

# DISTRIBUTION OF HFE ALLELES AND HLA/HFE HAPLOTYPES

## IN BLOOD DONORS RESIDENT IN WALES

WELSH BLOOD SERVICE  
GWASANAETH GWAED CYMRU

WELSH TRANSPLANTATION AND  
IMMUNOGENETICS LABORATORY



C DARKE, M G GUTTRIDGE,  
K CARTER, S McNAMARA,  
J A F NAPIER AND M WORWOOD

HFE frequencies in relation to age, gender and place of residence

There were no significant differences ( $p > 0.05$ ) between the frequency of donor alleles/genotypes between subgroups divided on the basis of: gender, age (<31, >30 <51 and >51 years of age), age and gender combined; area of residence, based on major Welsh postcodes (over 95% of donors resided in South Wales: Swansea-13.3%, Cardiff-65.2%, Newport-16.7%, postcode areas).

All donor subgroups conformed to Hardy-Weinberg equilibrium and the expected proportion of homozygotes (all  $p$  values  $> 0.1$ ).

### HLA-B, HLA-A and HFE haplotypes

A total of 1,707 donors (16.2% of the study group) were, by chance, HLA-A,B,DR,DQ typed for the Welsh Bone Marrow Donor Registry.

Linkage disequilibrium ( $\chi^2$  value) and haplotype frequency (HF) estimates between HLA-A, B and HFE alleles showed significant ( $p$  corrected  $< 0.0001$ ) two-locus associations between:

| Haplotype     | HF    | $\chi^2$ value |
|---------------|-------|----------------|
| HLA-A1 HFE-1  | 0.176 | 0.028          |
| HLA-A25 HFE-2 | 0.011 | 0.008          |
| HLA-A29 HFE-2 | 0.020 | 0.012          |
| HLA-A3 HFE-3  | 0.036 | 0.026          |

In addition, B8/A1/HFE-1, B44/A29/HFE-2 and B7/A3/HFE-3 were shown to be the primary HFE-1,-2 and -3 bearing haplotypes:

| Haplotype         | HF    | $\chi^2$ value |
|-------------------|-------|----------------|
| HLA-B8 A1 HFE-1   | 0.107 | 0.084          |
| HLA-B44 A29 HFE-2 | 0.015 | 0.013          |
| HLA-B7 A3 HFE-3   | 0.021 | 0.019          |

### Comment

The number of donors identified as homozygous for the HFE-3 allele indicates that his haemochromatosis-associated genotype occurs at a rate of about 1 in 150 of the blood donor population in South Wales.

HFE-3 homozygotes were confirmed in all cases by repeat testing using PCR-SSP and heteroduplex analysis with original and subsequent samples.

No evidence was found for the theoretical HFE-4 allele possessing both mutations, i.e., there were no examples of subjects possessing both H63D and C282Y mutations in cis or lacking both H63 and C282.

The validity of our results was supported by the excellent goodness-of-fit to the expected phenotype distribution and the number of likely HFE homozygotes.

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Compiled by L Lane

### Introduction

Haemochromatosis is an autosomal recessive disorder common in northern European Caucasoids. The disease develops due to an increase in iron absorption leading to iron overload. HFE genes located on chromosome 6p22 and possessing C282Y or H63D mutations are closely associated with this condition.

As part of a study of HFE mutations and iron status we determined the HFE genotypes of 10,556 consenting blood donors (5,086-48.18% males and 5,470-51.82% females) living in Wales.

### Methods

The C282Y and H63D mutations were determined by PCR using sequence-specific primers (PCR-SSP). The routine assay, which employs four PCR-SSP amplifications, was supplemented with additional primers to identify the two mutations in cis (Guttridge et al. (1988) Vox Sang, 75, 258).

### HFE Frequencies

The frequencies of the HFE-1 (lacking both H63D and C282Y mutations), HFE-2 (possessing the H63D mutation) and HFE-3 (possessing the C282Y mutation) alleles were:

HFE-1 - 76.42% HFE-2 - 15.34% HFE-3 - 8.24% (Table 1)

Table 1. HFE frequencies

| Allele | No. with allele | Pheno-type freq (%) | Pheno-type freq | Gene freq. <sup>a</sup> | SE of GF <sup>b</sup> | No. of homozygotes |
|--------|-----------------|---------------------|-----------------|-------------------------|-----------------------|--------------------|
| HFE-1  | 9982            | 94.6                | 0.94562         | 0.76421                 | 0.00473               | 6152               |
| HFE-2  | 2990            | 28.3                | 0.28325         | 0.15342                 | 0.00259               | 249                |
| HFE-3  | 1667            | 15.8                | 0.15792         | 0.08237                 | 0.00193               | 72                 |

<sup>a</sup> By direct counting

<sup>b</sup> Standard Error of gene frequency

Seventy-two donors were homozygous for the HFE-3 allele (1 in 147), 1,595 were HFE-3 heterozygous (1 in 6.6), including 253 (1 in 42) who were HFE-2, 3 heterozygotes.

### Hardy-Weinberg and homozygosity analysis

The observed numbers of the 6 HFE genotypes showed a good fit to Hardy-Weinberg equilibrium ( $p > 0.8$ ) and the proportion of homozygous subjects was as expected ( $p > 0.7$ ).