

ORIGINAL ARTICLE

Prevalence of Genetic Haemochromatosis and Iron Overload in Patients Attending Rheumatology and Joint Replacement Clinics.

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Abstract

Background & aims

Genetic Haemochromatosis (GH) is common in North European and Celtic populations and is associated with arthropathy. We aimed to measure the frequency of the common GH mutations (C282Y and H63D), the carrier frequency of C282Y and markers of iron overload in patients who were referred to our rheumatology and joint replacement clinics.

Methods

Unselected patients attending these clinics were anonymously tested for the described mutations. Transferrin saturation and serum ferritin were also measured and if elevated, the patients had predictive counselling then named GH mutation testing. The carrier and mutation frequencies were also determined in 340 local controls.

Results

One hundred and sixty-one unselected patients attending these clinics were studied. The C282Y mutation carrier frequency was 1 in 5.2 in patients compared with 1 in 8.1 in controls ($p < 0.005$). The overall mutation frequencies were similar in patients and controls. One patient was found to be homozygous for the C282Y mutation and eight were compound heterozygotes. Seven other patients had a raised ferritin, one of whom was a C282Y heterozygote.

Conclusion

The C282Y carrier frequency is significantly higher in patients attending rheumatology and joint replacement clinics than in controls. Screening of these patients for GH should be considered.

Key words

Haemochromatosis, arthritis, iron storage disorders

Introduction

Genetic haemochromatosis (GH) is an autosomal recessive condition causing iron overload in many organs including the liver, heart, pancreas, skin, gonads and joints.¹ The commonest gene defect, which was identified in 1996 and accounts for >90% of cases of GH in the United Kingdom,² occurs in the HFE gene on chromosome 6 resulting in a single amino acid substitution (C282Y mutation) in the gene product. The other common mutation (H63D) is only clinically relevant in the compound heterozygote form (C282Y/H63D). Genetic haemochromatosis is particularly common in North European and Celtic populations, including the West of Scotland.³ Due to the high prevalence in these areas, it has been suggested that high-risk groups, such as those with known associated organ dysfunction, should be screened for GH mutations.^{4,5}

Some authors have suggested that arthropathy may cause the greatest morbidity among GH patients.⁶ The most commonly affected joints in GH are the index and middle metacarpophalangeal and proximal interphalangeal joints, although there are reports of more widespread non-specific joint disease.^{7,8,9} However, arthropathy is common in the general population, and it is unclear whether GH is more common in patients presenting de novo with arthropathy compared with the general population.^{10,11}

The aim of our study was to assess the mutation and carrier frequencies of the common GH mutations in unselected patients attending rheumatology and joint replacement clinics in an area of high prevalence of GH. These frequencies were compared with a local control population.

Patients and Methods

Unselected patients were recruited from new referrals to our hospital's rheumatology and pre-operative joint replacement clinics. The patients were given a brief handout regarding the study aims and gave written informed consent for entry to the study prior to having extra blood samples taken at the clinic. They were tested for an anonymous HFE gene test, but a *named* serum ferritin and transferrin saturation. The initial HFE test was anonymised due to the ethical problem of possibly labelling a patient as having a genetic "disease" with possibly no biochemical or clinical penetrance of the condition.

A short history was taken assessing the possibility of known

heart disease, diabetes mellitus or liver disease. Patient characteristics are shown in Table I. If the named transferrin saturation or ferritin was found to be elevated, an appointment was made for the patient to attend the nurse led clinic where a named HFE gene test was performed with prior predictive genetic counselling. The result of this was discussed at a subsequent consultant led liver clinic.

Table I. Patient Characteristics and Iron Studies

	<u>Patients (n=161)</u>
Gender: <i>male / female</i>	47 / 114
Age in years; mean (+/-SD)	59.4 (+/-14.7)
Known heart disease (n)	23
Known diabetes mellitus (n)	5
Known liver disease (n)	4
% Transferrin saturation; mean (+/-SD)	18 (+/-9)
Number of patients with saturation > 45%	1
Ferritin (ug/L); mean (+/-SD)	96 (+/-130)
Number of patients with ferritin > 300ug/L	8

Three hundred and forty local controls were anonymously tested for GH mutations as part of a larger genetic disease prevalence and screening programme. We had no specific information on joint symptoms or iron status in this anonymous control group.

Full ethical approval for this study was sought and obtained from the local ethics committee.

Statistical Analysis

Student's T test was used to compare the frequency of the GH mutations and C282Y carrier frequency in the study population compared to the local controls, as well as comparing GH mutation frequencies between the rheumatology patients and the joint replacement clinics. Data are expressed as mean (+/-SD) unless otherwise stated and a significance level of <0.05 was chosen.

Results

A total of 161 patients were entered into the study - 71 from the rheumatology clinic and 90 from the joint replacement clinic (62 awaiting knee and 28 awaiting hip replacement). The serum ferritin and transferrin saturations of the study patients and the number with raised levels are shown in Table I. There were no differences in either test of iron overload between the rheumatology and joint replacement groups. One patient with a high ferritin was subsequently found to be homozygous for the C282Y mutation. Of the others with a raised ferritin, one was found to be heterozygote for the C282Y mutation. The one patient with a raised transferrin saturation was found to be a compound heterozygote (C282Y/H63D).

There was a significantly higher carrier frequency of the C282Y

mutation in patients compared with the control population, although the absolute mutation frequencies in patients were similar to controls (see Table II). There were no differences between the rheumatology and joint replacement patients regarding mutation frequencies or carrier rates.

Table II. Genetic Analyses

		<u>PATIENTS</u>	<u>CONTROLS</u>	
Carrier frequency*:	C282Y	1 in 5.2	1 in 8.1	p<0.005
Mutation frequency#:	C282Y	10.2%	7.4%	NS
	H63D	15.8%	15.5%	NS

* proportion of people who have the specific mutation on one of their chromosomes

frequency of the mutation in a given number of chromosomes

Discussion

Genetic Haemochromatosis is a common and under-diagnosed condition which can be easily treated by venesection if diagnosed early. The condition is particularly prevalent in North European and Celtic populations, including the West of Scotland.⁵ In this study, we report a carrier frequency of 1 in 8.1 for the common C282Y mutation in local controls. Although biochemical penetrance of GH is extremely high,^{9,12,13,14} clinical penetrance is much lower,¹⁵ therefore, screening of the general population is probably not indicated. Whilst screening of some high-risk groups such as patients referred to secondary care with raised liver function tests is commonly undertaken, the value of screening other high-risk groups remains unclear.

It is well recognised that C282Y homozygotes may develop arthropathy as part of the clinical spectrum of GH. Although it is unclear whether venesection reverses the arthritic manifestations of GH, early identification of the condition improves outcome from liver disease in particular and allows predictive testing of relatives.^{16,17}

Olynk et al reported a high incidence of GH mutations in patients attending a rheumatology clinic in Australia.⁹ However, Willis et al suggested that there was no increase in the prevalence of C282Y homozygotes amongst patients in the North of England with inflammatory arthritis.¹¹ In addition, Cadet and colleagues reported no increase in GH mutations in patients attending rheumatology clinics in France.¹⁸ In our study, we have shown a C282Y mutation carrier frequency of 1 in 5.2 among unselected patients attending our rheumatology and joint replacement clinics. This is significantly higher than the local control population, suggesting potential benefit from screening such patients for this condition.

Due to the raised serum ferritin levels seen in the acute phase reaction, the measurement of transferrin saturation is often considered to be the best initial screening test for GH. A level greater than 45% warrants further investigation.^{4,19} In our study, only one patient had a transferrin saturation greater than this figure, and they were later identified to be a compound heterozygote for both the C282Y and H63D mutations. Such individuals are at risk of developing iron overload and organ

damage, although less commonly than C282Y homozygotes.^{14,20,21} In our study, eight patients had a serum ferritin >300ug/L. Despite the poor specificity of a raised ferritin in these patients due to a possible acute phase reaction, one of these eight was subsequently found to be homozygous for the C282Y mutation. They were successfully commenced on a venesection programme and predictive testing was offered to their first-degree relatives. One other patient with a raised ferritin was found to be a C282Y heterozygote.

In summary, we have shown that the C282Y mutation carrier frequency is significantly higher in patients with arthritis compared to local controls in an area of high prevalence of GH. Screening of such patients by serum ferritin and transferrin saturation should be considered, with predictive genetic testing for GH mutations offered to those with raised levels. Whilst a cost-benefit analysis of this approach would be helpful, such a policy is likely to identify more patients with this condition and may improve their prognosis and allow predictive testing of first-degree relatives.

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Author contribution:

Drs. Stanley, Thorburn and Capell conceived and designed the study. Drs. Donnelly, Joshi, Cook and Sister Neilson and Charge nurse Reid collected and/or analysed the data. All authors were involved in the writing or reviewing of the article and approved the final manuscript.

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References

1. Bothwell TH, Charlton RW, Motulsky AG. Haemochromatosis. In: Scriver CR, Beaudet AL, Sly WS Valle D (eds) *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw-Hill 1995; 2237-69.
2. 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.
3. Campbell S, George DK, Robb SD, et al. The prevalence of haemochromatosis gene mutations in the West of Scotland and their relation to ischaemic heart disease. *Heart* 2003; 89: 1023-6.
4. Tavill AS. Diagnosis and management of hemochromatosis. *Hepatology* 2001; 33: 1321-1328.
5. Ho GT, Stanley AS. Haemochromatosis: where are all the patients? *Scott Med J* 2001; 46: 99-100.
6. Adams PC, Speechley M. The effect of arthritis on the quality of life in hereditary haemochromatosis. *J Rheumatol*; 1996; 23: 707-10.
7. Dymock IW, Hamilton EBD, Laws JW, Williams R. Arthropathy of haemochromatosis. *Ann Rheum Dis* 1970; 29: 469-76
8. Faraawi R, Harth M, Kertez A, Bell D. Arthritis in haemochromatosis. *J Rheumatol* 1993; 20: 488-52
9. Olynyk J, Hall P, Ahern M, Kwiatek R, Mackinnon M. Screening for genetic haemochromatosis in a rheumatology clinic. *Austr NZ J Med* 1994; 24: 22-5.
10. Ross JM, Kowalchuk RM, Shaulinsky J et al. Association of heterozygous hemochromatosis C282Y gene mutation with hand osteoarthritis. *J Rheumatol* 2003; 30: 121-25.
11. Willis G, Scott DGI, Jennings K, Smith K, Bukhari M, Wimperis JZ. HFE mutations in an inflammatory arthritis population. *Rheum* 2002; 41: 176-79.
12. Ryan E, Byrnes V, Coughlan B, Flanagan et al. Under diagnosis of hereditary haemochromatosis: lack of presentation or penetration? *Gut* 2002; 51: 108-12.
13. Powell LW, Summers KM, Board PG, Axelsen E, Webb S, Halliday JW. Expression of haemochromatosis in homozygous subjects. Implications for early diagnosis and prevention. *Gastroenterology* 1990; 98: 1625-32.
14. McCune CA, Ravine D, Carter K et al. Iron loading and morbidity among relatives of HFE C282Y homozygotes identified either by population genetic testing or presenting as patients. *Gut* 2006; 55: 554-562.
15. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G->A (C282Y) HFE haemochromatosis mutation in the USA. *Lancet* 2002; 359: 211-8.
16. Hamilton EB, Bomford AB, Laws JW, Williams R. The natural history of arthritis in idiopathic haemochromatosis: progression of the clinical and radiological features over ten years. *Q J Med* 1981; 50: 321-9.
17. Askari AD, Muir WA, Rosner IA, Moskowitz RW, McLaren GD, Braun WE. Arthritis of hemochromatosis. Clinical spectrum, relation to histocompatibility antigens and effectiveness of early phlebotomy. *Am J Med* 1983; 75: 957-65.
18. Cadet E, Capron D, Perez AS et al. A targeted approach significantly increases the identification rate of patients with underdiagnosed haemochromatosis. *J Int Med* 2003; 253: 217-224.
19. McLaren CE, McLachlan GJ, Halliday JW et al. Distribution of transferrin saturation in an Australian population: relevance to the early diagnosis of haemochromatosis. *Gastroenterology* 1998; 114: 543-9.
20. Merryweather-Clarke AT, Wormwood 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.
21. Jackson HA, Carter K, Darke C et al. HFE mutations, iron deficiency and overload in 10,500 blood donors. *Br J Haematol* 2001; 114: 474-84.