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The identification of a new HLA-DPB1 allele (*1302) in one family and the detection of a recombination event between the DR and the DQ regions in another Caucasian T1DGC family

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Abstract

The analysis of families collected by the T1DGC and typed at high resolution for the HLA class I and class II loci provided an opportunity for identifying new alleles and rare recombination events. In one American Caucasian family, a novel allele (HLA-DPB1*1302), detected as an unusual pattern of probe binding, was identified in the mother and in one child. Amplicons from both individuals were sequenced and a new variant of DPB1*1301 with an A->T mutation [TAC to TTC in codon 64, (amino acid 35); Y to F] was confirmed. In another American Caucasian family, one child inherited an unusual haplotype, DRB1*1501-DQA1*0102-DQB1*0609-DPA1*0103-DPB1*0601 resulting from a recombination between the DRB1 loci on the maternal chromosomes DRB1*1501-DQA1*0102-DQB1*0602-DPA1*0103-DPB1*0401 and DRB1*1302-DQA1*0102-DQB1*0609-DPA1*0103-DPB1*0601.

Keywords

HLA-DPB1; SSOP linear array assay; Mendelian inheritance; recombination event

In an international effort to study the genetics of type 1 diabetes, a new human leukocyte antigen (HLA)-DPB1 allele was identified in an American Caucasian family using a polymerase chain reaction (PCR)-based, DPA1-DPB1 co-amplification, SSOP linear array assay. The DPA1/DPB1 co-amplification assay is composed of a primer pair for each locus and 69 probes in a linear array format. Based on probe reactivity patterns, the *SCORE* and *STRIPSCAN* genotyping software could not assign a genotype to the mother. *STRIPSCAN* indicated 'possible new allele'. The closest assignment was DPB1*0601, 1301, with a difference of two probe reactivities. Because DPB1*0601 segregated within the family in normal Mendelian fashion, we concluded that the mother's genotype included the DPB1*0601 allele as well as a new DPB1*1301-related allele. The putative new allele differed from

DPB1*1301 by a positive probe signal for the EEFARF motif at protein position 33 and a very weak to negative signal for the EEYARF motif. The software interpreted the probe pattern of child 5 as *1301, *9001, but this observed probe pattern was also consistent with DPB1*0101 and the putative new *1301-related allele. Because the DPB1*9001 allele is very rare and was not present in either parent (deviation from Mendelian inheritance), we inferred that the child had inherited the new *1301-related allele from the mother and a DPB1*0101 allele from the father. Amplicons from both individuals were sequenced using the ABI 3730 sequencer, and a new variant of DPB1*1301 with an A→T mutation (TAC to TTC in codon 64; Y to F) was confirmed (see Fig. 1). The new DPB1 allele was probably generated from DPB1*1301 by a point mutation or an interallelic gene conversion event with an EEFARF-motif-containing allele. The Mendelian inheritance pattern, coupled with the knowledge of HLA allele frequencies, played a significant role in the identification of this new allele. This new allele has subsequently been termed DPB1*1302 by the World Health Organization (WHO) Nomenclature Committee.

A recombination event in an American Caucasian family from the Type 1 Diabetes Genetics Consortium (T1DGC) study was also observed producing a rare DRB1*1501-DQA1*0102-DQB1*0609-DPA1*0103-DPB1*0601 haplotype. The unusual haplotype in child #4009403 suggests a DR-DQ crossover between the two maternal chromosomes DRB1*1501-DQA1*0102-DQB1*0602-DPA1*0103-DPB1*0401 and DRB1*1302-DQA1*0102-DQB1*0609-DPA1*0103-DPB1*0601. It cannot be formally determined whether the crossover was between DRB1 and DQA1 or between DQA1 and DQB1 (because both maternal haplotypes were DQA1*0102) but between DRB1 and DQA1 is more likely given the much greater physical distance.

The name listed for this DPB1-1302 sequence has been officially assigned by the WHO Nomenclature Committee. This follows the agreed policy that, subject to the conditions stated in the most recent Nomenclature report (1), names will be assigned to new sequences as they are identified. Lists of such new names will be published in the following WHO Nomenclature report.

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References

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Prot Position      10      15      20
Nuc. Position
DPB1*010101      105      120      135      150
AG AAT TAC GTG TAC CAG GGA CGG CAG GAA TGC TAC GCG TTT AAT GGG ACA
DPB1*0902      --- --- --- --- --- TT- --- --- --- --- --- --- --- ---
DPB1*1301      --- --- --- --- --- TT- --- --- --- --- --- --- --- ---
DPB1*1302      --- --- --- --- --- TT- --- --- --- --- --- --- --- ---

Prot Position      25      30      35      40      45      225
Nuc. Position
DPB1*010101      CAG CGC TTC CTG GAG AGA TAC ATC TAC AAC CGG GAG GAG TAC GCG CGC TTC GAC AGC GAC GTG GGG GAG TTC CGG
DPB1*0902      --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
DPB1*1301      --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
DPB1*1302      --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---

Prot Position      50      55      60      65      70      300
Nuc. Position
DPB1*010101      GCG GTG ACG GAG CTG GGG CGG CCT GCT GCG GAG TAC TGG AAC AGC CAG AAG GAC ATC CTG GAG GAG AAG CGG GCA
DPB1*0902      --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
DPB1*1301      --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
DPB1*1302      --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---

Prot Position      75      80      85      90      360
Nuc. Position
DPB1*010101      GTG CCG GAC AGG GTA TGC AGA CAC AAC TAC GAG CTG GAC GAG GCC GTG ACC CTG CAG CGC CGA G
DPB1*0902      --- --- --- --- A- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
DPB1*1301      --- --- --- --- A- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
DPB1*1302      --- --- --- --- A- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---

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Figure 1.

Alignment of the exon 2 sequence of the novel human leukocyte antigen-DPB1*1302 allele compared with the DPB1*0902 and the DPB1*1301 alleles. The new DPB1*1302 allele differs from the DPB1*0902 and the DPB1*1301 alleles only at nucleotide position 191 (A→T mutation boxed). Dashes indicate identity with the consensus sequence. (The genotyping software was not updated with the relatively new DPB1*0902 allele when the new DPB1*1302 allele was identified).