Original articles

Global prevalence of putative haemochromatosis mutations

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Abstract

Haemochromatosis is a genetic disease associated with progressive iron overload, and is common among populations of northern European origin. HLA-H is a recently reported candidate gene for this condition. Two mutations have been identified, a substitution of cysteine for tyrosine at amino acid 282 (C282Y, nucleotide 845) and of histidine for aspartate at amino acid 63 (H63D, nucleotide 187). Over 90% of UK haemochromatosis patients are homozygous for the C282Y mutation. We have examined 5956 chromosomes (2978 people) for the presence of HLA-H C282Y and H63D by PCR followed by restriction enzyme analysis. We have found world wide allele frequencies of 1.9% for C282Y and 8.1% for H63D. The highest frequencies were 10% for C282Y in 90 Irish chromosomes and 30.4% for H63D in 56 Basque chromosomes. C282Y was most frequent in northern European populations and absent from 1042 African chromosomes, 484 Asian chromosomes, and 644 Australasian chromosomes. The distribution of the C282Y mutation coincides with that of populations in which haemochromatosis has been reported and is consistent with the theory of a north European origin for the mutation. The H63D polymorphism is more widely distributed and its connection with haemochromatosis remains unclear.

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Keywords: haemochromatosis; HLA-H; north European/Celtic populations.

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Haemochromatosis is an autosomal recessive disorder in which increased iron absorption causes iron overload, eventually resulting in tissue damage which can be fatal if undetected.[1] However, life expectancy is normal if iron is removed by venesection in the precirrhotic stage of the disease.[2] Patients often do not present until middle age and genetic testing of populations of northern European origin, in which the disease frequency has been estimated at 1/300,[3–7] would identify those at risk before the development of tissue damage because of iron overload. Feder *et al*[8] have recently identified two mutations in HLA-H, a candidate gene for haemochromatosis on chromosome 6 (6p22.1): a G to an A at nucleotide 845 in the codon of amino acid 282, changing cysteine to tyrosine, and a C to a G at nucleotide 187 in the codon of amino acid 63, changing histidine to aspartate. Feder *et al*[8] found that 83% of 178 haemochromatosis patients were homozygous for the C282Y mutation. The UK Haemochromatosis Consortium (submitted for publication) has found that over 90% of 115 UK patients were homozygous for the mutation, with H63D allele frequencies of 2% in patients and 16% in controls. Jazwinska *et al*[9] found that 100% of 112 Caucasian Australian patients with a positive family history of haemochromatosis were homozygous for the C282Y mutation, and Beutler *et al*[10] and Jouanolle *et al*[11] found that 82.3% and 92.4% of Caucasian haemochromatosis patients in the USA and Brittany, respectively, were homozygous for C282Y, and found H63D allele frequencies of 5.4% and 3.4% in patients and 15-16.5% in controls. Calandro *et al*[12] reported that 80% of 56 patients in the USA were homozygous for the C282Y mutation. Therefore, C282Y is an excellent marker for the disease, whether or not HLA-H is confirmed to be the haemochromatosis gene. What role, if any, H63D plays in haemochromatosis remains to be established.

We have analysed 5956 chromosomes for these mutations, in order to ascertain the relationship between their prevalence and that of the disease in populations with different frequencies of haemochromatosis.

Methods

The origin of DNA samples is shown in the footnotes to table 1. All populations screened were anonymous to the authors. The two regions of the HLA-H gene containing the proposed mutations were amplified by PCR[8] before restriction fragment length polymorphism (RFLP) analysis. For both PCR products, primers were designed to include an internal restriction enzyme site in the product, to act as a control for complete digestion. Both

PCR reactions were performed using an annealing temperature of 58°C.

For the H63D mutation, the following primers gave a product of 294 bp: H63DF: 5' ACA TGG TTA AGG CCT GTT GC; H63DR: 5' CTT GCT GTG GTT GTG ATT TTC C. Following digestion with *Mbo*I, those products carrying the mutation gave restriction fragments of 237 and 57 bp, while fragments lacking the mutation contained an extra *Mbo*I site and gave restriction fragments of 138, 99, and 57 bp.

For the C282Y mutation, the following primers gave a product of 343 bp: C282YF: 5' CAA GTG CCT CCT TTG GTG AAG GTG ACA CAT; C282YR: 5' CTC AGG CAC TCC TCT CAA CC. Following digestion with *Rsa*I, those fragments containing the mutation carried an additional *Rsa*I site, resulting in products of 203, 111, and 29 bp, whereas those

Table 1 Genotype frequencies for mutations in HLA-H

Population	*Total No*	*HH/CC*	*HD/CC*	*DD/CC*	*HH/CY*	*HD/CY*	*HH/YY*	*H63D allele frequency (%, ±95% CI)*	*C282Y allele frequency (%, ±95% CI)*
Europe									
British									
*UK	368	249	77	0	28	12	2	12.1 (±2.4)	6.0 (±1.8)
†Irish	45	23	13	0	5	4	0	18.9 (±8.3)	10 (±6.3)
Total British	413	272	90	0	33	16	2	12.8 (±2.3)	6.4 (±1.7)
‡Icelanders	90	63	14	1	9	3	0	10.6 (±4.6)	6.7 (±3.7)
‡Norwegians	94	63	17	2	12	0	0	11.2 (±4.6)	6.4 (±3.6)
Former USSR									
†Mekhelta Highlands	63	50	10	1	2	0	0	9.5 (±5.2)	1.6 (±2.2)
†Mekhelta Lowlands	45	38	6	0	1	0	0	6.7 (±5.3)	1.1 (±2.2)
Total Mekhelta	108	88	16	1	3	0	0	8.3 (±3.8)	1.4 (±1.6)
†Udmurts	46	33	12	1	0	0	0	15.2 (±7.5)	0 (+3.2)
Total Former USSR	154	121	28	2	3	0	0	10.4 (±3.5)	1.0 (±1.1)
†Finns	38	29	9	0	0	0	0	11.8 (±7.4)	0 (+3.8)
†Danes	37	23	6	1	6	1	0	12.2 (±7.6)	9.5 (±6.8)
†Netherlanders	39	17	18	2	1	1	0	29.5 (±10.3)	2.6 (±3.6)
†Germans	53	36	11	4	1	1	0	18.9 (±7.6)	1.9 (±2.7)
†Bavarians	62	41	14	0	7	0	0	11.3 (±5.7)	5.6 (±4.1)
Total Germans	115	77	25	4	8	1	0	14.8 (±4.7)	3.9 (±2.6)
†Ashkenazi Jews	35	29	6	0	0	0	0	8.6 (±8.4)	0 (+4.1)
‖ Italians	91	69	19	2	1	0	0	12.6 (±4.9)	0.5 (±1.0)
†§Greeks	139	105	25	4	5	0	0	11.9 (±3.9)	1.4 (±1.4)
§Greek Cypriots	57	39	16	2	0	0	0	17.5 (±7.1)	0 (+2.6)
Total Greeks	196	144	41	6	5	0	0	13.5 (±3.5)	1.3 (±1.1)
†Turks	31	21	9	1	0	0	0	17.7 (±9.7)	0 (+4.6)
§Turkish Cypriots	39	32	6	1	0	0	0	10.3 (±6.9)	0 (+3.7)
Total Turks	70	53	15	2	0	0	0	13.6 (±5.8)	0 (+2.1)
Spanish									
†Basques	28	14	7	5	2	0	0	30.4 (±12.3)	3.6 (±5.0)
†Catalans	50	27	18	2	1	2	0	24.0 (±8.5)	3.0 (±3.4)
Total Spanish	78	41	25	7	3	2	0	26.3 (±7.0)	3.2 (±2.8)
Total Europe	1450	1001	313	29	81	24	2	13.6 (±1.3)	3.8 (±0.7)
Africa/Middle East									
‖ Saudi Arabians	118	98	20	0	0	0	0	8.5 (±3.6)	0 (+1.3)
¶Gambians	39	38	1	0	0	0	0	1.3 (±2.6)	0 (+3.7)
†Senegalese	130	130	0	0	0	0	0	0 (+1.1)	0 (+1.1)
‖ Kenyans	78	76	2	0	0	0	0	1.3 (±1.8)	0 (+1.9)
†Nigerians	80	77	3	0	0	0	0	1.9 (±2.2)	0 (+1.8)
**Zambians	76	75	1	0	0	0	0	0.7 (±1.4)	0 (+1.9)
Total Africa/Middle East	521	494	27	0	0	0	0	2.6 (±1.0)	0 (+0.3)
Indian subcontinent									
§Sri Lankans	109	90	18	1	0	0	0	9.2 (±3.9)	0 (+1.4)
§Indians/Pakistanis	106	89	16	0	1	0	0	7.5 (±3.6)	0.5 (±1.0)
Total Indian subcontinent	215	179	34	1	1	0	0	8.4 (±2.7)	0.2 (±0.4)
Asia									
†§Hong Kong Chinese	72	68	4	0	0	0	0	2.8 (±2.7)	0 (+2.0)
†Taiwanese Aboriginals	80	80	0	0	0	0	0	0 (+1.8)	0 (+1.8)
†Indonesians	90	85	5	0	0	0	0	2.8 (±2.5)	0 (+1.6)
Total Asia	242	233	9	0	0	0	0	1.9 (±1.2)	0 (+0.6)
Australasia									
Papua New Guineans									
¶Highlands	41	41	0	0	0	0	0	0 (+3.5)	0 (+3.5)
¶Lowlands	98	98	0	0	0	0	0	0 (+1.5)	0 (+1.5)
Total Papua New Guinea	139	139	0	0	0	0	0	0 (+1.1)	0 (+1.1)
†Australian Aboriginals	93	93	0	0	0	0	0	0 (+1.6)	0 (+1.6)
‖ Vanuatuans	90	89	1	0	0	0	0	0.6 (±1.2)	0 (+1.6)
Total Australasia	322	321	1	0	0	0	0	0.2 (±0.9)	0 (+0.5)
Americas									
†Mexicans	54	47	7	0	0	0	0	6.5 (±4.7)	0 (2.7)
‖ Jamaicans	90	84	4	0	2	0	0	2.2 (±2.2)	1.1 (±1.6)
†Columbians	47	47	0	0	0	0	0	0 (+3.1)	0 (+3.1)
†Vancouver Island Indians	37	35	1	0	1	0	0	1.4 (±2.7)	1.4 (±2.7)
Total Americas	228	213	12	0	3	0	0	2.6 (±1.5)	0.7 (±0.8)
Total	2978	2441	396	30	85	24	2	8.1 (±0.7)	1.9 (±0.4)

H63D allele frequencies significantly greater in Europe than in Africa/Middle East ($p<0.0001$), Indian subcontinent ($p=0.0025$), Asia ($p<0.0001$), Australasia ($p<0.0001$), and Americas ($p<0.0001$) (χ^2 test).

C282Y frequencies significantly greater in Europe than in in Africa/Middle East ($p<0.0001$), Indian subcontinent ($p<0.0001$), Asia ($p<0.0001$), Australasia ($p<0.0001$), and Americas ($p=0.0006$) (χ^2 test).

Origins of samples: *=family studies of collagen disorders and polycystic kidney disease; †=anthropological community based surveys; ‡=blood donors; §=referrals for diagnosis of haemoglobinopathies; ‖ =community based surveys of haemoglobinopathies; ¶=community based malarial survey; **=neonatal survey of haemoglobinopathies.

Genotypes are given for amino acid 63 (H63D)/amino acid 282 (C282Y) of the polypeptide (C = cysteine, D = aspartic acid, H = histidine, Y = tyrosine). CC/HH is normal (wild type). The combinations DD/CY, DD/YY, and HD/YY were not found.

lacking the mutation yielded products of 203 and 140 bp.

Ninety-five percent confidence intervals were calculated assuming a binomial distribution, and χ^2 analysis was performed using Statview 4.1 (Abacus Concepts Inc, Berkeley, CA, USA).

Results

Results are shown in table 1. A total of 2900 European chromosomes was analysed and the C282Y and H63D mutations were observed at frequencies of 3.8% and 13.6%, respectively.

The H63D mutation was present in all European populations included in the study, at allele frequencies greater than 6%, and in Saudi Arabian, Indian Asian, and Mexican populations at 8.5%, 8.4%, and 6.5% respectively. It was present at lower frequencies in Africans, Asians, and native Americans, and was not found in Colombians, most Australasians (except a single Vanuatuan), Taiwanese Aboriginals, or Senegalese.

The C282Y mutation was found in all European populations studied except Udmurts, Ashkenazi Jews, Finns, Greek Cypriots, and Turkish Cypriots, and, with the exception of one Indian heterozygote and two Jamaican heterozygotes, was absent from all other populations. The highest allele frequencies were found in the UK (6.4% overall, including 10% in Irish chromosomes), Danes (9.6%), Icelanders (6.7%), Norwegians (6.4%), and Bavarians (5.6%).

Discussion

Feder *et al*[8] suggested that the H63D mutation increases the risk of haemochromatosis for C282Y heterozygotes, and that compound heterozygotes have a low penetrance iron storage disease. The UK Haemochromatosis Consortium (submitted for publication) found that three of 115 patients were compound heterozygotes suffering from mild disease, and four of 101 control subjects were compound heterozygotes who showed no signs of iron loading. In the present study, we have found a frequency of compound heterozygotes in the UK, Denmark, Iceland, and the Netherlands of approximately 1/30, which is much higher than previous estimates of haemochromatosis frequency. Therefore, if enhanced risk of disease exists for this genotype, our data support the hypothesis that it is low penetrance. An alternative explanation of the variation in the phenotype of compound heterozygotes is that the H63D polymorphism may be associated with more than one haplotype, only one of which carries a second mutation causing haemochromatosis. We have found high H63D frequencies in populations not previously reported to suffer from haemochromatosis. This finding sheds doubt on the significance of the mutation in this disease, and indicates that it is unlikely to be implicated independently of another mutation.

The C282Y mutation was most prevalent in north European populations, and absent from 3056 non-European chromosomes studied except for three chromosomes (one Indian and two Jamaican). These results strongly suggest that the mutation originated in northern Europe, which is where haemochromatosis is generally accepted to have arisen. Simon *et al*[13 14] have postulated that the geographical distribution of haemochromatosis is similar to the migration pattern of Celtic peoples, and Smith *et al*[15] concluded that there was a significantly higher prevalence of haemochromatosis in Americans of British/Irish descent compared with that of Americans of other Caucasian descent. The distribution of the C282Y mutation is therefore similar to that of haemochromatosis. The presence of the allele in Indian and Jamaican populations at trace levels may be because of admixture with Europeans in the history of these peoples.

The high percentage of C282Y heterozygotes found in north European populations indicates homozygote frequencies of 1/100 in Ireland, 1/278 in the rest of the UK (we found 2/368 = 1/184), 1/111 in Denmark, 1/223 in Iceland, and 1/244 in Norway. A previous estimate of the haemochromatosis frequency in Denmark is 1/217-1/270,[7] considerably lower than our extrapolated frequency of 1/111. This discrepancy may have arisen because of the small sample number of 37 Danes included in the present study, or may indicate that a large number of Danish haemochromatotics are undiagnosed. A haemochromatosis frequency of 1/270 indicates an allele frequency of 6.1%, which is within our 95% confidence limits.

These observed allele frequencies are comparable with previous estimates of haemochromatosis frequencies in populations of north European origin of 1/200-1/300 in predominantly Caucasian Australians,[6] French Bretons,[3] Swedes (Jutlanders),[4] and North Americans.[5] Low frequencies have previously been observed in Finns,[16] who are known to differ genetically from other north European populations,[17] and our findings are consistent with this.

Haemochromatosis has not been confirmed in those populations lacking the C282Y mutation. There have been isolated reports of non-chromosome 6 linked iron overload in a Chinese woman,[18] in a Melanesian kindred,[19] and many accounts of African siderosis.[20-24] This condition was first recognised in the Bantu tribe of southern Africa. Bantu siderosis may be distinguished from haemochromatosis in that the levels of iron deposited in the liver and bone marrow are comparable in siderosis, but in haemochromatosis, the liver is the major site of iron storage.[23] An additional example of non-chromosome 6 linked hyperferritinaemia with normal serum iron has recently been described in overweight French subjects.[25] There have also been reports of a hereditary hyperferritinaemia in France and Italy which is associated with a congenital cataract condition, in which raised serum ferritin is not related to iron overload.[26 27] It is important not to confuse haemochromatosis with other iron overload disorders. In 1965, a world study of haemochromatosis distribution concluded that the highest incidence of haemochromatosis occurred in Africans of the Bantu tribe, while the

lowest frequencies were observed among the English and Scandinavians.[28] However, with the benefit of 30 years of research, notably the discovery of linkage to the MHC region on chromosome 6 (6p21.3)[29] and the identification of a candidate gene,[8] it is now clear that the converse is true.

Other conditions and mutations for which a Celtic or North European origin has been implicated are described in references 30-38. Asthma affects 1/7 children in the UK, and a genome screen has recently established linkage to the marker D6S276,[39] 2 Mb from HLA-H on chromosome 6 (6p22.1). It is conceivable that an HLA mutation may be involved in asthma, and given the high frequency of H63D in north European populations, the possibility of such an association should not be ignored.

We have identified several northern European populations in which there is a high incidence of the C282Y mutation, an excellent marker for the haemochromatosis gene. We suggest that it is now important to initiate a genetic screening programme followed by measurements of transferrin saturation and hepatic iron index in homozygotes, to confirm the nature and severity of the disease, and to implement therapeutic phlebotomy where appropriate. This approach is financially advantageous[40] and will be a major advance in preventative health care.

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