Curr Gastroenterol Rep (2010) 12:7–12
DOI 10.1007/s11894-009-0078-3

Phenotypic Expression of Hereditary Hemochromatosis: What Have We Learned from the Population Studies?

Eng K. Gan · Oyekoya T. Ayonrinde · Debbie Trinder · John K. Olynyk

Published online: 26 January 2010

Abstract Profound advances in our knowledge of hereditary hemochromatosis (HH) during the past 150 years have resulted in two distinct "iron ages": the pre-*HFE* gene era and the post-*HFE* gene era. During these periods, family studies, HLA association studies, and ultimately *HFE* gene studies in various populations informed us of the genotypic prevalence as well as the clinical and biochemical penetrance of HH. We learned that HH has a highly variable clinical penetrance in susceptible individuals of Northern European ancestry. Further, we now recognize that the natural history of HH is not as discrete as previously believed, because genetic and environmental modifiers of disease penetrance are increasingly identified as influencing the clinical expression of HH.

Keywords Hereditary hemochromatosis · HFE · Iron · Phenotype · Genotype · Screening · Ferritin · Liver

Introduction

The genetic mutations that define *HFE*-related hereditary hemochromatosis (HH) are common in general populations of northern European origin. That finding notwithstanding, multiple studies during the past decade have demonstrated the clinical and biochemical penetrance of HH to be lower than initially suspected. Furthermore, early diagnosis resulting from improved knowledge and cascade screening, as well as genetic and environmental interactions, may have influenced the natural history and phenotypic expression of HH for many individuals. The classical clinical presentations of HH described prior to discovery of the *HFE* gene are less frequently encountered. We have learned much from the cohort and general population studies undertaken prior to and following discovery of the *HFE* gene, and these are summarized in this review.

E. K. Gan · O. T. Ayonrinde · D. Trinder · J. K. Olynyk (✉)
School of Medicine and Pharmacology,
University of Western Australia, Fremantle Hospital,
PO Box 480, Fremantle 6959 WA, Australia
e-mail: john.olynyk@uwa.edu.au

The Pre-*HFE* Gene Era: Emergence of HH as an Important Clinical Entity

The association between liver iron overload and cirrhosis was recognized in 1865 by Trousseau [1]. However, it was only in 1935, with the publication of Sheldon's [2] monograph detailing 311 cases, that a coherent and unique clinicopathologic entity began to emerge. At that stage, HH was thought to be rare, affecting 1 in 2,000 to 5,000 individuals. It had been speculated that the disorder was a result of an inborn error of metabolism. Sheldon [2] concluded that "idiopathic" hemochromatosis was inherited in a recessive mode, average survival was 2 years, and mortality was caused by diabetes or infections in the preinsulin era.

In 1955, Finch and Finch [3] proposed that iron-storage disease resulted from abnormal absorption of iron from the diet and from blood transfusion, and they defined HH as a disorder characterized by a generalized increase in iron stores, which resulted in tissue damage in multiple organs. Biochemical abnormalities were the earliest phenotypic observation, as evidenced by increased plasma iron and saturation of the iron-binding protein (later shown to be transferrin). Plasma iron elevation was universal in symptomatic patients. Hepatomegaly was common. Strikingly, more than half of decompensated patients had minimal liver biochemical test disturbance, despite hepatomegaly and biopsy-proven fibrosis, indicating that the disease process was insidious. Clinical manifestations occurred at midlife in about two thirds of cases. The risk of liver cancer increased

with age. Common extrahepatic manifestations included skin pigmentation, diabetes, and cardiac problems. The incidence of hemochromatosis now appeared much more common than that reported by Sheldon [2]. Mortality was estimated at 1 in 7,000 hospital admissions [4].

A therapeutic benefit of phlebotomy began to emerge from clinical studies [5, 6]. Phlebotomy therapy resulted in improved survival, normalization of liver biochemistry, decreased skin pigmentation and hepatomegaly, and improvement in diabetes. However, no effects were discernible on portal hypertension, testicular atrophy, or arthropathy. Mortality in HH was now thought to be primarily from cirrhosis-related hepatocellular carcinoma, independent of phlebotomy therapy. Bomford and Williams [6] also noted a higher mortality rate from extrahepatic neoplasms.

By 1962, the genetic inheritance of HH became clearer through careful family studies [7]. The genetic basis was further consolidated in 1977 by the work of Simon et al. [8], who reported close linkage between the presence of HH and the HLA class 1 loci, with an autosomal recessive mode of inheritance emerging. The advancement of genotyping and family screening contributed to increased numbers of cases being detected. HLA typing revealed that HH might be present in 0.79% to 1.2% of Caucasian populations [9–11]. This observation was extended by Leggett et al. [12], in a study of healthy individuals taken from a non-blood bank population. Biochemical penetrance (defined as transferrin saturation greater than 45%) was high, and two thirds of those affected had liver biopsy-confirmed HH. Leggett et al. [12] reported the prevalence of HH to be 1 in 300 individuals in the healthy population.

Our understanding of the clinical importance of HH was further clarified by large cohort studies, which highlighted the importance of early diagnosis and early phlebotomy in improving the prognosis [13–16]. Niederau et al. [14] reported findings on 251 patients with clinical, biochemical, and histologic evidence of HH between 1947 and 1991. Biochemically, two thirds had elevated serum aminotransferase levels and patients with cirrhosis had higher serum iron indices compared with noncirrhotic individuals. Cirrhosis was found in 60% of patients and almost all were symptomatic of weakness, lethargy, and loss of libido compared with noncirrhotics. Extrahepatic cardiac and endocrine complications, including diabetes mellitus, were more common in cirrhotic patients. Morbidity was mainly from liver cirrhosis and diabetes mellitus. Excess mortality resulted from liver cancer (mortality ratio 119), followed by diabetes (mortality ratio 14), cardiomyopathy (mortality ratio 14), and cirrhosis (mortality ratio 10). Adams et al. [13] confirmed that cirrhotic patients were 5.5 times more likely than noncirrhotics to develop liver cancer. Nondiabetic subjects or those without cirrhosis had morbidity and mortality profiles similar to those of the general population [13, 14].

The Post-*HFE* Gene Era: Refinement of Clinical, Genetic, and Environmental Influences

By 1996, intensive genetic research led to the discovery of a candidate gene for HH, termed *HFE*, a new major histocompatibility complex class I-like molecule located on chromosome 6 [17]. The landmark discovery of this gene provided greater understanding of the genesis of iron overload and the effect of mutations in the gene. Two common mutations were identified in the gene product: first, tyrosine is substituted for cysteine at amino acid 282 (C282Y) and second, aspartate is substituted for histidine at amino acid 63 (H63D). Homozygosity for C282Y was observed in 85% to 90% of patients of northern European origin with typical HH [18–21], although it was relatively rare in non-Caucasian populations [22, 23].

During the first decade after discovery of the *HFE* gene, several cross-sectional studies indicated a wide variation in the biochemical penetrance of the disorder, as evidenced by elevated serum ferritin levels (Table 1). When stratified according to gender, biochemical iron overload was found in 70% to 88% of men and 30% to 60% of women homozygous for the C282Y mutation [22, 24–26]. High clinical penetrance was found in a cross-sectional population study of individuals of predominantly northern European descent from Busselton in Western Australia, with 0.5% of the population homozygous for the C282Y mutation. Clinical penetrance (defined as hepatomegaly, skin pigmentation, or arthropathy) was present in 50% of C282Y homozygous subjects. About 25% of these patients had liver biopsy-proven fibrosis and 10% had cirrhosis on liver biopsy. Interestingly, 25% of the homozygotes had no clinical symptoms or overt signs, with corresponding normal range serum ferritin over 4 years of follow-up.

In one of the largest population-based screening projects reported after discovery of the *HFE* gene, more than 65,000 individuals age 20 years or older in a Norwegian county underwent determination of transferrin saturation [27]. Subjects with transferrin saturation above a threshold value of 55% were genotyped. The incidence of homozygous C282Y was estimated at 4.1 per 1,000 women and 6.8 per 1,000 men, and 322 women and 300 men had confirmed transferrin saturation above the threshold levels. Of these, 137 women and 205 men had elevated serum ferritin concentration. Liver biopsy was performed in 50 women and 129 men; increased iron stores were universal in the liver biopsy specimens but at least moderate fibrosis and/or cirrhosis was seen in only 10% of biopsied cases. Fatigue and joint pain were the most common extrahepatic

Table 1 Summary of major cross-sectional population studies

Study	Sample size	C282Y homozygosity	Elevated ferritin,%	Disease definition	Fibrosis/cirrhosis
Olynyk et al. [24]	3,011	1:190	50%	Hepatomegaly, skin pigmentation, arthropathy	Fibrosis, 25% Cirrhosis, 10%
Asberg et al. [27]	65,238	Unknown	Unknown	Fatigue, arthralgia, impotence, diabetes mellitus	Fibrosis, 8% Cirrhosis, 3%
Beutler et al. [25]	41,038	1:270	76% men 54% women	Abnormal LFT	25% fibrosis or cirrhosis
Deugnier et al. [26]	9,396	1:175	70% men 33% women	Diabetes, abnormal LFT, arthritis	Unknown
Adams et al. [22]	99,711	1:227	88% men 57% women	Liver disease	Unknown
Delatycki et al. [28]	11,307	1:240	Unknown	Diabetes, liver disease, arthritis	Fibrosis, 4%

LFT liver function test

manifestations in 13% to 20% of newly diagnosed HH subjects, followed by impotence and diabetes mellitus (4%).

A French clinic-based study of 9,396 subjects also confirmed that 0.5% of the population were homozygous for C282Y, consistent with the earlier studies [26]. Ninety percent of male C282Y homozygotes had at least one clinical symptom compared with 60% of females. Family history of iron excess and chronic fatigue was a common denominator for both genders. Twenty percent of homozygous subjects had arthritis, and 5% to 10% had diabetes or increased alanine transaminase levels.

Genotypic screening in more than 11,000 Australian community residents was done in 2005 by Delatycki et al. [28], and again confirmed a prevalence rate of 0.5% for C282Y homozygosity. Symptoms of tiredness were more common in homozygotes. An additional benefit of this study was that a follow-up questionnaire administered to C282Y homozygous subjects diagnosed by genetic screening indicated that genetic screening was acceptable to the population.

Adams et al. [22] showed that C282Y homozygosity is rare in nonwhite populations. In this North American study, 99,711 primary care participants were tested for genetic mutations and iron indices and underwent clinical assessment. The authors found the prevalence of C282Y mutation to be highest in whites (0.44%) and lowest in Asians (0.000039%). Self-reported history of liver disease was significantly higher in male C282Y homozygotes and compound heterozygotes.

Contrary to the relatively high clinical expression in other population studies, Beutler et al. [25], in a study of 41,000 patients recruited from health appraisal clinics, reported that less than 1% of C282Y homozygotes developed an overt clinical phenotype. However, the majority of clinically diagnosed C282Y homozygotes diagnosed prior to the commencement of this study were excluded from the analysis. Plasma type IV collagen was used as a surrogate of hepatic fibrosis and indicated that up to 25% of subjects might have liver fibrosis, although no statistically significant relationship was seen between collagen type IV and serum ferritin concentrations. Surprisingly, the combination of symptoms (general health, chronic fatigue, joint symptoms, skin pigmentation, impotence, diabetes, arrhythmia, and elevated aspartate transaminase) that represent the common clinical features of HH were no more prevalent in C282Y homozygotes than in controls.

It was apparent from the cross-sectional population studies performed up to 2005 that the biochemical and clinical expression of disease in HH was highly variable. It was also evident that longitudinal studies would be needed to define the true natural history of progression of HH. Olynyk et al. [29] followed the fate of 12 untreated C282Y homozygotes over 17 years. Median transferrin saturation value increased from 42% to 76%, but serum ferritin levels varied markedly. Six of 12 C282Y homozygotes underwent biopsy at the end of follow-up; of those, 50% had advanced fibrosis with concurrent serum ferritin levels exceeding 500 μg/L. Clinically, only one patient had diabetes in 1981 and by the end of the study, skin pigmentation developed in 3 of 12 patients, arthritis in 4 of 12 patients, and hepatomegaly in 2 of 12 patients. Similar findings were reported by Andersen et al. [30] from 23 untreated C282Y homozygotes studied over a period of 25 years, and none developed clinically overt hemochromatosis.

In 2006, the US Preventive Health Services Task Force systemically reviewed HH with specific attention to the issues of clinical penetrance and screening, and concluded that larger longitudinal studies would be required to consolidate understanding of the natural history of disease and the marked variance in clinical expression in terms of putative genetic and environmental modifiers [31]. These issues were comprehensively addressed by Allen et al. [32••], who conducted a study based on 31,192 persons of Northern European descent who were part of the prospective longitudinal study known as the Melbourne Collaborative Cohort Study. This cohort was recruited between

1990 and 1994 through the Australian electoral roll, community announcement, and advertisement. At initial recruitment to the study, the mean age of subjects was 55 years. Participants underwent clinical assessment and genetic and biochemical evaluation (termed baseline assessments). *HFE* genotyping of 31,192 baseline samples was performed and investigators were blinded to the genotype until all clinical assessments were completed. From this cohort, 1,438 subjects—including all C282Y homozygotes and a stratified random sample of subjects from the remaining groups with other HFE genotypes—were evaluated in a follow-up study 12 years after initial recruitment (termed the HealthIron cohort). There were 203 C282Y homozygotes, 242 compound heterozygotes, 337 C282Y heterozygotes, and 147 H63D heterozygote/homozygotes identified. At baseline, 84% of male and 65% of female C282Y homozygotes had elevated serum ferritin levels, and 37% of male and 3% of female HH C282Y homozygotes had ferritin levels exceeding 1,000 μg/L [32••, 33••]. C282Y homozygous males had up to a 50% likelihood of progression to serum ferritin levels exceeding 1,000 μg/L after 12 years if they had baseline serum ferritin values of 300 to 1,000 μg/L. With similar baseline values, C282Y homozygous females had up to a 20% likelihood of progression to serum ferritin levels exceeding 1,000 μg/L after 12 years. For both genders, the risk of biochemical progression over a 12-year period to ferritin levels exceeding 1,000 μg/L was less than 15% if they had normal baseline serum ferritin values [33••]. C282Y homozygotes who are likely to develop serum ferritin levels sufficient to place them at risk of iron overload–related disease will have done so by the age of 55 years.

The term "iron overload–related disease" was introduced by Allen et al. [32••] in 2008 and is defined as the presence of documented iron overload combined with one of the following: cirrhosis, liver fibrosis, hepatocellular carcinoma, elevated aminotransferase levels, physician-diagnosed symptomatic hemochromatosis, or arthropathy of the second and third metacarpophalangeal joints. Fatigue, liver disease, and increased levels of aminotransferase were more prevalent in male C282Y homozygotes with ferritin levels exceeding 1,000 μg/L compared with other *HFE* genotypes. Regardless of serum ferritin, arthritis was more common in male C282Y homozygotes compared with other genotypes. In contrast, use of arthritis medications and abnormal liver function tests were the only feature more common to female C282Y homozygotes with ferritin levels exceeding 1,000 μg/L compared with other genotypes. Iron overload–related disease was present in 28% of men and 1% of women at the age 65. The threshold value for serum ferritin levels exceeding 1,000 μg/L is important because it is known that the risk of significant liver fibrosis and cirrhosis is increased above this level [21, 34, 35••, 36]. Nevertheless, liver fibrosis is reversible with phlebotomy therapy [35••], underscoring the importance of diagnosis and initiating phlebotomy therapy before cirrhosis becomes established.

Apart from primary liver cancer, C282Y and H63D mutations have also been implicated in development of extrahepatic cancers. H63D homozygosity was shown to be a significant genetic modifier of carcinogenesis in hereditary nonpolyposis colorectal cancer, where it results in a threefold increased risk of cancer in *MMR* gene mutation carriers and earlier onset of cancer [37•]. C282Y homozygosity results in a twofold increased risk of breast cancer in women [38, 39•] and colorectal cancer in men and women [39•]. Adding further to the emerging evidence base that supports a role for iron as a cofactor in carcinogenesis, Zacharski et al. [40] showed that reduction of iron stores is associated with a reduced risk of cancer.

The risk of iron overload–related disease in C282Y/H63D compound heterozygotes was generally thought to be less than that of C282Y homozygotes. Using the HealthIron cohort, Gurrin et al. [41••] conducted a longitudinal 12-year clinical follow-up study of 180 untreated compound heterozygotes (84 males) compared with 330 randomly selected wild-type control subjects. Compared with controls, mean serum ferritin levels and transferrin saturation were significantly higher for both genders, although both were within normal ranges, consistent with earlier reports [24, 42]. Serum ferritin levels did not increase significantly in male or postmenopausal female compound heterozygotes after middle age. Reassuringly, only one male subject (who also had other liver disease risk factors) and none of the female subjects developed iron overload–related disease.

Results from the HealthIron cohort study have provided fertile ground for further exploration into the genetic and environmental modifiers of iron overload. A novel association between serum ferritin and *CYBRD1* (the gene encoding the duodenal reductase DCYTB) was identified recently [43]. Constantine et al. [43] observed that C282Y homozygous subjects with one or two copies of the *rs88409* single nucleotide polymorphism (SNP) in *CYBRD1* had substantially lower levels of serum ferritin compared with C282Y homozygotes who did not possess this common mutation. It is estimated that this mutation alone accounts for 12% of the variance in iron loading in the C282Y homozygotes. Using a cohort of twins and their siblings, Benyamin et al. [44] conducted a genome-wide association study on four serum markers of iron status (iron, transferrin, transferrin saturation, and ferritin). As well as the already described effect of *HFE* C282Y on all four markers, they found strong associations between a *TMPRSS6* SNP (*rs4820268*) and serum iron. Several transferrin SNPs (*rs3811647, rs1358024, 4525863,* and

rs6794945 in adjacent signal recognition particle receptor, B subunits) were also found to influence serum transferrin [44]. In addition, C282Y homozygotes with mutations in other genes of iron metabolism including *Hamp* (hepcidin), *HJV* (hemojuvelin), *BMP* (bone morphogenic protein) and *Hp* (haptoglobin) were identified to modify iron overload [45–48].

Independent of iron overload, other genetic factors can influence the susceptibility of the liver to injury. Polymorphisms in profibrogenic genes (eg, *TGF-β*), could influence the development of fibrosis and cirrhosis [49]. Important environmental modifiers of accelerated iron loading include excessive alcohol consumption and meat intake in postmenopausal women [50, 51]. In contrast, consumption of non-citrus fruits may confer protection against iron loading [52]. Excessive alcohol consumption also accelerates fibrogenesis through oxidative stress [53, 54]. In addition to alcohol, concurrent viral hepatitis and hepatic steatosis play an important role in modifying fibrogenesis in patients with genetic iron loading [55, 56].

With the evolution and contribution of knowledge regarding genotypic, biochemical, and clinical penetrance of HH from the population studies, we have moved from enthusiasm for introduction of widespread population screening to a more considered debate and analysis of the most cost-effective approach to screening [31]. Conducting sequential screening (genotype following documentation of elevated transferrin saturation) among males may be the most cost-effective approach, with a cost of 41,000 Euro per life-year gained [57•].

Conclusions

The seminal clinical studies of HH conducted over the past 150 years have enriched our knowledge of this common disorder. We now recognize that the biochemical and clinical penetrance are highly variable. We have learned much regarding the natural history of untreated HH, and this knowledge will determine the development of future approaches to population screening. We are also on the cusp of greater understanding of genetic and environmental modifiers of disease penetrance that may be amenable to clinical intervention.

Acknowledgments The authors are supported by a National Health and Medical Research Council of Australia grant to DT and JKO (572601) and a National Health and Medical Research Council of Australia practitioner fellowship to JKO (513761); a Gastroenterological Society of Australia senior research fellowship to DT; and a postgraduate clinical research scholarship to EKG.

Disclosure No potential conflict of interest relevant to this article was reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Trousseau A: **Glycosurie; diabete sucre**. *Clinique medicale de l'Hotel-Dieu de Paris* 1865, 2:663–698.
2. Sheldon JH: **Hemochromatosis**. London: Oxford University Press; 1935.
3. Finch SC, Finch CA: **Idiopathic hemochromatosis, an iron storage disease. A. Iron metabolism in hemochromatosis**. *Medicine (Baltimore)* 1955, 34:381–430.
4. MacSween RN, Scott AR: **Hepatic cirrhosis: a clinicopathological review of 520 cases**. *J Clin Pathol* 1973, 26:936–942.
5. Davis WD, Arrowsmith WR: **The effect of repeated phlebotomies in hemochromatosis; report of three cases**. *J Lab Clin Med* 1952, 39:526–532.
6. Bomford A, Williams R: **Long-term results of venesection therapy in idiopathic haemochromatosis**. *Q J Med* 1976, 45:611–623.
7. Bothwell TH, Cohen I, Abrahams OL, Perold SM: **A familial study in idiopathic hemochromatosis**. *Am J Med* 1959, 27:730–738.
8. Simon M, Bourel M, Genetet B, Fauchet R: **Idiopathic hemochromatosis. Demonstration of recessive transmission and early detection by family HLA typing**. *N Engl J Med* 1977, 297:1017–1021.
9. Bassett ML, Doran TJ, Halliday JW, et al.: **Idiopathic hemochromatosis: demonstration of homozygous-heterozygous mating by HLA typing of families**. *Hum Genet* 1982, 60:352–356.
10. Dadone MM, Kushner JP, Edwards CQ, et al.: **Hereditary hemochromatosis. Analysis of laboratory expression of the disease by genotype in 18 pedigrees**. *Am J Clin Pathol* 1982, 78:196–207.
11. Borwein ST, Ghent CN, Flanagan PR, et al.: **Genetic and phenotypic expression of hemochromatosis in Canadians**. *Clin Invest Med* 1983, 6:171–179.
12. Leggett BA, Halliday JW, Brown NN, et al.: **Prevalence of haemochromatosis amongst asymptomatic Australians**. *Br J Haematol* 1990, 74:525–530.
13. Adams PC, Speechley M, Kertesz AE: **Long-term survival analysis in hereditary hemochromatosis**. *Gastroenterology* 1991, 101:368–372.
14. Niederau C, Fischer R, Purschel A, et al.: **Long-term survival in patients with hereditary hemochromatosis**. *Gastroenterology* 1996, 110:1107–1119.
15. Niederau C, Fischer R, Sonnenberg A, et al.: **Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis**. *N Engl J Med* 1985, 313:1256–1262.
16. Fargion S, Mandelli C, Piperno A, et al.: **Survival and prognostic factors in 212 Italian patients with genetic hemochromatosis.** *Hepatology* 1992, 15:655–659.
17. Feder JN, Gnirke A, Thomas W, et al.: **A novel MHC class 1-like gene is mutated in patients with hereditary haemochromatosis**. *Nat Genet* 1996, 13:399–408.
18. Beutler E, Gelbart T, West C, et al.: **Mutation analysis in hereditary hemochromatosis**. *Blood Cells Mol Dis* 1996, 22:187–194.
19. Jazwinska EC, Cullen LM, Busfield F, et al.: **Haemochromatosis and HLA-H**. *Nat Genet* 1996, 14:249–251.
20. Rossi E, Henderson S, Chin CY, et al.: **Genotyping as a diagnostic aid in genetic haemochromatosis**. *J Gastroenterol Hepatol* 1999, 14:427–430.
21. Bacon BR, Olynyk JK, Brunt EM, et al.: **HFE genotype in patients with hemochromatosis and other liver diseases**. *Ann Intern Med* 1999, 130:953–962.

22. Adams PC, Reboussin DM, Barton JC, et al.: **Hemochromatosis and iron-overload screening in a racially diverse population**. *N Engl J Med* 2005, 352:1769–1778.
23. Merryweather-Clarke AT, Pointon JJ, Shearman JD, Robson KJ: **Global prevalence of putative haemochromatosis mutations**. *J Med Genet* 1997, 34:275–278.
24. Olynyk JK, Cullen DJ, Aquilia S, et al.: **A population-based study of the clinical expression of the hemochromatosis gene**. *N Engl J Med* 1999, 341:718–724.
25. Beutler E, Felitti VJ, Koziol JA, et al.: **Penetrance of 845G–>A (C282Y) HFE hereditary haemochromatosis mutation in the USA**. *The Lancet* 2002, 359:211–218.
26. Deugnier Y, Jouanolle A-M, Chaperon J, et al.: **Gender-specific phenotypic expression and screening strategies in C282Y-linked haemochromatosis: a study of 9396 French people**. *Br J Haematol* 2002, 118:1170–1178.
27. Asberg A, Hveem K, Thorstensen K, et al.: **Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons**. *Scand J Gastroenterol* 2001, 36:1108–1115.
28. Delatycki MB, Allen KJ, Nisselle AE, et al.: **Use of community genetic screening to prevent HFE-associated hereditary haemochromatosis**. *The Lancet* 2005, 366:314–316.
29. Olynyk JK, Hagan SE, Cullen DJ, et al.: **Evolution of untreated hereditary hemochromatosis in the Busselton population: a 17-year study**. *Mayo Clinic Proceedings* 2004, 79:309–313.
30. Andersen RV, Tybjaerg-Hansen A, Appleyard M, et al.: **Hemochromatosis mutations in the general population: iron overload progression rate**. *Blood* 2004, 103:2914–2919.
31. Whitlock EP, Garlitz BA, Harris EL, et al.: **Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive services task force**. *Ann Intern Med* 2006, 145:209–223.
32. •• Allen KJ, Gurrin LC, Constantine CC, et al.: **Iron-overload-related disease in HFE hereditary hemochromatosis**. *N Engl J Med* 2008, 358:221–230. *This article presents data on the natural history of untreated disease in 203 newly diagnosed HFE C282Y homozygotes. It introduced for the first time the term "iron overload–related" diseases*.
33. •• Gurrin LC, Osborne NJ, Constantine CC, et al.: **The natural history of serum iron indices for HFE C282Y homozygosity associated with hereditary hemochromatosis**. *Gastroenterology* 2008, 135:1945–1952. *This article presents data on penetrance and natural history of development of elevated iron parameters in untreated HFE C282Y homozygotes*.
34. Guyader D, Jacquelinet C, Moirand R, et al.: **Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis**. *Gastroenterology* 1998, 115:929–936.
35. •• Powell LW, Dixon JL, Ramm GA, et al.: **Screening for hemochromatosis in asymptomatic subjects with or without a family history**. *Arch Intern Med* 2006, 166:294–301. *This article presents data on penetrance of liver disease and clinical symptoms in 672 newly diagnosed HFE C282Y homozygotes*.
36. Olynyk JK, St Pierre TG, Britton RS, et al.: **Duration of hepatic iron exposure increases the risk of significant fibrosis in hereditary hemochromatosis: a new role for magnetic resonance imaging**. *Am J Gastroenterol* 2005, 100:837–841.
37. • Shi Z, Johnstone D, Talseth-Palmer BA, et al.: **Haemochromatosis HFE gene polymorphisms as potential modifiers of hereditary nonpolyposis colorectal cancer risk and onset age**. *International Journal of Cancer* 2009, 125:78–83. *This article presents data on link between H63D homozygosity, MMR mutation, and colorectal cancer in HNPCC patients*.
38. Gunel-Ozcan A, Alyilmaz-Bekmez S, Guler EN, Guc D: **HFE H63D mutation frequency shows an increase in Turkish women with breast cancer**. *BMC Cancer* 2006, 6:37.
39. • Osbourne NJ, Gurrin LC, Allen KJ, et al.: **HFE C282Y homozygotes are at increased risk of breast and colorectal cancer**. *Hepatology* 2009 (Epub ahead of print). *This article presents data on link between C282Y homozygosity and colorectal and breast cancer in HH*.
40. Zacharski LR, Chow BK, Howes PS, et al.: **Decreased cancer risk after iron reduction in patients with peripheral arterial disease: results from a randomized trial**. *J Natl Cancer Inst* 2008, 100:996–1002.
41. •• Gurrin LC, Bertalli NA, Dalton GW, et al.: **HFE C282Y/H63D compound heterozygotes are at low risk of hemochromatosis-related morbidity**. Hepatology 2009, 50:94–101. *This article presents data on Iron-overload related disease in HFE compound heterozygotes*.
42. Rossi E, Olynyk JK, Cullen DJ, et al.: **Compound heterozygous hemochromatosis genotype predicts increased iron and erythrocyte indices in women**. *Clin Chem* 2000, 46:162–166.
43. Constantine CC, Anderson GJ, Vulpe CD, et al.: **A novel association between a SNP in CYBRD1 and serum ferritin levels in a cohort study of HFE hereditary haemochromatosis**. *Br J Haematol* 2009, 147:140–149.
44. Benyamin B, McRae AF, Zhu G, et al.: **Variants in Tf and HFE explain approximately 40% of genetic variation in serum-transferrin levels**. *Am J Hum Genet* 2009, 84:60–65.
45. Jacolot S, Le Gac G, Scotet V, et al.: **Hamp as a modifier gene that increases the phenotypic expression of the HFE C282Y homozygous genotype**. *Blood* 2004, 103:2835–2840.
46. Le Gac G, Scotet V, Ka C, et at.: **The recently identified type 2a juvenile haemochromatosis gene (HJV), a second candidate modifier of the C282Y homozygous phenotype**. *Hum Mol Genet* 2004, 13:1913–1918.
47. Milet J, Dehais V, Bourgain C, et al.: **Common variants in the bmp2, bmp4, and HJV genes of the hepcidin regulation pathway modulate HFE hemochromatosis penetrance**. *Am J Hum Genet* 2007, 81:799–807.
48. Van Vlierberghe H, Langlois M, Delanghe J, et al.: **Haptoglobin phenotype 2-2 overrepresentation in C282Y hemochromatotic patients**. *J Hepatol* 2001, 35:707–711.
49. Osterreicher CH, Datz C, Stickel F, et al.: **TGF-β1 codon 25 gene polymorphism is associated with cirrhosis in patients with hereditary hemochromatosis**. *Cytokine* 2005, 31:142–148.
50. Moirand R, Lescoat G, Delamaire D, et al.: **Increase in glycosylated and nonglycosylated serum ferritin in chronic alcoholism and their evolution during alcohol withdrawal**. *Alcohol Clin Exp Res* 1991, 15:963–969.
51. Cade JE, Moreton JA, O'Hara B, et al.: **Diet and genetic factors associated with iron status in middle-aged women**. *Am J Clin Nutr* 2005, 82:813–820.
52. Milward EA, Baines SK, Knuiman MW, et al.: **Noncitrus fruits as novel dietary environmental modifiers of iron stores in people with or without HFE gene mutations**. *Mayo Clin Proc* 2008, 83:543–549.
53. Adams PC, Agnew S: **Alcoholism in hereditary hemochromatosis revisited: Prevalence and clinical consequences among homozygous siblings**. *Hepatology* 1996, 23:724–727.
54. Fletcher LM, Dixon JL, Purdie DM, et al.: **Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis**. *Gastroenterology* 2002, 122:281–289.
55. Diwakaran HH, Befeler AS, Britton RS, et al.: **Accelerated hepatic fibrosis in patients with combined hereditary hemochromatosis and chronic hepatitis C infection**. *J Hepatol* 2002, 36:687–691.
56. Powell EE, Ali A, Clouston AD, et al.: **Steatosis is a cofactor in liver injury in hemochromatosis**. *Gastroenterology* 2005, 129:1937–1943.
57. • Rogowski WH: **The cost-effectiveness of screening for hereditary hemochromatosis in germany: a remodeling study**. *Med Decis Making* 2009, 29:224–238. *This article presents various screening strategies and their cost-effectiveness*.