of Japanese hemochromatosis.

HJV was first cloned in the patients with 1q-linked hemochromatosis (4, 5). All patients except one had juvenile hemochromatosis. A 49-year-old Greek patient with iron overload-induced hepatic fibrosis, hypogonadism and skin pigmentation was homozygous for I281T in *HJV* (5). In contrast, all 3 Japanese cases of *HJV* hemochromatosis were found in the middle-aged patients with the classic triad of

cirrhosis, diabetes and skin pigmentation (17). These different phenotypes suggested that the genetic background does not always determine the phenotype of hemochromatosis. One patient was infected by *Helicobacter pylori*, which has the potential to cause iron deficiency (49).

The phenotypes of ferroportin disease remain controversial. Iron overload due to mutations in *SLC40A1* has a dominant inheritance and a variable clinical phenotype, such that some patients show early Kupffer cell iron loading and

a low transferrin saturation (7, 8), while others show mixed type iron loading in the hepatocytes and Kupffer cells, and a high transferrin saturation (50). Further studies are needed to define the factors involved in the parenchymal iron loading of the disease. Because the disorder of the iron exporter is autosomal dominant and includes subjects with isolated hyperferritinemia without any organ damage, it might be classified as a disease entity different from hemochromatosis (51).

References

1. Britton R. Metal-induced hepatotoxicity. *Semin Liver Dis* **16**: 2-12, 1996.
2. Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* **13**: 399-408, 1996.
3. Camaschella C, Roetto A, Cali A, et al. The gene TFR2 is mutated in a new type of haemochromatosis mapping to 7q22. *Nat Genet* **25**: 14-15, 2000.
4. Papanikolaou G, Politou M, Roetto A, et al. Linkage to chromosome 1q in Greek families with juvenile hemochromatosis. *Blood Cells Mol Dis* **27**: 744-749, 2001.
5. Papanikolaou G, Samuels ME, Ludwig EH, et al. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. *Nat Genet* **36**: 77-82, 2004.
6. Roetto A, Papanikolaou G, Plotou M, et al. Mutant antimicrobial hepcidin is associated with severe juvenile hemochromatosis. *Nat Genet* **33**: 21-22, 2003.
7. Njajou OT, Vaessen N, Joosse M, et al. A mutation in SLC11A3 is associated with autosomal dominant hemochromatosis. *Nat Genet* **28**: 213-214, 2001.
8. Montosi G, Donovan A, Totaro A, et al. Autosomal-dominant hemochromatosis is associated with a mutation in the ferroportin (SLC11A3) gene. *J Clin Invest* **108**: 619-623, 2001.
9. Kato J, Fujikawa K, Kanda M, et al. A mutation, in the iron-responsive element of H ferritin mRNA, causing autosomal dominant iron overload. *Am J Hum Genet* **69**: 191-197, 2001.
10. Camaschella C, Roetto A, De Gobbi M. Genetic haemochromatosis: genes and mutations associated with iron loading. *Best Pract Res Clin Haematol* **15**: 261-276, 2002.
11. Sham RL, Ou CY, Cappuccio J, Braggins C, Dunnigan K, Phatak PD. Correlation between genotype and phenotype in hereditary hemochromatosis: analysis of 61 cases. *Blood Cells Mol Dis* **23**: 314-320, 1997.
12. Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. *N Engl J Med* **341**: 718-724, 1999.
13. Miyajima H, Nishimura Y, Mizoguchi K, Sakamoto M, Shimizu T, Honda N. Familial apoceruloplasmin deficiency associated with blepharospasm and retinal degeneration. *Neurology* **37**: 761-767, 1987.
14. Yoshida K, Furihata K, Takeda S, et al. A mutation in the ceruloplasmin gene is associated with systemic hemosiderosis in humans. *Nat Genet* **9**: 267-272, 1995.
15. Sohda T, Okubo R, Kamimura S, Ohkawara T. Hemochromatosis with HFE gene mutation in a Japanese patient. *Am J Gastroenterol* **96**: 2487-2488, 2001.
16. Imanishi H, Liu W, Cheng J, Ikeda N, Amuro Y, Hada T. Idiopathic hemochromatosis with the mutation of Ala176Val heterozygous for HFE gene. *Intern Med* **40**: 479-483, 2001.
17. Koyama C, Hayashi H, Wakusawa S, et al. Three patients with middle-age-onset hemochromatosis caused by novel mutations in the hemojuvelin gene. *J Hepatol* **43**: 740-742, 2005.
18. Hattori A, Wakusawa S, Hayashi H, et al. AVAQ 594-597 deletion of the Tfr2 gene in a Japanese family with hemochromatosis. *Hepatol Res* **26**: 154-156, 2003.
19. Koyama C, Wakusawa S, Hayashi H, et al. Two novel mutations, L490R and V561X, in the transferrin receptor 2 in Japanese patients with hemochromatosis. *Haematologica* **90**: 302-307, 2005.
20. Liu W, Shimomura S, Imanishi H, et al. Hemochromatosis with mutation of the ferroportin 1 (IREG1) gene. *Intern Med* **44**: 285-289, 2005.
21. Koyama C, Wakusawa S, Hayashi H, et al. A Japanese family with ferroportin disease caused by a novel mutation of SLC40A1 gene: hyperferritinemia associated with a relatively low transferrin saturation of iron. *Intern Med* **44**: 990-993, 2005.
22. Sohda T, Yanai J, Soejima H, Tamura K. Frequencies in the Japanese populations of the HFE gene. *Biochem Genet* **37**: 63-68, 1999.
23. Shiono Y, Ikeda R, Hayashi H, et al. C282Y and H63D mutations in the HFE gene have no effect on iron overload disorders in Japan. *Intern Med* **40**: 852-856, 2001.
24. Shiono Y, Hayashi H, Wakusawa S, et al. Body iron stores and iron restoration rate in Japanese patients with chronic hepatitis C as measured during therapeutic iron removal revealed neither increased iron stores nor effects of C282Y and H63D mutations on iron indices. *Nagoya J Med Sci* **64**: 51-57, 2001.
25. Lanzara C, Roetto A, Daraio F, et al. Spectrum of hemojuvelin gene mutations in 1q-linked juvenile hemochromatosis. *Blood* **103**: 4317-4321, 2004.
26. Huang FW, Rubio-Aliaga I, Kushner JP, Andrews NC, Fleming MD. Identification of a novel mutation (C321X) in HJV. *Blood* **104**: 2176-2177, 2004.
27. Lee PL, Beutler E, Rao SV, Barton JC. Genetic abnormalities and juvenile hemochromatosis: mutations of the HJV gene encoding hemojuvelin. *Blood* **103**: 4669-4671, 2004.
28. Lee PL, Barton JC, Brandhagen D, Beutler E. Hemojuvelin (HJV) mutations in persons of European, African-American and Asian ancestry with adult onset haemochromatosis. *Br J Haematol* **127**: 224-229, 2004.
29. Roetto A, Totaro A, Piperno A, et al. New mutation inactivating transferrin receptor 2 in hemochromatosis type 3. *Blood* **97**: 2555-2560, 2001.
30. Barton EH, West PA, Rivers CA, Barton JC, Acton RT. Transferrin receptor-2 (TFR2) mutation Y250X in Alabama Caucasian and African American subjects with and without primary iron overload. *Blood Cells Mol Dis* **27**: 279-284, 2001.
31. Lee PL, Halloran C, West C, Beutler E. Mutation analysis of the transferrin receptor-2 gene in patients with iron overload. *Blood Cells Mol Dis* **27**: 285-289, 2001.
32. Gordeuk VR, Caleffi A, Corradini E, et al. Iron overload in Africans and African-Americans and a common mutation in the SLC40A1 (ferroportin 1) gene. *Blood Cells Mol Dis* **31**: 299-304, 2003.
33. Beutler E, Barton JC, Felitti VJ, et al. Ferroportin 1 (SLC40A1)

- variant associated with iron overload in African-Americans. *Blood Cells Mol Dis* **31**: 305-309, 2003.
34. Cemonesi L, Forni GL, Soriani N, et al. Genetic and clinical heterogeneity of ferroportin disease. *Br J Haematol* **131**: 663-670, 2005.
 35. Fujita J, Inagaki Y, Yonei Y, et al. A Japanese case of idiopathic hemochromatosis with analysis of HFE gene mutations and a review of literature on HLA phenotypes in the Japanese cases. *Nippon Shokakibyo Gakkai* **97**: 472-477, 2000 (in Japanese).
 36. Barton JC, Lee PL, Bertoli LF, Beutler E. Iron overload in an African American woman with SS hemoglobinopathy and a promoter mutation in the X-linked erythroid-specific 5-aminolevulinate synthase (ALAS2) gene. *Blood Cells Mol Dis* **34**: 226-228, 2005.
 37. Monteleone G, Del Vecchio Blanco G, Monteleone I, et al. Post-transcriptional regulation of Smad7 in the gut of patients with inflammatory bowel disease. *Gastroenterology* **129**: 1420-1429, 2005.
 38. Merryweather-Clarke AT, Cadet E, Bomford A, et al. Digenic inheritance of mutations in HAMP and HFE results in different types of haemochromatosis. *Hum Mol Genet* **12**: 2241-2247, 2003.
 39. Jacolot S, Le Gac G, Scotet V, Quere I, Mura C, Ferec C. HAMP as a modifier gene that increases the phenotypic expression of the HFE pC282Y homozygous genotype. *Blood* **103**: 2835-2840, 2004.
 40. Biasiotto G, Roetto A, Daraio F, et al. Identification of new mutations of hepcidin and hemojuvelin in patients with HFE C282Y allele. *Blood Cells Mol Dis* **33**: 338-343, 2004.
 41. Pietrangelo A, Caleffi A, Henrion J, et al. Juvenile hemochromatosis associated with pathogenic mutations of adult hemochromatosis genes. *Gastroenterology* **128**: 47-49, 2005.
 42. Ryan E, Byrnes V, Coughlan B, et al. Underdiagnosis of hereditary haemochromatosis: lack of presentation or penetration? *Gut* **51**: 108-112, 2002.
 43. Deugnier Y, Jouanolle AM, Chaperon J, et al. Gender-specific phenotypic expression and screening strategies in C282Y-linked haemochromatosis: a study of 9396 French people. *Br J Haematol* **118**: 1170-1178, 2002.
 44. Lazarescu A, Snively BM, Adams PC. Phenotype variation in C282Y homozygotes for the hemochromatosis gene. *Clin Gastroenterol Hepatol* **3**: 1043-1046, 2005.
 45. Scotet V, Merour MC, Mercier AY, et al. Hereditary hemochromatosis: effect of excessive alcohol consumption on disease expression in patients homozygous for the C282Y mutation. *Am J Epidemiol* **158**: 129-134, 2003.
 46. Geier A, Gartung C, Theurl I, et al. Occult celiac disease prevents penetrance of hemochromatosis. *World J Gastroenterol* **11**: 3323-3326, 2005.
 47. Laine F, Jouanolle AM, Morcet J, et al. Phenotypic expression in detected C282Y homozygous women depends on body mass index. *J Hepatol* **43**: 1055-1059, 2005.
 48. Le Gac G, Mons F, Jacolot S, Scotet S, Ferec C, Frebourg T. Early onset hereditary hemochromatosis resulting from a novel TFR2 gene nonsense mutation (R105X) in two siblings of north French descent. *Br J Haematol* **125**: 674-678, 2004.
 49. Russo-Mancuso G, Branciforte F, Licciardello M, La Spina M. Iron deficiency anemia as the only sign of infection with *Helicobacter pylori*: a report of 9 pediatric cases. *Int J Hematol* **78**: 429-431, 2003.
 50. Wallace DF, Clark RM, Harley HA, Subramaniam VN. Autosomal dominant iron overload due to a novel mutation of ferroportin1 associated with parenchymal iron loading and cirrhosis. *J Hepatol* **40**: 710-713, 2004.
 51. Pietrangelo A. Hereditary hemochromatosis--a new look at an old disease. *N Engl J Med* **350**: 2383-2397, 2004.