DRB1*13:13 allele has a structure similar to that of the DRB1*08 group

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Abstract

Purpose: The DRB1*13:13 allele is thought to have an unusual structure. We have extended the sequence information to help elucidate the gene structure.

Results: The DNA sequence for DRB1*13:13 has been scant. A more complete sequence derived here confirms the unusual structure for a DR13 allele. The early part of the gene has a typical DR13 (DR52) structure. After codon 70 (exon 2), the sequence switches to a DR8-DRB3 like sequence.

Introduction

Previous work (Kotsch and Blasczyk, 2000) has shown that a DRB1*13:13 haplotype does not have an associated DRB3 gene and lacks the DRB2 pseudogene suggesting a regional structure like that of the DR8 haplotype. For HLA typing purposes we wished to extend the known sequence for this allele. Using probe-based hybrid capture and subsequent sequencing of genomic fragments from cell line TER269 (XX406) a DNA sequence for DRB1*13:13 was assembled using TypeStream Visual (TSV) software.

The DRB1*13:13 allele sequence has been extended to include exon 1 and the surrounding region. This sequence is similar to other DRB1*13 alleles. A contiguous sequence from the end of intron 1 to the beginning of the 3'UTR shows that the sequence up to codon 70 of exon 2 is identical to that of DRB1*13:03:01:01. From codon 71 of exon 2 to the end of the sequence (approximately nucleotide 97 of the 3'UTR) is identical to that of DRB1*08:03:02:02.

The DR8 haplotype has been hypothesized to result from a genetic contraction (our estimated deletion of 63.7 kb) between DRB1*12 and DRB3 (Svensson et al., 1996).

The exact mechanism to generate DRB1*13:13 remains open whether by gene conversion using the DR8 haplotype as template or by independent regional contraction between DRB1*13 and DRB3. However, the existence of this allele sequence raises the possibility that other alleles associated with the DR52 supergroup may also lack a DRB3 gene. This will have implications regarding exact HLA typing and matching.

For HLA typing purposes we wished to extend the known sequence for this allele.

Materials and Methods

Sample Preparation

DNA from the TER269 cell line (One Lambda collection) was harvested for sequencing using standard genomic DNA collection techniques.

Method

Probe based hybrid capture of targeted genomic DNA fragments were sequenced (outlined in poster by H.O. Lopez et al.)

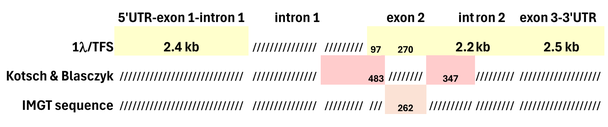
Data Analysis

TypeStream Visual Software (TSV™, ThermoFisher Scientific) was used to assemble the DNA sequence.

Results

Sequence information of DRB1*13:13 has been expanded to include over half of the predicted 14kb sequence. All of the coding regions are included.

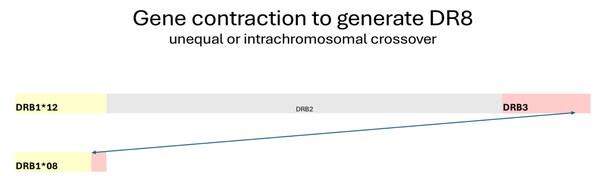
Figure 1. Comparison of the sequences for DRB1*13:13



As shown in Figure 1, the IMGT sequence contains only most of exon 2; The Kotsch and Blasczyk sequence contains the intron region around exon 2. The sequence derived at One Lambda/ThermoFisher includes all of the exons, some UTR sequences, introns 2-5, and a large portion of intron 1.

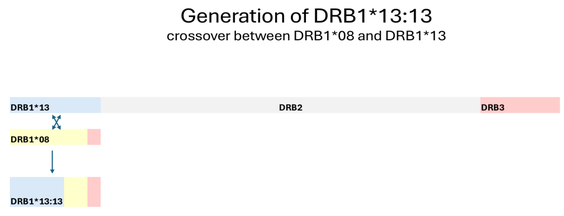
Hash marks represent unsequenced regions. We will complete the sequence of intron 1 in the near future. Thus far the sequence indicates that the late region of the gene has sequence identical to DRB1*08:03:02:02, which is known to be similar to DRB3 downstream from intron 3.

Figure 2. Mechanism to generate DRB1*08



An unequal crossover between chromosomes or an intrachromosomal crossover between homologous regions leads to loss of sequence. Here a DRB1*08 could be generated by fusion of the latter part of DRB3 to the earlier part of DRB1*12. (Andersson et al.)

Figure 3. Mechanism to generate DRB1*13:13



A reciprocal crossover between a DRB1*13 allele and a DRB1*08 allele in the late part of exon 2 could generate a DRB1*13 allele with no association to DRB3 (Kotsch and Blasczyk).

Conclusions

- Our increased coverage of the DRB1*13:13 sequence confirms that this DR13 allele contains a large portion of DRB1*08 sequence. This is not a unique event as a recently identified distinct sequence (Planelles,D. and Rodriguez-Cebria,M., 2024, GenBank: PP502395) shows a similar structure.
- The process to generate DRB1*13:13 suggests a reciprocal product having a DRB1*08 allele associated with a DRB3 may exist. DRB1*08:77 could be an example of this.
- Well-established locus associations in the DRB region of the MHC are becoming more variable. High resolution typing may require testing for each locus rather than relying on established associations.

References

1. Andersson, G. etal. Immunogenetics 28:1-5, 1988.
2. Kotsch, K. and Blasczyk, R. J. of Immunology 165:5664-5670 (2000)
3. Lopez, H. O. et al. ASHI 2024 poster session "Multi-Center Evaluation of 19 Loci Hybrid Capture NGS Assay on Illumina Instruments"

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