MOLECULAR, SEROLOGICAL AND GENETIC STUDIES ON TWO NEW HLA-DRB1 ALLELES - DRB1*0704 AND DRB1*1507

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Introduction

During routine HLA-A,B,C,DR,DQ typing by PCR-SSP of blood donors for the Welsh Bone Marrow Donors Registry (WBMDR) we encountered two Caucasoid subjects with the following HLA-Class II phenotypes:

ROS - HLA-DRB1*03, 'blank'; DRB3*; DRB4*; DQB1*02, DQB1*03

LJM - HLA-DRB1*0701, 'blank'; DRB4*; DRB5*; DQB1*06, DQB1*03

Serological HLA-A, B, DR Typing

In view of the unexpected DRB4* gene and DQB1*03 allele in ROS and the DRB5* gene and DQB1*06 allele in LJM both donors were typed by classical serology using our routine HLA-A,B,DR,DQ typing trays.

Serological typing confirmed the PCR-SSP derived phenotypes but in addition unambiguously assigned ROS as DR7 positive (temporarily termed DR7ROS) and LJM as DR15 positive (DR15LJM). These further specificities were compatible with the unexpected DRB3/4 and DQB1 genes in both donors.

Nucleotide sequencing

Nucleotide sequencing of exon 2 of DR7ROS and DR15LJM was undertaken using the ABI Prism Cycle Sequencing Ready Reaction Kit on templates prepared in duplicate and analysed on the ABI 373 DNA Sequencer. This showed that:

DRB1*07ROS (subsequently named DRB1*0704) differed from DRB1*0701 by five consecutive nucleotides at positions 217 to 221 of exon 2 encoding two amino acids substitutions of tyrosine to asparagine at codon 77 and valine to tyrosine at codon 78.

DRB1*15LJM (DRB1*1507) differed from DRB1*1501 by a single nucleotide at position 127 encoding an amino acid substitution of phenylalanine to tyrosine at codon 47 (Figure 1).

HLA-DRB1*0704 bearing haplotype

Family studies indicated that DRB1*0704 was present on the haplotype:

HLA-A*01; B*57; Cw*0602; DRB1*0704; DRB4*0103102N; DQA1*0201; DQB1*0303; C4A6; C4B1 (DPA1, DPB1 and Bf were not able to be delineated).

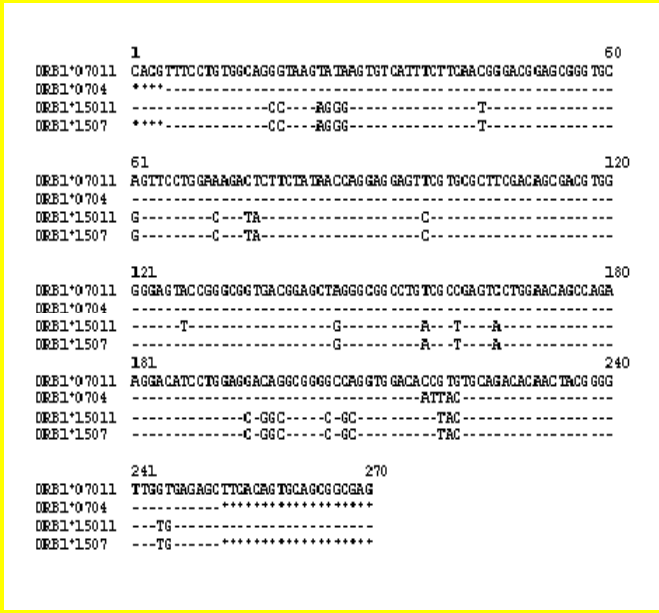

Figure 1. Nucleotide sequence of HLA-DRB1*0704, DRB1*15011, and DRB1*1507 alligned against DRB1*07011. Dashes indicate identity with DRB1*07011; stars denote undefined bases.

HLA-DRB1*1507 bearing haplotype

A family study of LJM was not possible. However, local linkage disequilibrium data indicated that the likely DRB1*1507 bearing haplotype was:

HLA-A*2601; B*27052; Cw*0704/11/12; DRB1*1507; DQA1*0102; DQB1*0602; DPA1*0103/05; DPB1*0401; BfS; C4A3; C4B1.

Frequency of HLA-DRB1*0704 and DRB1*1507

The HLA-assignment of DRB1 alleles was reviewed in 19,113 PCR-SSP DR and DQ typed donors from the WBMDR. No further examples of DRB1*0704 or DRB1*1507 were found.

Correction was made for the inability to detect DRB1*0704 with DRB1*04, DRB1*07 and DRB1*09 and DRB1*1507 with DRB1*15 or DRB1*16.

These data (n=17,863 for DRB1*0704 and n=18,704 for DRB1*1507) indicated that both DRB1*0704 and DRB1*1507 have a phenotype frequency of < 0.01% and a gene frequency of < 0.00003 in the WBMDR panel consisting predominately of Northern European Caucasoids residing in Wales.

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