Inborn errors of metabolism: iron

Mark Worwood

Department of Haematology, University of Wales College of Medicine, Cardiff, UK

The iron content of the body is normally closely regulated. Despite this, iron deficiency anaemia is common in women because iron losses due to menstruation and childbirth are not always compensated for by iron absorption from the diet. The role of transferrin in delivering iron to cells and of ferritin in storing iron within cells is well understood but the proteins involved in iron transport across membranes are only now being investigated. Relatively few genetic disorders affecting iron metabolism are known and most are rare. This paper briefly describes pyridoxine responsive sideroblastic anaemia, hyperferritinaemia-cataract syndrome, atransferrinaemia and genetic haemochromatosis. Rather than rare, the latter is one of the most common inherited disorders in northern European populations. Mutations in genes regulating membrane iron transport causing simple iron deficiency have not yet been described.

Iron

Iron is the second most abundant metal in the earth's crust and yet one-third of the world's population suffers from iron deficiency anaemia. Iron is essential for oxygen transport and utilisation and many oxidation–reduction reactions yet, in excess, it is toxic. Not surprisingly, iron metabolism is tightly regulated and it might be supposed that there would be many inherited disorders resulting from changes to genes controlling iron transport and storage as well as the synthesis and breakdown of iron containing proteins. So far, surprisingly few have been described and all but one of these conditions are rare. None of these cause simple iron deficiency anaemia.

Correspondence to: Professor M Worwood, Department of Haematology, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

The iron content of the body and its distribution among the various proteins is summarised in Table 1. Most of the iron is present in the oxygen carrying protein of the red blood cell – haemoglobin. Iron turnover (Fig. 1) is also dominated by the synthesis and breakdown of haemoglobin. Haem is synthesised in nucleated red cells in the bone marrow by a pathway beginning with the synthesis of 5-aminolevulinic

Table 1 Distribution of iron in the body (70 kg man)

Protein	Location	Fe content (mg)
Haemoglobin	Erythrocytes	3000
Myoglobin	Muscle	400
Cytochromes, other haem and Fe, S proteins	All tissues	50
Transferrin	Plasma and extravascular fluid	5
Ferritin and haemosiderin	Liver, spleen and bone marrow	0–1000

acid from glycine and ending with the incorporation of iron into protoporphyrin IX. Haem breakdown takes place in phagocytic cells, largely those in the spleen, liver and bone marrow and the iron released is again used for haem synthesis. Relatively little iron is lost from the body (about 1 mg/day in men) and these losses are not influenced by body iron content or the requirement of the body for iron. The body iron content is maintained by variation in the amount of iron absorbed.

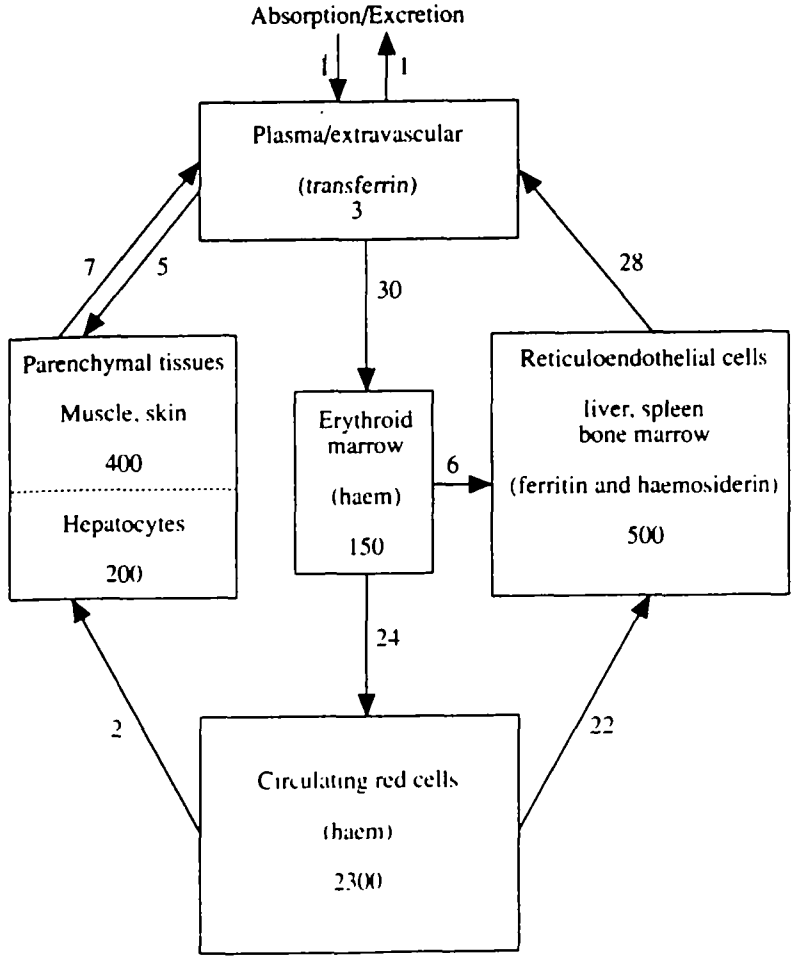

Fig. 1 The major pathways of iron metabolism in man. Numbers in boxes are mg. Numbers against arrows are mg Fe/day. The iron in muscle is largely haem and in hepatocytes is largely ferritin.

Table 2 Some proteins regulating iron metabolism

Name	Gene symbol	Map location	Cellular location (cell type/subcell distrib)	Function
Ferritin (H)	FTH1	11q13		
	FTHL1-4	1p31-p22; 1q32.2-q42; 2q32-q33; 3q21-q23		
	FTHL7 8	13q12; Xq26-q28;		
	10-16	5; 8; 9; 14; 17; 6p; 11q13		
	FTHP1	6p21.3-p12		
Ferritin (L)	FTL	19q13.3-q13.4	Widespread/cytosol	Iron storage
	FTLL1	20q12-qter		
	FTLL2	Xp22.3-p21.2		
Transferrin	TF	3q21	Plasma	Iron transport
Transferrin receptor	TFRC	3q26.2-qter	Widespread/plasma membrane	Iron transport
Lactoferrin	LTF	3q21	Plasma/milk	Iron transport
Iron regulatory binding protein	IREB1	9p22-q32	Widespread/cytosol	Post transcriptional regulation
	IRP2			
δ-Aminolevulinate synthase 1 and 3 (liver)	ALAS1 and 3	3q21	Mitochondria	Haem synthesis
δ-Aminolevulinate synthase 2 (erythroid)	ALAS2	Xp11-q12	Mitochondria	Haem synthesis
Haptoglobin	HP	16q22.1	Plasma	Haemoglobin binding
Haemopexin	HPX	11p15.5-15.4	Plasma	Haem binding
Ferrochelatase	FECH	18q21.3	Mitochondrial	Haem synthesis
Haem oxygenase (inducible)	HMOX	22q12	Phagocytes/ER*	Haem breakdown
Haem oxygenase (constitutive)	HMOX2	16p13.3	General/ER	Haem breakdown
Nramp I	-	2q35	General/membranes	Membrane iron transport
Nramp 2	-	12q13	Phagocytes/membranes	Membrane iron transport
HFE [3]	–	6p21.3	?/membranes	Regulation of iron absorption

Data from Worwood[30] except Nramp 1 (Blackwell *et al*[31]), Nramp 2 (Vidal *et al*[32]) and HFE (Feder *et al*[17]).

However, in women, menstruation and childbirth increase iron losses to an average of 2 or more mg/day. Iron absorption may not increase sufficiently to compensate for these iron losses and this may eventually lead to the development of iron deficiency anaemia. In most men and postmenopausal women there is some 'storage' iron. This is iron in ferritin, or its insoluble derivative, haemosiderin, which is available for haem synthesis if necessary. Many young women have little or no storage iron. Brock *et al*[1] provides a recent review of iron metabolism.

Transferrin and ferritin are responsible for extracellular transport and intracellular storage, respectively (Table 2). Most cells obtain iron from transferrin which binds to transferrin receptors on the cell surface. This is followed by internalisation into vesicles with release of iron into the cells and recycling of the apotransferrin to the plasma. How non-transferrin iron crosses membranes and how iron is absorbed in gut epithelial cells has long been a mystery but recently the gene for a mammalian intestinal iron transporter has been cloned. Called duodenal divalent cation transporter DCT1[2], it was isolated from the duodenal mucosa of iron deficient rats and is almost identical to the mouse NRAMP2 protein. Mice with autosomal recessive microcytic anaemia (mk) have reduced iron absorption and the NRAMP2 gene is mutated[3] in this strain. The same mutation is found in the anaemic Belgrade rat[4]. NRAMPI is a homologous, iron-binding membrane protein[5] which may transport iron released from senescent red cells out of siderosomes in macrophages. Mutations associated with abnormalities in iron metabolism in human NRAMP genes have not yet been described but may cause inherited anaemias. The HFE gene (see later) codes for an HLA class I like, membrane protein which appears to limit iron absorption in the small intestine when iron stores are adequate. Mutations in these genes cause haemochromatosis (see later). The HFE protein appears to bind to the transferrin receptor and reduce its affinity for transferrin[6].

Inborn errors of iron metabolism

I shall describe inherited conditions which disrupt the iron status of the body or which directly affect the function of iron containing proteins. The various conditions are summarised in Table 3.

Congenital atransferrinaemia

This is a very rare condition first described by Heilmeyer *et al*[7] and characterised by the virtual absence of transferrin in the plasma. Most cases presented in the first few months of life but in one family the patient

Table 3

Disorder	Protein affected	Gene location	Genetic change	Inheritance	Phenotype	Frequency	Clinical outcome	References
Atransferrinaemia	Transferrin	3q21	Point mutations?	Autosomal recessive	Severe macrocytic, hypochromic anaemia with tissue iron overload	Very rare (7 cases world-wide)	Early death from iron overload but treatment with purified apotransferrin possible	Heilmeyer *et al*[7], Hayashi *et al*[8]
X-linked pyridoxine responsive sideroblastic anaemia	5-aminolevulinate synthase (erythroid specific or ALAS2)	Xp11.12	Point mutations	X-linked	Hypochromic anaemia with iron accumulation in mitochondria of erythroblasts ('ringed sideroblasts')	Rare	Death from iron accumulation. Anaemia often responds to pyridoxine and iron removal by chelation or phlebotomy	May & Bishop[10]
Hereditary hyperferritinaemia–cataract syndrome	L subunit of ferritin	19q13.3-13.4	Point mutations in iron-responsive element (IRE) and deletions	Autosomal dominant	High serum ferritin levels and cataract	Rare? 4 families described so far	Cataracts caused by accumulation of L type ferritin in lens	Beaumont *et al*[33], Cazzola *et al*[34]
Genetic haemochromatosis	HFE	6p21.3	Point mutations	Autosomal recessive	Tissue iron accumulation	Common in N Europe (incidence up to 1 in 100)	Cirrhosis, diabetes, skin pigmentation, iron removal by phlebotomy	Worwood[35]

presented age 7 years and responded to the infusions of apotransferrin — eventually developing normally without further therapy. The authors described the condition as 'familial hypotransferrinemia' – the proband being a compound heterozygote for 'null' and 'variant' mutations[8].

Inherited sideroblastic anaemias

The sideroblastic anaemias are characterised by hypochromic anaemia of variable degree, progressive iron accumulation and the presence of ringed sideroblasts (iron laden mitochondria) in the bone marrow erythroblasts[9]. X-linked sideroblastic anaemia, the most common inherited form, is caused by mutations in the erythroid-specific 5-aminolevulinate synthase gene[10]. There are also rarer, autosomally inherited sideroblastic anaemias and sideroblastic anaemias caused by mitochondrial mutations (part of the multi-system disorder called Pearson's syndrome. So far, 15 different ALAS2 mutations have been found in 15 unrelated families. All have been missense mutations[10]. In most patients with the X-linked form, the anaemia responds, to a varying extent, to pyridoxine which is metabolised to pyridoxal 5′ phosphate, the cofactor for the enzyme.

A feature of this condition is its variable age of onset from birth to over 75 years of age. Apart from the anaemia, the main complication is iron overload. The haem synthesis deficiency leads to ineffective erythropoiesis, with an increased number of erythroblasts and an increased demand for iron. This leads to increased iron absorption and accumulation of the unused iron in the tissues, particularly the liver, heart, pancreas and pituitary, leading to endocrine disorders, arthritis, cirrhosis and heart failure. Co-inheritance of the C282Y mutation of the HFE gene may enhance iron loading but this is not necessary for iron loading[11].

Detection and removal of excess iron is essential. Removal may be carried out by phlebotomy, despite the anaemia[11], but chelation therapy is required if the iron excess is likely to lead to organ failure. Removal of excess iron may enhance erythropoiesis. Venesection must be adequate and continued until the excess iron is removed. As iron absorption may reach 10 mg/day during phlebotomy, treatment is likely to be prolonged.

Hereditary hyperferritinaemia-cataract syndrome

Although only a few families have been described so far, this condition should be considered in people with unexplained high serum ferritin levels who are apparently healthy. Increased use of the serum ferritin assay in hospital eye clinics may uncover more cases.

Haemochromatosis

Haemochromatosis is the clinical condition of iron overload; genetic haemochromatosis refers to the inheritance of the iron loading phenotype (formerly called idiopathic or HLA-linked haemochromatosis). In haemochromatosis too much iron is absorbed from the diet. Iron accumulation in many organs causes the clinical manifestations including diabetes and cirrhosis of the liver. Such clinical problems are usually seen in middle age but sometimes occur in people as young as 20 years. Haemochromatosis is inherited in autosomal recessive fashion. The excess iron can be removed by venesection. It may be necessary to remove 500 ml of blood weekly for up to 2 years in order to achieve this. If detected before the development of cirrhosis, iron removal usually prevents the clinical problems and restores normal life expectancy. Once cirrhosis has developed this cannot be reversed[12]. Early diagnosis has been difficult because the screening tests based on measurement of serum transferrin saturation and serum ferritin concentration not only give many false positive results but do not always identify patients in the early stages of iron accumulation. Haemochromatosis is one of the most common recessive genetic disorders in Northern Europe. Surveys in which iron accumulation was detected by biochemical screening and confirmed by liver biopsy have indicated a gene frequency of about 5% with about 10% of the population carrying one copy of the gene and 1 in 400 having the condition (*see* Worwood[13]). People with one copy of the gene rarely accumulate enough iron to cause tissue damage but may be less likely to suffer from iron deficiency. This condition is not the same as the so-called 'African' iron overload which may also have a genetic component[14], the rarer 'juvenile' haemochromatosis[15] and 'neonatal' haemochromatosis[16].

New findings

The recent publication by Feder *et al*[17] identified a genetic change which appears to cause most cases of haemochromatosis. The gene involved is an HLA class I like gene (HFE) situated approximately 4.5 Mb from HLA-A on chromosome 6. A change in a single amino acid was found on over 90% of haemochromatosis associated chromosomes compared with about 6% of chromosomes from the general population. In northern Europe, 90% of patients are homozygous for this change (Cys282Tyr), *i.e.* have two copies of the altered gene. A few patients are compound heterozygotes for Cys282Tyr and a second mutation (His63Asp) but His63Asp is relatively common in the general population and on its own does not appear to cause iron overload. The remaining patients with a confirmed diagnosis of haemochromatosis

Table 4 Genotype frequencies (%) for mutations in the HFE gene in patients with haemochromatosis

Country/region	No of subjects	Genotypes (C282Y/H63D)					
		++/−	+−/+−	+−/−−	−−/−−	−−/+−	−−/++
Australia	112	100	0	0	0	0	0
Ireland[a]	60	95	1.7	1.7	3.4	0	0
Sweden[b]	87	92	3.4	1.1	1.1	1.1	1.1
Brittany	132	92	2.3	2.3	0	1.5	1.5
UK	115	91	2.6	0.9	4.3	0	0.9
Germany	57	90	3.5	1.8	0	5.2	0
USA	178	83	4.5	0.6	1.2	0	0.5
USA	147	82	5.4	1.4	6.8	2.7	1.4
France	94	72	4.3	4.3	8.5	8.5	2.1
Italy	75	64	6.7	2.7	21	4.0	1.3
USA (Alabama)	74	60	5.4	15	8.1	8.1	4.0

The selected studies include more than 50 subjects. Three systems of mutation nomenclature are in use for the HFE genes: amino acid (3 letter abbreviation), amino acid (single letter) or cDNA based[36]. The mutations are, therefore, described as Cys282Tyr, C282Y or 845A; His63Asp, H63D or 187G. Unless otherwise indicated, references to the various reports are given in Worwood[13].
[a]Ryan *et al*[37]; [b]Cardoso et al[38].

appear to lack mutations in this gene. In southern Europe fewer patients are homozygous for the C282Y mutation (Table 4).

Haemochromatosis has always been considered to be a European disorder and a study of the world-wide distribution of the HFE mutations confirms this. The C282Y mutation is confined to populations of European origin although the H63D mutation is found outside Europe[18]. Within Europe, the C282Y mutation is most prevalent in the so-called Celtic countries (see Table 5) but when and where the original mutation occurred remains the subject of debate.

In the UK, mutation screening now provides a test which is positive in over 90% of patients. Coupled with measurements of iron status, it is now possible to detect iron accumulation due to haemochromatosis early and prevent the development of iron overload and its clinical consequences. Iron overload caused by increased iron absorption is sometimes seen with other conditions such as porphyria cutanea tarda, β-thalassaemia intermedia, hereditary spherocytosis and sideroblastic anaemia. In porphyria cutanea tarda[19], up to 50% of patients may also have one or two haemochromatosis genes, but iron overload may develop in patients with PCT in the absence of the HFE gene.

Diagnosis of iron overload

Diagnosis of iron overload requires the demonstration of a transferrin saturation of > 55% (men) or > 50% (women) on two samples, the

Table 5 Frequency (%) of the C282Y mutation in population samples from various countries or regions in Europe and Algeria. There are more than 90 subjects in each sample

Country/region	Frequency (%)	Reference
Iceland	4.5	
North Finland	5.2	Beckman *et al*[28]
Sweden		
Umea	7.5	Beckman *et al*[28]
Norway	6.4	
Denmark	6.8	Steffensen *et al*[27]
UK		
Belfast	9.9	Murphy *et al*[24]
Oxford	9 0	Mullighan *et al*[25]
Norwich	8.5	
South Wales	8.2	M Worwood, C Darke and MG Guttridge Survey of 10,000 blood donors. (Unpublished)
Jersey	8.3	
France	4.2	
Britanny Finistère	9.4	
Brest	7.3	Mura *et al*[26]
Rennes	2.9	
Germany	5.2	
Austria	4.1	
Spain	3.0	Oliva *et al*[29]
Italy	0 5	
Greece	1.4	
Algeria	0.	

Data are % of chromosomes carrying C282Y mutation and were summarised in Worwood[13], unless indicated otherwise. Note the surprising variations between adjacent regions, probably reflecting variation due to sample size as well as population differences. Allele frequencies for the H63D mutation are about 12%[18], with the highest frequency reported for Spain.

second of which should be a fasting sample. The serum ferritin concentration is usually elevated, but may not be in the early stages of iron accumulation. Confirmation requires the demonstration of iron overload in the liver (hepatic iron index, μmol Fe/g dry wt divided by age, > 2.0) or the removal of > 4 g Fe by regular weekly venesection. The value of liver biopsy in young patients with evidence of iron accumulation but no clinical signs is presently the subject of debate[20].

Treatment

Unless another condition prevents it, venesection is the preferred treatment. One unit of blood (approximately 450 ml, containing about 200 mg Fe) should be removed each week. The decline in iron storage levels is followed by measuring serum ferritin which may fluctuate initially. The full blood count should be monitored to make sure that the patient

does not become anaemic. Treatment should be continued until the ferritin concentration is < 20 μg/l, and the transferrin saturation is < 16%.

Maintenance therapy

Patients may need several venesections per year to maintain normal levels of storage iron. The transferrin saturation should not be allowed to exceed 50% and the ferritin concentration should be kept below 50 μg/l.

Testing of family members

The family should be offered testing to identify other possible homozygotes once an affected subject has been identified. As heterozygosity is common, it is not unusual to find haemochromatosis in two generations because a patient has a heterozygous partner. Children over the age of 15 years should, therefore, be offered testing as well as parents and siblings of the patient. **Testing of relatives should be accompanied by the provision of appropriate information.** Transferrin saturation and serum ferritin concentration should be measured. For genetic testing, mutation analysis is usually sufficient if the proband is homozygous for the Cys282Tyr mutation or is heterozygous for both Cys282Tyr and His63Asp.

Population screening?

Haemochromatosis is common and treatable but pressure for the introduction of universal genetic screening[21] must be resisted until the clinical penetrance of the disorder is known. A study of blood donors in Jersey[22] and of post-mortem deaths in the USA[23] indicates at least a 10-fold higher frequency of homozygosity for HFE-C282Y than for clinical haemochromatosis. Many studies of clinical penetrance are now in progress.

References

1 Brock JH, Halliday JW, Pippard MJ, Powell LW. *Iron Metabolism in Health and Disease.* London: Saunders, 1994

2 Gunshin H, Mackenzie B, Berger UV *et al.* Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature* 1997; 388: 482–8

3 Fleming MD, Trenor CC, Su MA *et al.* Microcytic anaemia mice have a mutation in Nramp2, a candidate iron transporter gene. *Nat Genet* 1997; 16: 383–6

4 Fleming MD, Romano MA, Su MA, Garrick LM, Garrick MD, Andrews NC. Nramp2 is mutated in the anemic Belgrade (b) rat: Evidence of a role for Nramp2 in endosomal iron transport. *Proc Natl Acad Sci USA* 1998; 95: 1148–53

5 Atkinson PGP, Blackwell JM, Barton CH. Nramp1 locus encodes a 65 kDa interferon-gamma-inducible protein in murine macrophages. *Biochem J* 1997; 325: 779–86
6 Feder JN, Penny DM, Irrinki A *et al.* The hemochromatosis gene product complexes with the transferrin receptor and lowers its affinity for ligand binding. *Proc Natl Acad Sci USA* 1998; 95: 1472–7
7 Heilmeyer L, Keller W, Vivell O *et al.* Kongenitale Atransferrinemia bei einem sieben jahr alten Kind. *Dtsch Med Wochenschr* 1961; 86: 1745–51
8 Hayashi A, Wada Y, Suzuki T, Shimizu A. Studies on familial hypotransferrinemia: unique clinical course and molecular pathology. *Am J Hum Genet* 1993; 53: 201–13
9 Bottomley SS. The sideroblastic anemias. In: Lee RG, Bithell TC, Foester J, Athens JW (Eds) *Wintrobe's Clinical Hematology*. Philadelphia: Lea and Febiger, 1993; 852–71
10 May A, Bishop DF. The molecular biology and pyridoxine responsiveness of X-linked sideroblastic anaemia. *Haematologica* 1998; 83: 56–70
11 Cotter PD, May A, Li L *et al.* Four new mutations in the erythroid-specific 5-aminolevulinate synthase (ALAS2) gene causing X-linked sideroblastic anemia: increased pyridoxine responsiveness after removal of iron overload by phlebotomy and coinheritance of hereditary hemochromatosis. *Blood* 1999; 93: 1–14
12 Bothwell TH, Macphail AP. Hereditary hemochromatosis: Etiologic, pathologic, and clinical aspects. *Semin Hematol* 1998; 35: 55–71
13 Worwood M. Haemochromatosis: pathological or beneficial. *Schweiz Med Wochenschr* 1998; 128: 1925–35
14 Moyo VM, Mandishona E, Hasstedt SJ *et al.* Evidence of genetic transmission in African iron overload. *Blood* 1998; 91: 1076–82
15 Camaschella C, Roetto A, Cicilano M *et al.* Juvenile and adult hemochromatosis are distinct genetic disorders. *Eur J Hum Genet* 1997; 5: 371–5
16 Knisely AS, Magid MS, Dische MR, Cutz E. Neonatal hemochromatosis. *Birth Defects* 1987; 23: 75–102
17 Feder JN, Gnirke A, Thomas W *et al.* A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996; 13: 399–408
18 Merryweatherclarke AT, Pointon JJ, Shearman JD, Robson KJH. Global prevalence of putative haemochromatosis mutations. *J Med Genet* 1997; 34: 275–8
19 Elder GH, Worwood M. Mutations in the hemochromatosis gene, porphyria cutanea tarda, and iron overload. *Hepatology* 1998; 27: 289–91
20 Guyader D, Jacquelinet C, Moirand R *et al.* Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis. *Gastroenterology* 1998; 115: 929–36
21 Barton JC, Bertoli LF. Hemochromatosis: The genetic disorder of the twenty-first century. *Nat Med* 1996; 2: 394–5
22 Merryweather-Clarke AT, Worwood M, Parkinson L *et al.* The effect of HFE mutations on serum ferritin and transferrin saturation in the Jersey population. *Br J Haematol* 1998; 101: 369–73
23 Yang QH, Mcdonnell SM, Khoury MJ, Cono J, Parrish RG. Hemochromatosis-associated mortality in the United States from 1979 to 1992: an analysis of multiple-cause mortality data. *Ann Intern Med* 1998; 129: 946–53
24 Murphy S, Curran MD, McDougall N, Callender ME, O'Brien CJ, Middleton D. High incidence of the Cys 282 Tyr mutation in the HFE gene in the Irish population – implications for haemochromatosis. *Tissue Antigens* 1998; 52: 484–8
25 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
26 Mura C, Nousbaum JB, Verger P *et al.* Phenotype-genotype correlation in haemochromatosis subjects. *Hum Genet* 1997; 101: 271–6
27 Steffensen R, Varming K, Jersild C. Determination of gene frequencies for two common haemochromatosis mutations in the Danish population by a novel polymerase chain reaction with sequence-specific primers. *Tissue Antigens* 1998; 52: 230–5
28 Beckman LE, Saha N, Spitsyn V, Vanlandeghem G, Beckman L. Ethnic differences in the HFE codon 282 (Cys/Tyr) polymorphism. *Hum Hered* 1997; 47: 263–7
29 Sanchez M, Bruguera M, Bosch J, Rodes J, Ballesta F, Oliva R. Prevalence of the Cys282Tyr and His63Asp HFE gene mutations in Spanish patients with hereditary hemochromatosis and in controls. *J Hepatol* 1998; 29: 725–8

30 Worwood M. Genetics of haemochromatosis. *Baillière's Clin Haematol* 1994; 7: 903–18
31 Blackwell JM, Barton CH, White JK, Searle S, Baker AM, Shaw MA. Genomic organization and sequence of the human NRAMP gene: identification and mapping of a promoter region polymorphism. *Mol Med* 1995; 1: 194–205
32 Vidal S, Belouchi AM, Cellier M, Beatty B, Gros P. Cloning and characterization of a second human Nramp gene on chromosome 12q13. *Mamm Genome* 1999; 6: 224–30
33 Beaumont C, Leneuve P, Devaux I *et al.* Mutation in the iron responsive element of the L ferritin mRNA in a family with dominant hyperferritinaemia and cataract. *Nat Genet* 1995; 11: 444–6
34 Cazzola M, Bergamaschi G, Tonon L *et al.* Hereditary hyperferritinemia-cataract syndrome: Relationship between phenotypes and specific mutations in the iron-responsive element of ferritin light-chain mRNA. *Blood* 1997; 90: 814–21
35 Worwood M. Haemochromatosis. *Clin Lab Haematol* 1998; 20: 65–70
36 Beutler E, Gelbart T, West C *et al.* Mutation analysis in hereditary hemochromatosis. *Blood Cell Mol Dis* 1996; 22: 187–94
37 Ryan E, Okeane C, Crowe J. Hemochromatosis in Ireland and HFE. *Blood Cell Mol Dis* 1998; 24: 428–32
38 Cardoso EMP, Stal P, Hagen K *et al.* HFE mutations in patients with hereditary haemochromatosis in Sweden. *J Intern Med* 1998; 243: 203–8