

Instructions for Confirmation of HLA Typing (Form 2005)

This section of the CIBMTR Forms Instruction Manual is intended to be a resource for completing the Confirmation of HLA Typing Form.

E-mail comments regarding the content of the CIBMTR Forms Instruction Manual to: CIBMTRFormsManualComments@nmdp.org. Comments will be considered for future manual updates and revisions. For questions that require an immediate response, please contact your transplant center’s CIBMTR CRC.

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Confirmation of HLA Typing Data

For transplants using an NMDP donor or cord blood unit, the donor’s HLA typing is reported on NMDP Form 22 (Confirmation of Donor HLA Typing) and the recipient’s HLA typing is reported on NMDP Form 117 (Final Recipient HLA Typing).

In all other situations, the Confirmation of HLA Typing form (Form 2005) is used to report HLA typing for both the donor and recipient on the Transplant Essential Data (TED) and comprehensive report form (CRF) tracks. This includes:

- Non-NMDP unrelated donor
- Non-NMDP unrelated cord blood unit
- Related cord blood unit
- HLA matched relative donor
- HLA mismatched relative donor

- Recipient of any of the donor types listed above

A separate Form 2005 should be completed for each recipient, cord blood unit, or non-NMDP donor; however, only the recipient form is required for syngeneic transplants. Both maternal and paternal typing should be submitted, if available, for all mismatched related donor transplants on the CRF track. Additionally, cord blood maternal typing should be submitted, if available, for all unrelated cord blood transplants on the CRF track.

The human immune system recognizes and defends against threats from outside the body. An important component of the immune system is the human leukocyte antigen (HLA) genes. These genes produce proteins, some of which are expressed on the surface of cells. These surface proteins allow cells to recognize self from non-self. Cells with matching proteins are recognized as self and passed over. However, when the proteins do not match between cells, one cell is identified as non-self, and an immune reaction is triggered to destroy it.

If the HLA of a donor and a recipient do not match closely, the immune response could result in the recipient's body attacking the transplanted cells (resulting in graft failure), or the transplanted cells attacking the recipient's body (graft-versus-host disease).

HLA genes are divided into three classes. The two classes that are important in matching donors and recipients are class I (HLA-A, B, C) and class II (includes HLA-DR, DQ). All HLA genes are encoded on an area of chromosome six known as the Major Histocompatibility Complex (MHC).

Finding a good donor-recipient HLA match can be difficult because HLA is highly polymorphic, or variable. It can be completely unique to an individual. Since DNA is inherited from parents, the likelihood of a complete match is greater between full biological siblings than two unrelated individuals. Each individual has two copies of chromosome six (one from each parent). This means that each parent will be a haploidentical (half) match. A full sibling will have a 25% chance of being an identical HLA match, a 25% chance of being completely non-identical, and a 50% chance of being a haploidentical match.

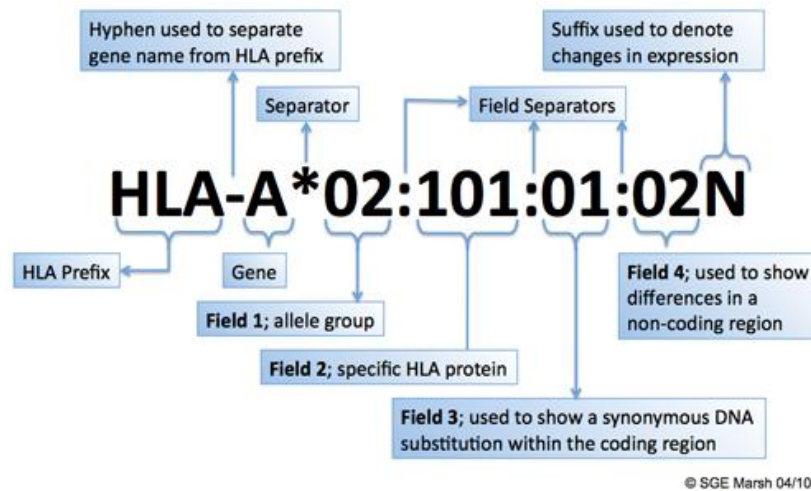
Figure 1. Example of single HLA-A locus inheritance

HLA-A Heredity		Biological Mother	
		HLA-A*01	HLA-A*03
Biological Father	HLA-A*02	01, 02	03, 02

HLA-A*24	01, 24	03, 24
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The nomenclature (naming system) of HLA is an ever-evolving field, with an international committee dedicated to maintaining standards for identifying the genes and their allele sequences. Allele names consist of 3 to 5 parts, depending on what is known about that individual allele.

Figure 2. HLA nomenclature



Anthony Nolan Research Institute. (2010). *HLA Nomenclature*. Web. 04 April 2013.
<http://hla.alleles.org/nomenclature/naming.html>

The HLA prefix will precede the specific HLA locus (gene), which will be separated from allele-specific information by an asterisk. The first field will refer to a broad group of alleles (otherwise known as the “allele family”); this designation will be separated from the next field by a colon. The second field will refer to the specific allele, which yields a specific HLA protein. Third and fourth fields may be specified, but are considered less important since they represent differences at a DNA level, rather than at a level of protein expression, due to a synonymous coding region (exon) or substitution in the non-coding region of the gene (intron). The name may be followed by a letter, which can alter the meaning of the preceding nomenclature. For example, the letter “N” signifies a null allele that does not test serologically.

DNA testing is done at low, intermediate, or high resolution.

Low-resolution testing is equivalent to serologic testing that identifies the allele group as represented by the first field of an HLA name (e.g., HLA-A*02).

Intermediate-resolution testing is molecular testing that may have remaining ambiguities. It reports allele groups that may contain 2 to 100 or more alleles. The nomenclature for these ambiguities is not internationally standardized; it is defined by the reporting lab or organization. NMDP reports frequently include letter sets that refer to possible genotypes within an allele group. Other laboratories may list all possible genotypes (e.g., DRB1*01:01 or 01:02, DRB1*01:01/01:02), where each specified allele is possible at a single locus.

High-resolution testing, or testing at the molecular level, provides further information about the gene itself, including what specific proteins will be expressed by the cells and even differences in sequence that do not impact protein expression. For cellular transplant, matching at the high resolution level is critically important.

Complete this form specifying the recipient or donor HLA *at the level it was typed*.

For a glossary of terms used in this section of the manual, see [Appendix B](#).

Key Fields

Accuracy of the Key Fields is essential for ensuring that:

- Data are being reported for the correct recipient.
- Outcomes data accurately reflects appropriate transplant type and product for each transplant center.
- Data are being shared with the correct donor center, cord blood bank, cooperative registry, or other agency.

The Key Fields precede the form body and are automatically populated in the FormsNet3SM application based on information provided on the CRID Assignment Form 2804. If errors are noted in the key fields, correct Form 2804 and then review it for accuracy. After Form 2804 has been corrected, verify data has been updated on all completed forms. If the data has not been updated automatically, centers will need to reprocess the completed forms to correct the key field data. If errors are noted in key fields for second or subsequent transplants, contact your CRC to make any necessary corrections to the transplant or product type. Transplant and product type will not be automatically populated on product or donor specific forms (Forms 2004, 2005, and 2006) and will need to be manually reported.

Donor/Cord Blood Unit Identification

Question 1: Specify the person for whom this typing is being done

Indicate whether the reported HLA typing is the final recipient typing, from a related donor (biological mother, biological father, or other biological relative), an unrelated donor with product procured from a source other than the NMDP, a non-NMDP cord blood unit, or maternal HLA typing for a cord blood unit with product procured from a source other than the NMDP. The HLA typing must be reported for a non-NMDP cord blood unit; maternal typing is optional. Report related or autologous cord blood units as non-NMDP cord blood units.

If the reported HLA typing is for:

- The recipient, go to question 13.
- The recipient's biological relative, go to question 5.
- PBSC or bone marrow donor not related to the recipient, go to question 2.
- Cord blood unit with typing sample taken from the cord blood unit or infant, go to question 3.
- Maternal HLA typing, go to question 3.

Question 2: Non-NMDP unrelated donor ID

Specify the unrelated donor identification number used by the donor registry to identify and track the peripheral blood stem cell or bone marrow donor. Continue with question 7.

Question 3: Non-NMDP cord blood unit ID

Specify the cord blood unit identification number used by the cord blood bank to identify and track the unit. If reporting confirmatory typing on the cord blood unit, continue with question 4. If reporting maternal HLA typing, continue with question 12.

Question 4: Is cord blood unit maternal HLA typing available?

Maternal HLA that is not inherited by the fetus, or non-inherited maternal antigens (NIMAs), may be used to select between comparable mismatched cord blood units. Studies have found that NIMA-matched cord blood transplantation may be associated with improved outcomes when compared to equivalent NIMA-mismatched cord blood transplantation.

Indicate if the maternal HLA typing is available and continue with question 7; if yes, also complete Form 2005 reporting maternal HLA typing.

Question 5: Specify recipient's biological relative and typing

If confirmation of HLA typing is being reported on a donor who is biologically related to the recipient, specify their relationship.

- Mother: The HLA typing is being reported on a donor who is the recipient's biological mother.
- Father: The HLA typing is being reported on a donor who is the recipient's biological father.
- Sibling: The HLA typing is being reported on a donor who shares the same biological mother *and* father.
- Syngeneic twin: The HLA typing is being reported on a donor who is the recipient's monozygotic (identical) twin. Monozygotic twins arise from the division of a single implanted egg, resulting in two embryos that share the same chromosomal profile.
- Fraternal twin: The HLA typing is being reported on a donor who is the recipient's dizygotic twin. Dizygotic twins arise from two eggs being independently fertilized and implanted, resulting in two embryos that are the same age but are unlikely to share the same chromosomal profile.
- Child: The HLA typing is being reported on a donor who is the recipient's biological child.
- Aunt: The HLA typing is being reported on a donor who is the recipient's biological parent's sister.
- Uncle: The HLA typing is being reported on a donor who is the recipient's biological parent's brother.
- Cousin: The HLA typing is being reported on a donor who is the child of the recipient's aunt or uncle.
- Other biological relative: The HLA typing is being reported on a donor who does not fit the definition of other biological relatives specified above. Specify the other biological relative's *relationship* to the recipient (do *not* report the donor's name) and if preliminary or confirmatory typing was done in question 6.

Questions 7-8: Date of birth (donor/infant)

Indicate whether the donor's or infant cord donor's date of birth is "known" or "unknown." If "known," report the date of birth in question 8. If the date of birth is known, it is not necessary to complete questions 9-10 specifying the donor's or infant cord donor's age. If "unknown," continue with question 9.

Questions 9-10: Age (donor/infant)

Indicate whether the donor's or infant cord donor's age at the time of HLA typing is "known" or "unknown." If "known," report the donor's or infant cord donor's age in question 10. If the infant's age is less than one year, report as months rounded

to the nearest whole month. If the HLA typing was done at birth or prenatally, report "0" months. If "unknown," continue with question 11.

Question 11: Sex (donor/infant)

Indicate the biological sex of the donor or infant cord donor.

Question 12: Was the person for whom this typing is being done used as the donor?

Indicate if the reported typing is for the individual selected as the donor. Reporting typing done on family members not selected as donors is optional, but may be beneficial for additional HLA studies.

HLA Typing by DNA Technology

Complete this section for all typing done by DNA based methods. Examples of HLA typing by DNA technology may include: sequence-specific primer (SSP), sequence-specific oligonucleotide probe (SSOP), and sequence-based typing (SBT).

DNA technology can be used to type for a single allele, combinations of alleles (allele strings), or a "generic" allele designation similar to a serologic typing result. For this reason, the number of digits reported, as well as the number of alleles, will vary.

Laboratories may use " / ", " - " or a combination of numbers and letters on the typing report as a shorthand notation for the results. Transcribe the information onto the form as directly as possible. The letters, called allele codes, will be 1 or more characters in length and represent a combination of possible alleles at a locus. The same allele combination may be reported several different ways (e.g., DRB1*01:01 or 01:02, DRB1*01:01/01:02, DRB1*01:01/02, or DRB1*01:AB).

There will be two alleles reported for each locus, unless the individual is presumed homozygous (i.e., carries two copies of the same allele) at a locus. Transcribe the first allele designation in the first box, and the second allele designation in the second box. If the person is homozygous, leave the second box blank.

Question 13: Was documentation submitted to the CIBMTR (e.g., lab report)?

Indicate if a copy of the HLA typing report is attached. Use the Log of Appended Documents (Form 2800) to attach a copy of the HLA typing laboratory report. Attaching a copy of the laboratory report assists in confirming the reporting of HLA typing and reduces the need for later data queries.

Class I

Questions 14-15: Locus A

Indicate whether the allele designations at HLA-A are “known” or “unknown.” If known, report the first A* allele and second A* allele designations in question 15; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 16. If question 14 is “unknown,” then question 36 (“A” antigens defined by serologic typing) is required.

Questions 16-17: Locus B

Indicate whether the allele designations at HLA-B are “known” or “unknown.” If known, report the first B* allele and second B* allele designations in question 17; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 18. If question 16 is “unknown,” then question 39 (“B” antigens defined by serologic typing) is required.

Questions 18-19: Locus C

Indicate whether the allele designations at HLA-C are “known” or “unknown.” If known, report the first C* allele and second C* allele designations in question 19; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 20.

Class II

Questions 20-21: Locus DRB1

Indicate whether the allele designations at HLA-DRB1 are “known” or “unknown.” If known, report the first DRB1* allele and second DRB1* allele designations in question 21; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 22.

Class II (Optional)

Questions 22-23: Locus DRB3

Indicate whether the allele designations at HLA-DRB3 are “known” or “unknown.” If known, report the first DRB3* allele and second DRB3* allele designations in question 23; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 24.

Questions 24-25: Locus DRB4

Indicate whether the allele designations at HLA-DRB4 are “known” or “unknown.” If known, report the first DRB4* allele and second DRB4* allele designations in question 25; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 26.

Questions 26-27: Locus DRB5

Indicate whether the allele designations at HLA-DRB5 are “known” or “unknown.” If known, report the first DRB5* allele and second DRB5* allele designations in question 27; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 28.

Questions 28-29: Locus DQB1

Indicate whether the allele designations at HLA-DQB1 are “known” or “unknown.” If known, report the first DQB1* allele and second DQB1* allele designations in question 29; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 30.

Questions 30-31: Locus DPB1

Indicate whether the allele designations at HLA-DPB1 are “known” or “unknown.” If known, report the first DPB1* allele and second DPB1* allele designations in question 31; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 32.

Questions 32-33: Locus DQA1

Indicate whether the allele designations at HLA-DQA1 are “known” or “unknown.” If known, report the first DQA1* allele and second DQA1* allele designations in question 33; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 34.

Questions 34-35: Locus DPA1

Indicate whether the allele designations at HLA-DPA1 are “known” or “unknown.” If known, report the first DPA1* allele and second DPA1* allele designations in question 35; report a single allele, a string of alleles, or an allele code.

If “unknown,” continue with question 36.

Antigens Defined by Serologic Typing

Complete this section for all serologic typing. If serologic typing was not performed, leave this section blank. Report broad antigens only when your laboratory was not able to confirm typing for a known split antigen.

Each HLA locus has a serologically defined “X” antigen specificity: AX, BX, CX, DRX, DPX, and DQX. At this time, an “X” specificity is defined as “unknown but known to be different from the other antigen at that locus.” This is different from a blank specificity, which is assumed to be the same as the other antigen at that locus.” When comparisons between recipient and donor antigens involve an “X” or “blank” specificity, the “X” or “blank” is assumed to be homozygous for the antigen reported at the locus. In other words, the search algorithm treats typing containing “blank” or “X” antigens in the same manner as known homozygous typing.

Questions 36-38: Number of A antigens provided

Indicate if one or two HLA-A antigens were tested. If one antigen was tested, report the first antigen specificity in question 37 and continue with question 39.

If two antigens were tested, report the first antigen specificity in question 37 and the second antigen specificity in question 38. Continue with question 39.

Questions 39-41: Number of B antigens provided

Indicate if one or two HLA-B antigens were tested. If one antigen was tested, report the first antigen specificity in question 40 and continue with question 42.

If two antigens were tested, report the first antigen specificity in question 40 and the second antigen specificity in question 41. Continue with question 42.

Optional Antigen Reporting

Questions 42-44: Number of C antigens provided

Indicate if one or two HLA-C antigens were tested. If one antigen was tested, report the first antigen specificity in question 43 and continue with question 45.

If two antigens were tested, report the first antigen specificity in question 43 and the second antigen specificity in question 44. Continue with question 45.

Question 45: Specificity Bw4 present?

Bw4 refers to an epitope expressed by HLA-B alleles; epitopes are presented on the surface of the antigen and are recognized by the immune system. Bw4 and Bw6 are mutually exclusive and may confer reactivity with lymphocytes. Select “yes” if Bw4 specificity is present. Leave blank if specificity for Bw4 was not tested.

Question 46: Specificity Bw6 present?

Bw6 refers to an epitope expressed by HLA-B alleles; epitopes are presented on the surface of the antigen and are recognized by the immune system. Bw4 and Bw6 are mutually exclusive and may confer reactivity with lymphocytes. Select

“yes” if Bw6 specificity is present. Leave blank if specificity for Bw6 was not tested.

Questions 47-49: Number of DR antigens provided

Indicate if one or two HLA-DR antigens were tested. If one antigen was tested, report the first antigen specificity in question 48 and continue with question 50.

If two antigens were tested, report the first antigen specificity in question 48 and the second antigen specificity in question 49. Continue with question 50.

Question 50: Specificity DR51 present?

HLA-DR51 is an HLA-DR variant that recognizes antigens from HLA-DRB5. Select “yes” if DR51 specificity is present. Leave blank if specificity for DR51 was not tested.

Question 51: Specificity DR52 present?

HLA-DR52 is an HLA-DR variant that recognizes antigens from HLA-DRB3. Select “yes” if DR52 specificity is present. Leave blank if specificity for DR52 was not tested.

Question 52: Specificity DR53 present?

HLA-DR53 is an HLA-DR variant that recognizes antigens from HLA-DRB4. Select “yes” if DR53 specificity is present. Leave blank if specificity for DR53 was not tested.

Questions 53-55: Number of DQ antigens provided

Indicate if one or two HLA-DQ antigens were tested. If one antigen was tested, report the first antigen specificity in question 54 and continue with question 56.

If two antigens were tested, report the first antigen specificity in question 54 and the second antigen specificity in question 55. Continue with question 56.

Questions 56-58: Number of DP antigens provided

Indicate if one or two HLA-DP antigens were tested. If one antigen was tested, report the first antigen specificity in question 57 and continue with the signature section.

If two antigens were tested, report the first antigen specificity in question 57 and the second antigen specificity in question 58. Continue with the signature section.

Signature

The FormsNet3SM application will automatically populate the signature data fields, including name and email address of person completing the form and date upon submission of the form.