H63D is an haemochromatosis associated allele

Editor,—The UK Haemochromatosis Consortium’s report (Gut 1997;41:841–4) questions the importance of the H63D allele in hereditary haemochromatosis (HHc). In their commentary, Goldwurm and Powell (Gut 1997;41:855–6) also doubt the relevance of H63D. However, there is compelling evidence that the H63D allele is associated with HHc.1 3

To evaluate the association of H63D with haemochromatosis, one must first recognise that H63D and C282Y are independent mutations of the HFE gene. Because the C282Y mutation is so common and is highly penetrant, homozygous C282Y predominates among cases of haemochromatosis, and H63D is not observed in C282Y homozygotes. If one excludes from analysis the C282Y homozygotes, then the strong association of H63D with HHc becomes apparent. For five large series from North America2 4 that have been analysed in this manner, we found a highly significant (p=0.00001) two-fold enrichment of HHc cases with H63D, compared with random control cases. For studies reported from Europe,5 6 we also found a highly significant “enrichment”, in which groups with HHc have roughly twice the frequency of H63D compared with control groups: Borot et al, p=0.003; Jouanolle et al, p=0.0004; Carella et al, p=0.003; Martinez et al, p=0.0000002; and Gottschalk et al, p=0.02. When all the data reported from Europe and from North America are combined, including those of the Consortium, the association of H63D with HHc is quite significant (p<0.00001).

The strong association of H63D with haemochromatosis might depend on the fact that patients who are compound heterozygotes—that is, C282Y/H63D, are at risk of clinically significant iron overload. Therefore, one may question whether H63D itself is associated with haemochromatosis. We have tested this possible relationship by re-analysing all the published data (combining data from 10 studies, including those of the UK Haemochromatosis Consortium). In this re-analysis, we have compared the frequency of homozygous H63D, of which approximately 50 cases have now been described (a third with clinically significant iron overload), with the combined frequencies of homozygous C282Y (that is, homozygous normal) and heterozygous H63D (that is, C282C/H63D), in random controls and patients with haemochromatosis, after exclusion of all cases that have C282Y. Thus, we have tested the effect of H63D independently of any effect that might be observed in cases that also have C282Y. In this analysis of 1093 control subjects and 163 patients with HHc, we found that the proportion of H63D homozygotes (6%) in the latter group was nearly three times higher than the proportion of H63D homozygotes in the control group (2.2%). χ2=8.4, p=0.0038. This significant enrichment of HHc cases with homozygous H63D is highly greater than that which we and others have observed when comparing the proportion of H63D alleles in controls and HHc cases prior to exclusion of all C282Y heterozygotes from the analysis.

These analyses confirm that H63D is an independent risk factor for HHc and not just a polymorphism of the HFE gene. Others independently performed similar analyses of subsets of the data we analysed, and came to the same conclusions.1 3 However, although there is compelling evidence for this association, it is also important to note that the H63D allele has low penetrance.1 3 11 Analytical studies of the genotype distributions in the various studies suggests that H63D homozygotes have only a two- to fivefold increased risk for developing HHc compared with normal controls.

Is a single test for C282Y sufficient for ascertaining HHc? In Italy and in Alabama, USA, fewer than 70% of patients with HHc are homozygous for C282Y. Even in the UK, where a high frequency of C282Y has been observed, 10% of HHc cases cannot be detected if one uses a test for C282Y only, and more than 30% in Alabama and in Italy (excluding Brittany). Clinicians may be misled to believe that patients who are not homozygous for C282Y do not have HHc. Testing for H63D helps to close this gap. Even if tests were available for both HHc alleles, too many cases would not be correctly ascertained if clinicians rely solely on the DNA tests of the HFE gene to make this diagnosis. With addition of the test for the H63D mutation the interpretation of results must take into account the low penetrance of the C282Y/H63D and H63D/63D genotypes. However, this is true also for interpretation of C282Y test results as the genotype C282Y/C282Y also shows incomplete penetrance. The DNA test is a useful diagnostic method but, as with most laboratory tests, results must be interpreted in the context of other clinical and laboratory findings.

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Reply

Editor,—We thank Fairbanks et al for their comments and agree with their conclusion that the H63D mutation may be associated with iron accumulation. This is supported by the recent finding that the HFE protein with the H63D mutation does not reduce the affinity of transferrin for its receptor in the same way as the wild type protein.1 However, we reserve judgment about combining data from various groups of patient and controls where the frequency of the mutations in the general population varies greatly.

We should, however, point out that our study of the UK patients was completed before November 1996 and submitted in December 1996. Most of the studies referred to by Fairbanks et al have been published since that time.1 3 We found four “compound heterozygotes” with iron overload and two others who had a diagnosis of haemochromatosis but did not have sufficient iron accumulation to satisfy our criteria for iron overload. Since then two of us (MW (http://www.uwcm.ac.uk/uwcm/hg/worwood/) and WMCR) have been providing a diagnostic service for haemochromatosis. We test for both mutations and regard testing for transferrin saturation and ferritin as essential in making a diagnosis. The H63D mutation is valuable not only because compound heterozygotes must be regarded as “at risk for iron accumulation”1 but also because the test provides a check on the results for the C282Y mutation. We have never seen an example of a subject homozygous for C282Y who also has the H63D mutation.

Table 1 shows the genotypes for 423 samples received in the haemochromatosis testing service for haemochromatosis. We test for both mutations and regard testing for transferrin saturation and ferritin as essential in making a diagnosis. The H63D mutation is valuable not only because compound heterozygotes must be regarded as “at risk for iron accumulation”1 but also because the test provides a check on the results for the C282Y mutation. We have never seen an example of a subject homozygous for C282Y who also has the H63D mutation.

Table 1 Samples received at University Hospital of Wales and the Wexsey Regional Clinical Genetics Laboratory for genotyping (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>H63D/C282Y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (n+1)</td>
</tr>
<tr>
<td>South Wales</td>
<td></td>
</tr>
<tr>
<td>Requests</td>
<td>423   27.0 7.3 29.8 9.9 0.9 25.1</td>
</tr>
<tr>
<td>Normal</td>
<td>113   9.1 16.3 29.1 17.3 4.1 18.9</td>
</tr>
<tr>
<td>Wexsey</td>
<td>42    26.2 14.3 16.6 9.5 2.4 31.0</td>
</tr>
</tbody>
</table>

haemochromatosis or patients suspected of having the condition. Note the increased frequency of the compound heterozygotes compared with control subjects (blood donors from South Wales studied by MW and KJHR and colleagues). However, there is a decreased frequency for H63D homozygotes in Cardiff but not in Wexsex, suggesting regional variation. Although expressing frequencies in terms of non-C282Y chromosomes may demonstrate an enrichment in haemochromatosis, we have seen only one further case of clinical iron overload in people homozygous for H63D and that was in Wexsex.

That the clinical penetrance of the H63D mutation is very low is supported by studies of blood donors from South Wales (by MW and KJHR and colleagues). Patients carrying either the homozygous C282Y genotype or both mutations (H63D/C282Y) had increased transferrin saturation and serum ferritin concentrations compared with subjects with other genotypes. There was no evidence that heterozygotes or subjects homozygous for H63D had raised iron stores. However, much larger studies will be needed to establish any relations between genotype and iron status in normal subjects.

We would also point out that in a study published last April describing the global prevalence of the H63D and C282Y mutations,2 the C282Y mutation was almost entirely restricted to peoples of Northwest European origin, whereas the H63D mutation had a more global distribution although it was still highest in parts of Europe. The belief that genetic haemochromatosis was a disease limited to peoples of European extraction may explain why it has only been observed in these populations due to selection bias. However, the problem arises as to why in places such as India and Saudi Arabia the H63D allele frequencies are over 5% and haemochromatosis has not been reported or recognised in these populations. Is the H63D allele conferring protection against anaemia due to diseases such as malaria or hookworm, or anaemia due to multiple pregnancies thus producing a more apparent variant against diagnosing haemochromatosis? Clearly even in the developed world the penetrance of the disease in H63D homozygotes is variable so it might be expected that in conjunction with factors such as malnutrition the H63D allele may be playing a protective rather than disease causing role. It is also important to point out that both C282Y and H63D mutations have been implicated in iron overload in sporadic porphyria cutanea tarda10 and therefore these mutations should also be considered when studying patients with this condition.

We therefore agree with Fairbanks et al that the diagnosis of haemochromatosis requires testing for both the common mutations as well as careful assessment of iron status and other clinical and laboratory findings, and we welcome their analysis. The accumulation of both genetic and biological data following early studies of genotype, including our own, underline the rapidity with which the field is developing and illustrate the need for a regular revision of diagnostic, screening, and management guidelines. We believe that appropriate management of patients with mutations in HFE or clinical evidence of iron overload in the absence of mutations requires the integration of diagnostic and clinical genetics, and clinical hepatology services as provided in Southampton. We urgently need reliable information about the clinical penetrance of the H63D mutation. There are a number of studies in progress which will provide information about this, including a study of 10 000 blood donors in South Wales funded by the Wexsex Office of Research and Development for Health and Social Care (MW).

We thank John Harvey of the Wexsex Regional Genetics Laboratory, and Martin Hooper (Department of Immunology) and Diana Eccles (Department of Clinical Genetics) of the Southampton University Hospital Trust.

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2 Borot N, Roth M-P, Malfroy L, et al. The HFE gene and iron metabolism have advanced very rapidly in the short time since the discovery of the HFE gene. We agree that whereas the initial evidence suggested that any role of the second (H63D) mutation in HFE was minor and possibly confined to the compound heterozygous (C282Y/H63D) state,2 recent emerging evidence has indicated that H63D has a significant independent role in iron overload. Indeed, in the very short time since Fairbanks et al's letter was written additional clinical evidence confirming such an independent role has emerged3 and the molecular basis has been partly elucidated. In cultivated cells, the C282Y mutation prevents the association of the mutant HFE protein with the transferrin receptor (TIR). In contrast, wild type HFE protein decreases the affinity of the TIR for transferrin and over expressed H63D protein lacks this effect.4 Thus, H63D has an independent, more subtle, effect on iron metabolism than C282Y, presumably involving the affinity of TIR for transferrin on the cell surface.

The key clinical question now relates to the degree of iron overload and severity of disease resulting from the H63D mutation. The emerging data would suggest that compound (C282Y/H63D) heterozygotes do not develop iron overload of a degree previously recognised as haemochromatosis HLA associated HH, as a group do not have as severe iron overload as C282Y homozygotes5 and that iron stores in H63D homozygotes are less—that is, H63D has both low penetrance and comparatively low expressivity.

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BOOK REVIEWS


This is an unusual and very welcome book. In fact, I have now welcomed it four times, once when I bought it myself and three times since, when I have received it for review. The numbers of people doing significant numbers of endoscopy varies from the cholangiopancreatography (ERCP) examinations in neonates and children is very small and the world leader is Moses Guelrud. It is, therefore, highly appropriate that he should be the main author of this book. In fact, one wonders what the other two authors did as the acknowledgements make it clear that all the cases were seen in Venezuela, Dr Guelrud’s base. As it happens, the writing is a secondary part of the book, since, of the 150 pages, only 35.8 are text, 20 are given over to references and 82 pages are made up of pictures, almost all radiographs, a total number of 205 illustrations. The remaining 12.5 pages are blank or titles pages.

Much of the text is, appropriately, devoted to diagnostic and therapeutic ERCP studies in adults as the numbers in children are small. This is particularly true of the sections on choledochal and pancreatic pseudocysts. The opening chapter, which includes data on sedation, anaesthetics and monitoring, is well written and sensible, but it does raise the question of who should be doing paediatric ERCP however. It cannot be sensible for paediatricians to perform ERCP only on children. Unless they are also doing adult cases on a regular basis, it will not be possible to do enough cases to keep skills at an adequate level for the very difficult neonatal cases. In the United Kingdom a handful of institutions perform this procedure, and this is appropriate.

This is a detailed treatment of what is described as anomalous pancreatico-biliary union which has nothing to do with a collection of surgeons, physicians and radiologists with many handbooks but rather is the condition sometimes called a long common channel which is especially associated with choledochal cyst and recurrent pancreatitis. However, the main raison d’être of this book is the radiographs. ERCP in children, because of the small numbers, still rather lends itself to anecdotes, small series and the syndrome of “look what I’ve done”. Dr Guelrud, however, has done a lot and the excellent x-ray pictures in this book attest to that fact.

Critical analysis is harder to find. For example, many endoscopic therapeutic techniques are described in primary sclerosing cholangitis (PSC) but there is really no attempt to place them in the overall scheme of things in this condition, especially in paediatric PSC where the place of anti-inflammatory therapy has been so well described. Furthermore, the place of ERCP as a diagnostic test in children has not really been critically analysed vis-a-vis magnetic resonance cholangiopancreatography (MRCP).

I do have some slight quarrel with the definition of pancreatic as in this book there was included a 19 year old with PSC and a 17 year old with ascariasis. In most units these would be regarded as adult. It is difficult to know at whom the book is aimed. Personally, as I do a lot of paediatric ERCP’s I have found it a delight to read and have admired the x ray images. Paediatric ERCP, especially in neonates and very early infants, is such clear pictures as it is possible to get in adults and Dr Guelrud is to be congratulated on his nice films. It will be a useful source of reference for radiologists who see few cases. I am very grateful for the authors for having produced this book but it is difficult to think it will sell in large numbers.

M L WILKINSON


Which medical specialty has seen the greatest developments over the past 25 years? Who has profited most from the clinical application of the relentless increase in scientific understanding, the quantum leaps in technology and the broadening of the range of therapeutic options (which extend far beyond drugs)? It’s a question that any individual specialist would find hard to answer—maybe we are all just too close to our own field. However, although one can admire what technological development has brought to cardiology, how imaging has transformed neurology and what therapeutic advances have done for infections in so many fields, I doubt that any specialty has benefited more than our own. It is the coincidence (if both meanings of the word) that fibre-optic technology, imaging (especially, ultrasound and computed tomography) and real therapeutic advances have come together in the last quarter of the 20th century that has made gastroenterology the specialty that is most transformed.

I just do not know when publishers began to commission titles like the present offering but you can get some sort of perspective on the pace of therapeutic advance by wiping the dust of some of the more elderly volumes in the gastroenterology section of your institution’s library. An article written in the early 1970s on the medical treatment of peptic ulcer bears little more relationship to today’s practice than “cupping” and “bleeding” for pulmonary tuberculosis do to modern chemotherapy. One does not know what the future holds for gastroenterology but I do believe that the period that we are now living through will come to be seen as the Golden Age for gut specialists. “Bliss was it in that dawn to be alive/But to be young was very heaven!”

Lewis and Dubois have edited a good, though flawed, book on gastrointestinal pharmacology. Perhaps the most obvious problem can readily be picked from the title page: there are 12 chapters and although half of these concern medical conditions or diseases (for example, treatment of gastrointestinal malignancy, inflammatory bowel disease, portal hypertension in cirrhosis), the others deal, not with disease, but drug class. These include H2 receptor antagonists and proton pump inhibitors. Does the world really need more review articles on antisecretory agents? The same feeling of overwhelming is divided into two unequal camps. On the one hand, there are those who are to be seen feverishly tearing off the plastic wrappers of their gastrointestinal journals in order to get at the latest trial of a 6-day versus 7-day regimen of “this weekole, croprycin and pukcillion” in the for all eternity eradication of you-know-what. On the other hand, there are— I rather suspect— rather large numbers of people doing significant numbers of ERCP, especially in neonates and very young infants, who have been given the unequal struggle of stifling a yawn when the eye dwells on this sort of endlessly repetitious tosh.

Not that these chapters are poor, far from it. But given the usefulness of the disease related chapters, it is a shame that the editors could not have “disguised” their obvious need to have something on ulcer drugs within a disease category. However, the selection of drug class based titles for their own chapters (co-written with others) perhaps indicates their chosen approach. There is a very useful review of sedation for endoscopy by Ginsberg and a stimulating piece on gastrointestinal cancer by Marshall. By far the best drug class chapter is a very classy piece indeed by Jensen on peptide therapy.

All the authors work in North America so may the occasional flavour of jingoism in the prose should not come as too great a surprise. I suppose some gastrointestinal pharmacologists do see themselves as heroic patriots in the battle against disease. Still, I think I could have had a little less of the militaristic cliches (of which armamentarium is the most overworked).

FORGACS


It is now almost 30 years since John Spencer’s paper on the use of pH monitoring in the diagnosis of gastro-oesophageal reflux and 25 years since DeMeester and colleagues quantified and further explored this method. Since then laboratories have been born, grown up and flourished. There has been an explosion in the technology associated with measurement of oesophageal dysfunction both in terms of the assessment of reflux disease and also the evaluation of motility disturbances.

This outstanding book comes from 24 authors who are predominantly members of the Clinical Measurement Associate Group of the British Society of Gastroenterology. It looks in depth at virtually all aspects of the assessment of oesophageal function. Oesophageal laboratories are very much the meeting point of many medical specialties and the diversity of the authors of this volume testifies to this. This book is primarily directed at those people who either run such laboratories or wish to set one up. It is also an invaluable reference guide for the many specialists who treat patients for oesophageal function testing, including medical and surgical gastroenterologists, paediatricians, and those involved in managing patients with atypical symptoms of reflux disease such as non-cardiac chest pain, globus and respiratory symptoms.

This book is very much in the category of when, why and how to do it, and will guide the reader through the bewildering range of sophisticated equipment available for oesophageal testing. It explores the benefits, for instance, of the water perfused manometry equipment versus the solid state and the advantages of the Doppler sleeve. It provides an excellent scheme for the place of pH
monitoring in clinical practice, indicating which patients would benefit and those in whom the test would be inappropriate and discusses the use of the symptom index in answering the very important question of whether the patient’s symptoms are actually pruritus and related to the abnormalities demonstrated via the pH probe.

Each chapter is short, clear, well illustrated, and well referenced. As expected, most of the book is devoted to static manometry and ambulatory pH monitoring. There is, however, a particularly useful section on ambulatory manometry and its particular usefulness in the diagnosis of that elusive condition dif- fuse oesophageal spasm. The section on the upper oesophageal sphincter, which gives rise to great difficulties to many investigators, is an outstanding summary of the current state of knowledge. There are very few omissions—possibly a short section on bile monitoring would have been helpful.

There are always practical “wrinkles” which are important to understand for maintaining the accuracy of any tests. These are important not only in carrying out the investigation but also the interpretation of results and are essential in maintaining the high standards currently in use in oesophageal laboratories in the UK. This excellent book is a tribute to the Clinical Measurement Associates and is essential reading for all those involved in the management of patients with oesophageal disease.

W JOWEN


This book is designed, as described in the introduction, to be viewed as a work in progress. It aims to bridge the knowledge gap between the personal physician and transplant centre personnel, and wishes in this to improve dialogue between these parties. It addresses care of the transplant patient in five sections. The first pertains to selection of the potential transplant patient, the second to management of the perioperative period, the third to chronic medical problems in the transplant recipient, the fourth addresses medical complication, and the fifth part, with one chapter, addresses liver transplantation in children.

The book is written in several fairly short chapters within these sections, and the authorship is drawn predominantly on the staff of the Duke University Medical Center, Durham, North Carolina, from whence the editors hail. The nature, therefore, of the text, advice given, and proposed plans of investigation are perhaps somewhat narrow in their perspective, and reflect very much views of a given centre, though the authors do comment frequently that this is the case, and that other centres may have other views.

In addition, given that the text originates in the USA, several of the chapters pertaining to cost and insurance companies may not be transferable to the medical care situation in Europe, where individual billed charges for liver transplantation could not be extrapolated to other medical providing services. Similarly, the chapters on donor procurement pertain really to the USA rather than Europe.

Thus, in summary, this book seems to bridge the knowledge base required by a general practitioner caring for a transplant patient with that of the transplantation services. It makes a good attempt at this, although it is very specific to the practices carried out at that individual centre, and most liver transplant centres will already provide the local practitioners, who will subsequently care for these patients in the community, with a large amount of text relating to shared practice protocols for that given centre.

With respect to its application for specialist practitioners caring for transplantation patients, it probably lacks a little in the amount and depth of information available, and there are many omissions that go into greater depth on this issue.

J WENDON

16th Leeds Course in Clinical Nutrition

The 16th Leeds Course in Clinical Nutrition will be held at the University of Leeds, UK, on 15-18 September 1998. Further information from: Ms Samantha Armitage, CVE Section, School of Continuing Medical Education, Continuing Education Building, Springfield Mount, Leeds LS2 9NG, UK. Tel: +44 113 233 3241; +44 113 233 3240; Email: s.armitage@leeds.ac.uk.

Current Trends in Colon and Rectal Surgery

The second postgraduate course in Current Trends in Colon and Rectal Surgery will be held in Sorrento (Naples), Italy, on 24-26 September 1998. Further information from: Dr Angela Palma, Organising Secretariat, Convention Planning s.a.s., via Fuoriporta 20, 80067 Sorrento, Napoli, Italy. Tel: +39 81 807 1981; Fax: +39 81 807 3039; Email: convplan@syrene.it; WWW: http://www.syrene.it/convplan/.

European Mucosal Immunology Meeting. The Cells and Molecules Important in Mucosal Tolerance and Inflammation

The European Mucosal Immunology Meeting. The Cells and Molecules Important in Mucosal Tolerance and Inflammation will be held at the Charterhouse Square Campus of St Bartholomew’s and the Royal London School of Medicine and Dentistry, London, UK, on 2-3 October 1998. Further information from: Professor T T MacDonald, Department of Paediatric Gastroenterology, St Bartholomew’s Hospital, London EC1A 7BE. Email: t.t.macdonald@mds.qmw.ac.uk.

Laparoscopic Surgery

A Course on Laparoscopic Surgery will be held at the University Hospital Saint Pierre, Brussels, Belgium, on 17-20 November 1998. Further information from: Conference Services S.A., Avenue de l’Observatoire 5, bte 17, B-1180 Brussels, Belgium. Email: conference.services@skynet.be.

Second Inflammatory Bowel Disease Meeting

The Second Inflammatory Bowel Disease Meeting will be held at Chester Town Hall, Chester, UK, on 23-24 November 1998. Further information from: Professor J M Rhodes, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP. Tel: +44 151 706 3558; Fax: +44 151 706 5832.

13th International Workshop on Therapeutic Endoscopy

The 13th International Workshop on Therapeutic Endoscopy will be held at the Endoscopy Centre, Prince of Wales Hospital, Hong Kong, on 1-3 December 1998. Further information from: Professor Sydney Chung, Endoscopy Centre, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong. Tel: +852 2632 2233; Fax: +852 2635 0075.

European Postgraduate Gastro-Surgical School Symposia

The 7th Course on Digestive Endoscopy - Liver will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 3-4 September 1998. Registration fee: NLG 450.00.

H. pylori: from Bench to Bedside will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 24-25 September 1998. Registration fee: NLG 300.00.

Minimally Invasive Surgery: A Critical Evaluation will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 13 November 1998. Registration fee: NLG 200.00.

From Gene to Cure II: Bilio-pancreatic malignancy will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 4-5 February 1999.

Further information from: Helma Stockmann, Managing Director, European Postgraduate Gastro-Surgical School, G-4-zauid, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 566 3926; Fax: +31 20 566 6569 or 691 4858; Email: w.j.stockman@amc.uva.nl.

Sir Francis Avery Jones BSG Research Award 1999

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1999 Award. Applications (TWENTY COPIES) should include:

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- An outline of the proposed content of the lecture, including title
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Entrants must be 40 years or less on 31 December 1998 but need not be a member of the BSG. The recipient will be required to deliver a 40 minute lecture at the Annual Meeting of the Society in March 1999. Applications (TWENTY COPIES) should be made to the Honorary Secretary, BSG, 3 St Andrews Place, London NW1 4LB, by 1 December 1998.
H63D is an haemochromatosis associated allele

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