

**OPTN Histocompatibility Committee
Meeting Summary
August 30, 2021
Conference Call**

**Peter Lalli, Ph.D., D(ABHI), Chair
John Lunz, Ph.D., D(ABHI), Vice Chair**

Introduction

The Histocompatibility Committee met via Citrix GoToMeeting teleconference on 08/30/2021 to discuss the following agenda items:

1. Null Alleles
2. DQA1 Combined Alleles
3. DPB1 Frequencies

The following is a summary of the Committee's discussions.

1. Null Alleles

Committee leadership and UNOS staff presented on one question with the NMDP data set proposed to be used to calculate CPRA genotype frequencies.

Data summary:

- NMDP requires all null alleles to be distinguished (as of CIWD 3.0.0) except for A*11:69, A*24:132, A*68:11
 - None of these are reportable within the UNet systems for donor, candidate, or recipient typings
- These null alleles occur with a frequency of less 4 times in a data set of 16,099,561 in CIWD 3.0.0, meaning they would add a maximum of 0.000000019 CPRA points each to combined alleles
 - Lung has proposed that continuous distribution use 6-7 decimal places
- Question to the committee: Are there any concerns about leaving any typings in the data set that may contain these rarer null alleles?

Summary of discussion:

Members expressed no concerns about leaving the extremely rare null alleles in the data set, especially as they are not selectable for donor typings or unacceptable antigens.

2. DQA1 Combined Alleles

Data summary:

There are about 590,000 DQA1 typings in NMDP data set, and labs are not required for to type for DQA1 for donor recruitment typings.

The NMDP data set would have the following alleles combined due to typing at only exons 2/3:

| 1st allele in group | All ECD-combined alleles | Location of difference | Portion of protein |
|---------------------|--------------------------|---|--|
| 01:02 | 01:02, 01:11 | Exon 4, peptide 186 | Transmembrane region/Cytoplasmic tail |
| 01:01 | 01:01, 01:04, 01:05 | Exon 1, peptide -4; Exon 4, peptide 199 | Leader sequence, Transmembrane Region/Cytoplasmic tail |
| 03:02 | 03:02, 03:03 | Exon 1, peptide -6 | Leader sequence |
| 05:01 | 05:01, 05:05, 05:11 | Exon 1, peptide -13; Exon 4, peptides 171 and 200 | Leader sequence, Transmembrane Region/Cytoplasmic tail |
| 05:03 | 05:03, 05:07 | Exon 4, peptide 207 | Transmembrane region/Cytoplasmic tail |

Questions to committee: Is there clinical evidence or theory supporting differences in the leader sequence, transmembrane region, or cytoplasmic tail influencing antibody formation or recognition?

- Do we want to combine these extracellular domain equivalent alleles in the HLA equivalency tables for unacceptable antigen screening? Or do we want the CPRA equivalences and unacceptable antigen equivalences to be separate?

Summary of discussion:

Committee members agreed that these alleles may be selected separately infrequently, but in some cases a patient may be able to form an antibody to one and not the other. One committee member brought forward the example of DQA1*01:04 and 01:05, where due to their true alignment a portion of the extracellular domain is within exon 1, and while it's not distinguishable in this typing method it's clinically important for patients. Members agreed that removing these as separate unacceptable antigens may disadvantage some patients, and that removing them for the purpose of consistency with CPRA would not align with clinical practice.

Members agreed that in the cases discussed, CPRA equivalences and unacceptable antigen equivalences should be separate, until such a time the data allows for these alleles that are currently combined to be independent frequencies.

3. DPB1 Frequencies

Data summary:

Twenty eight instances of the DPB1s being combined in NMDP data set are already combined for donor screening in the OPTN HLA equivalency tables, with an exception of DPB1*105:01. The NMDP data set combines 105:01 with 665:01, 1072:01, and 1171:01. All of the alleles are in the 04:02 p group equivalency, but 105:01 is also reportable separately as a single unacceptable antigen in UNet, which only screens for itself and not the full p group. There are single antigen beads that contain 105:01 with a DPA1, but the only differences for these alleles are in Exons 1 and 4.

Questions to the committee: For 105:01, do we want to add 665:01, 1072:01, and 1171:01 as equivalences for its standalone unacceptable antigen assignment?

- Would we want to remove it as a separate unacceptable antigen, and only leave it in the 04:02 p group?
- Would we prefer to just have a disclaimer that the frequencies are combined for CPRA but not for unacceptable antigen screening?

Summary of discussion:

The CPRA contractor clarified that there were more DPB1 alleles that would be discrepant between the two data sets than the one identified. Members agreed that they needed to know the scope of the discrepancies prior to a full discussion.

Next steps:

UNOS staff will work with CPRA contractor to provide additional information on the scope of the discrepancies to the committee.

Upcoming Meetings

- September 14, 2021, 12 PM EDT, Teleconference
- October 12, 2021, 12 PM EDT, Teleconference

Attendance

- **Committee Members**
 - Amber Carriker
 - Bill Goggins
 - Caroline Alquist
 - Eric Weimer
 - Gerald Morris
 - Idoia Gimferrer
 - Jennifer Schiller
 - John Lunz
 - Karl Schillinger
 - Manu Varma
 - Marcelo Pando
 - Omar Moussa
 - Pete Lalli
 - Reut Hod Dvorai
 - Valia Bravo-Egana
 - Vikram Pattanayak
- **HRSA Representatives**
 - Jim Bowman
 - Marilyn Levi
 - Raelene Skerda
- **SRTR Staff**
 - Katie Audette
- **UNOS Staff**
 - Abby Fox
 - Betsy Gans
 - Courtney Jett
 - Emily Kniepp
 - Kelsi Lindblad
 - Rebecca Murdock
- **Other Attendees**
 - Medhat Askar
 - Loren Gragert