Genetic haemochromatosis (GH) is an inherited disorder of iron metabolism (Figure 1). It is characterised by an increase in iron uptake from the gut and progressive deposition of iron within major organs such as the liver, pancreas and heart and also in various other tissues. The deposition of iron may be accompanied by the development of structural damage and end-organ dysfunction.1

GH is an autosomal recessive disorder, which manifests primarily in Caucasians of northern European descent. It is likely that all affected individuals descended from a single family or community, most likely Celts.2

The most common genetic mutation leading to GH is a Cys282Tyr (C282Y) alteration in the HFE gene on the short arm of chromosome 6. The frequency of C282Y heterozygosity in screening studies in populations of northern European extraction is one in 200–300,3,4 while the frequency of heterogeneity is approximately 10 per cent, although it is higher in populations in Ireland and Brittany in northern France.2 A second mutation, His63Asp (H63D), has been identified; a small proportion of patients with GH are either homozygous for the H63D mutation or are compound C282Y–H63D heterozygotes.6

GH has long been considered a rare disorder, unlikely to be seen in general practice; however, recent population studies suggest that its prevalence in the northern European population is around 1 in 200, making it one of the most common genetic disorders. In the UK it is estimated that around 250,000 people have GH, with only some 5000 diagnosed.

UNDERDIAGNOSIS OF GENETIC HAEMOCHROMATOSIS

There is significant discrepancy between the rates of homozygosity and the frequency of clinically recognised disease. This could be attributed to either incomplete penetrance of the genetic mutation or high rates of undiagnosed disease.

Clinical penetration is undoubtedly low.7 Thus although biochemical penetrance, which is characterised by raised serum
ferritin concentrations and increased transferrin saturation, is found in 50–80 per cent of susceptible individuals, disease penetrance, for example, GH-related symptoms or evidence of organ damage, may be present in as few as 28 per cent of C282Y homozygous men and fewer than 1 per cent of women.7

However, there is also evidence that the disorder, even when symptomatic, is underdiagnosed. Thus, Ryan et al.6 found high rates of undiagnosed symptomatic disease in 79 C282Y homozygous individuals identified from family screening, such as fatigue (55 per cent men and 43 per cent women), arthropathy (35 per cent men and 21 per cent women) and impotence (19 per cent men).

One reason for the underdiagnosis is the non-specific, generalised nature of early symptoms; fatigue and muscle weakness are among those most commonly reported. In addition, arthropathy, caused by iron deposition and inflammation, is often misdiagnosed, delaying true diagnosis by around four years.1 Skin pigmentation caused by tandem melanin and iron deposition can be observed; however, because of preferential distribution in the axilla, nape of the neck, mucous membranes and over the genitals, it is easily missed (see Figure 1).

CLINICAL PRESENTATION
The classical picture is of a middle-aged man with skin pigmentation, hepatomegaly, arthralgia, diabetes, loss of body hair and impotence. However, most patients do not present in such an obvious way; indeed there is often a delay of five to eight years between presentation and diagnosis because of the non-specific nature of the presenting symptoms.8

Clinically overt GH is ten times more frequent in men than in women, primarily because of physiological iron loss from menstruation and pregnancy. GH is rarely diagnosed before the age of 20 years; the peak incidence is 40–60 years. Features may be non-specific or organ related (Box 1).

DIAGNOSIS
There should be a high degree of suspicion in middle-aged men presenting with cardiac disease who do not have risk factors for coronary heart disease and in individuals with diabetes with no family history or other risk factors. The situation is less clear with individuals presenting with liver disease, as many middle-aged men with GH also misuse alcohol; alcohol increases iron absorption and the consumption of excess alcohol may be in part responsible for disease expression. GH is not routinely considered as a possible diagnosis in men presenting with sexual dysfunction (Box 2).

In the majority of individuals, however, the diagnosis of GH is made as a result of the incidental finding of suggestive biochemical abnormalities or as a result of family screening. In patients with GH, serum iron levels are high, transferrin saturation is raised and serum ferritin levels generally exceed 1000µg/l.

Before the advent of genetic testing, needle liver biopsy was frequently used to assess hepatic histology and the deposited iron; this could be undertaken semiquantitatively using Perl’s stain, which identifies ferrous haematin (Figure 2) or by direct chemical measurement. Occasionally, the diagnosis of GH can be made incidentally on liver biopsy in individuals undergoing investigation for abnormal liver function tests or suspected alcohol-related liver disease.

Mutation analysis for C282Y or H63D will confirm the diagnosis. Family
screening can be undertaken by estimation of the serum ferritin, but genetic mutational analysis is being used more frequently, particularly in women and young adults.

MANAGEMENT
The management of GH centres primarily on effective deironing, which is achieved through regular venesection. Initially, this is undertaken weekly until the ferritin is normal – a process that can take 12–24 months. Thereafter, venesection is undertaken every three months. Blood from venesection is donated to the national blood banks unless there is a contraindication; blood from GH venesections makes up around 1 per cent of all donations.

If patients are diagnosed before end-organ damage develops, deironing is all that is required. If, alternatively, they already have established end-organ damage, deironing will help prevent further damage and will, in many instances, be associated with significant improvement in function.

SEXUAL DYSFUNCTION
A high proportion of men with GH suffer from sexual dysfunction. In a survey carried out by the Haemochromatosis Society, it was found that 46 per cent of men with GH had experienced loss of libido and 29 per cent impotence, prior to diagnosis. In patients who presented with impotence, the diagnosis of GH had been delayed by approximately nine years; this could result in dangerous disease progression and the development of significant end-organ damage.

The aetiology of the sexual dysfunction associated with GH is multifactorial. Iron is preferentially deposited in the gonadotrophs of the anterior pituitary gland, impairing the release of luteinising hormone and follicle-stimulating hormone, leading to hypogonadotrophic testicular failure manifest as loss of libido, impotence and eventually testicular atrophy and loss of secondary sexual characteristics.

Gonadal failure may also develop in association with the development of GH-associated liver disease. Serum testosterone levels are low in GH patients without liver disease, as are circulating oestrogen levels, in contrast to the situation in GH patients with liver disease, in whom circulating oestrogen levels are invariably high.

Iron deposition in the pituitary is irreversible so that, even if systemic iron overload is successfully reduced, reversal of the sexual dysfunction is rarely complete. Additional androgen therapy can be used to manage sexual dysfunction in selected patients; however, in cases with existing liver damage, androgen therapy must be avoided (Figure 3).

Sexual dysfunction occurs early, often before there are any other manifestations of GH. A case could, therefore, be made for screening patients presenting to sexual health services for this disorder; measurement of the serum ferritin level would be all that was required.

Declaration of interests: none declared.

REFERENCES
9. Haemochromatosis Society, Royal Free Hospital, questionnaire 2004–06.

Figure 3. Explant liver specimen showing haemochromatosis and hepatocellular carcinoma (courtesy of the Royal Free Hospital)

KEY POINTS
- Untreated genetic haemochromatosis (GH) can result in significant end-organ damage
- Measurement of serum ferritin can exclude GH or prompt further investigations
- Treatment with venesection is cheap and extremely effective
- Sexual dysfunction is common in GH; it is under-recognised and underdiagnosed
- In patients presenting with sexual dysfunction, the diagnosis of GH is delayed by about nine years