

# Features Hap-E and ATLAS

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## Antigen Recognition Domain explained

- The antigen recognition domain (ARD) is the binding groove of the HLA peptide. This is the region interacting with the presented antigen and T-cell receptor.
- All alleles that express the same amino acid sequence in this region are considered an allele match.
- The ARD is encoded on:
  - exon 2 & 3 for HLA class I
  - exon 2 for HLA class II

## 1. Null allele treatment

- Null alleles are treated as absent, i.e. the second typing matches as homozygous.
- Null allele matching rules are applied to:
  - All high resolution null alleles.
  - Null alleles as part of multi allele codes if the null allele is part of a haplotype matching the donor's (patient's) HLA typing.
- Null allele matching rules are only applied to one typing of the locus.

The following table explains situations where Hap-E performs null allele treatment and whether this is considered a (potential) match or not.

Patient typing	Donor typing	Hap-E	ATLAS
A*03:01, A*01:11N	A*03:01, A*03:01	matches	matches
A*03:01, A*01:11N	A*03:01, A*02:125N	matches	matches
If there is a haplotype compatible with the donor typing containing A*02:125N then			
A*03:01, A*01:11N	A*03:01, A*02:GFJM	matches	mismatches
A*03:01, A*03:01	A*03:01, A*02:XX	matches	mismatch, but in list as if no mismatch
A*03:01, A*03:01	A*03:01, A*01:01:01G	does not match	does not match

A*01:11N, A*02:125N	A*03:01, A*03:01	<b>does not match</b>	<b>does not match</b>
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02:GFJM 02:01/02:105/02:125N

## 2. Search with two mismatches

Hap-E search	ATLAS search
The two mismatches can be on any locus.	The two mismatches can be on any locus.

## 3. Donors with DNA and serologic typing

Hap-E search	ATLAS search
Only the DNA typing information is used for matching.	Only the DNA typing information is used for matching.

## 4. Serology handling

Hap-E search	ATLAS search
<b>Does not</b> assign expert assigned exceptions described in <a href="#">rel_dna_ser</a> e.g. Hap-E assigns A*02:55 to A(2)	<b>Does</b> assign expert assigned exceptions described in <a href="#">rel_dna_ser</a> e.g. ATLAS assigns A*02:55 to A(2) <b>and</b> A(28)

## 5. Returning donors without typing at DRB1

Hap-E search	ATLAS search
Yes, when default 'return only donors with typing at DRB1' filter has been switched off and donor does have typing at A+B and at least 1 of: C, DQB1 loci.	No, because donors without typing at DRB1 are not accepted by ATLAS as valid donors.

## 6. Match grades: Overview

Standard match grades
Applied to locus A, B, C, DRB1, DQB1

- A** Allele match
- P** Potential match
- M** Antigen mismatch
- L** Allele mismatch (antigen match)

## 7. DPB1-specific match grades

Hap-E search	ATLAS search
Applied to DPB1 only. Uses TCE3 model	Applied to DPB1 only. Uses TCE3 model
<ul style="list-style-type: none"> <li><b>A</b> Allele match</li> <li><b>Pe</b> Permissive mismatch</li> <li><b>G</b> Non-permissive mismatch in GvH direction</li> <li><b>H</b> Non-permissive mismatch in HvG direction <ul style="list-style-type: none"> <li>- Unknown (not determined, e.g. patient has no DPB1 typing)</li> </ul> </li> <li><b>X</b> No specification due to ambiguous or missing TCE assignment</li> </ul>	<ul style="list-style-type: none"> <li><b>A</b> Allele match</li> <li><b>Pe</b> Permissive mi</li> <li><b>G</b> Non-permissi direction</li> <li><b>H</b> Non-permissi direction <ul style="list-style-type: none"> <li>- Unknown or a</li> </ul> </li> </ul>

<p>Ambiguous typing can be determined.</p> <p>For an ambiguous case (i.e. depending on the realization of a multi allele code on DPB1 of patient or donor, the mismatch can be P, H or G) the probabilities are calculated based on DPB1 allele frequencies and are displayed when hovering over the displayed DPB1 match-grade icon of the donor or CBU:</p> <div> <div>DPB1</div> <div>Registry</div> <div>Sex</div> </div> <div> <div>01:01</div> <div>04:01</div> <div>M</div> </div> <div>hes</div> <div>ons:</div> <div> <div>X</div> <div>03:8</div> <div>(04:1</div> </div> <div> <div>Ambiguous or undetermined DPB1 match grade</div> <div> <div>Permissive: 64 %</div> <div>Non-permissive in HvG: 36 %</div> <div>Non-permissive in GvH: 0 %</div> <div>Non-determined: 0 %</div> </div> </div>
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## 8. Handling of HLA\*DRB3, DRB4, DRB5, DQA1 and other loci not considered for overall match probability

Hap-E search	ATLAS search
HLA*DRB3/4/5, DPA1, DQA1 and E are validated and shown in the full report, including information whether they are matched or not.	Loci other than A, B, C, DRB1, DQB1 and DPB1 are not validated or imported by ATLAS and therefore also not returned.

## 9. Handling of 'NEW' alleles

Handling of new alleles that do not have an official name yet.

For guidelines regarding implementation and reporting of 'NEW' alleles, please read <https://onlinelibrary.wiley.com/doi/10.1111/tan.15048>

Hap-E search	ATLAS search
Supported for Donors and Patients. However, Search & Match including Dataupload currently only supports NEW alleles for Patients. Therefore only NEW alleles for patients will be processed in Search & Match.	Currently not supported. Functionality will be added in the future.

## 10. Cord Blood search options

Hap-E search	ATLAS search
Allele matched: <ul style="list-style-type: none"> <li>n/10, n/8: up to 4 mismatches</li> <li>n/6 search: up to 3 mismatches</li> </ul>	Allele matched: <ul style="list-style-type: none"> <li>n/10, n/8: up to 4 mismatches</li> <li>n/6 search: up to 3 mismatches</li> </ul>
<ul style="list-style-type: none"> <li>n/6 search at HLA-A, B, DRB1 - class I matched at antigen level and class II matched at ARD level</li> </ul>	

## 11. 3 and 4 mismatch Cord Blood sorting

Hap-E search	ATLAS search
Resolution based scoring  CBUs with high resolution typing are ranked higher than less well typed CBUs in the 3 and 4 mismatch category.  e.g. DNA typed CBUs are ranked higher than serology typed CBUs	Match confidence based scoring  CBUs with a higher match confidence are ranked higher than CBUs with a lower match confidence in the 3 and 4 mismatch category.  e.g. CBUs with exact matches at considered loci are ranked higher than those with possible matches at considered loci.

## 12. Probability display

Hap-E search	ATLAS search
All probabilities are rounded to integer values.  0%: <ul style="list-style-type: none"> <li>Values <math>0 &lt; p &lt; 0.5</math></li> <li>No shared genotype between donor and patient.</li> </ul>	All probabilities are rounded to integer values.  0%: <ul style="list-style-type: none"> <li>Values <math>0 &lt; p &lt; 0.5</math></li> <li>No shared genotype between donor and patient.</li> </ul>

## 13.1 Locus match probabilities: Definition

Hap-E search	ATLAS search
<b>match, i.e. 10/10, 8/8 or 6/6</b> <ul style="list-style-type: none"> <li>The locus match probability is the <b>relative probability</b> that this locus is a match <b>in the 1 mismatch case</b>.</li> </ul> <b>mismatch, i.e. 9/10, 7/8 or 5/6</b> <ul style="list-style-type: none"> <li>The locus match probability is the <b>relative probability</b> that this locus is a match <b>in the 2 mismatch case</b>.</li> </ul> So this probability provides information on which locus the <b>next mismatch</b> will occur.	<b>match, i.e. 10/10, 8/8 or 6/6</b> <ul style="list-style-type: none"> <li>The locus match probability is the <b>probability</b> that this locus is a match <b>no matter the amount of overall mismatches</b>.</li> </ul> <b>mismatch, i.e. 9/10, 7/8 or 5/6</b> <ul style="list-style-type: none"> <li>The locus match probability is the <b>probability</b> that this locus is a match <b>no matter the amount of overall mismatches</b>.</li> </ul> So this probability provides information on the probability that <b>this locus</b> will be a match.

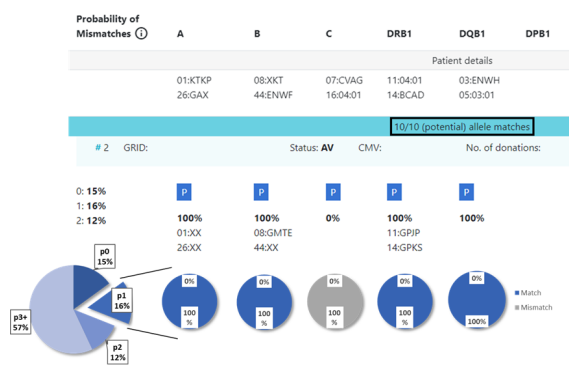
## 13.2 Locus match probabilities in search: Not displayed

In some cases the value is not defined and no locus match probability is displayed:

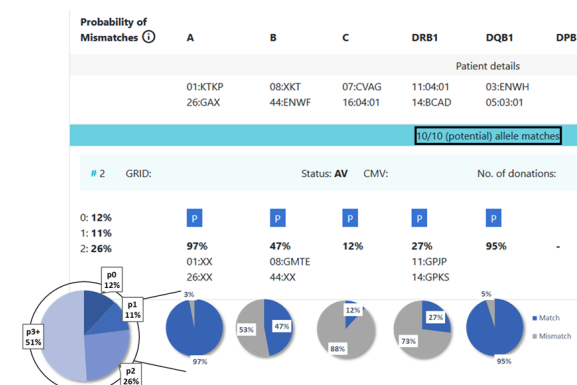
Hap-E search	ATLAS search
<b>match</b> <ul style="list-style-type: none"> <li>When <math>p1 = 0</math> (division by zero, not defined)</li> </ul>	<b>match</b> <ul style="list-style-type: none"> <li>Locus probabilities will always be displayed for explicable donors.</li> </ul>
<b>mismatch</b> <ul style="list-style-type: none"> <li>When <math>p2 = 0</math> (division by zero, not defined).</li> <li>When a donor/CBU already has at least two known mismatches. As Hap-E only calculates match probabilities for up to 2 mismatches, Hap-E also is not able to calculate the locus-specific match probabilities in case of the third mismatch.</li> </ul>	<b>mismatch</b> <ul style="list-style-type: none"> <li>Locus probabilities will always be displayed for explicable donors.</li> </ul>
<b>inexplicable donors</b> <ul style="list-style-type: none"> <li>When a donor's phenotype cannot be explained by the haplotype frequency sets used for probabilistic matching. It is therefore impossible to calculate match probabilities both at the considered loci in total and per-locus.</li> </ul>	<b>inexplicable donors</b> <ul style="list-style-type: none"> <li>When a donor's phenotype cannot be explained by the haplotype frequency sets used for probabilistic matching. It is therefore impossible to calculate match probabilities both at the considered loci in total and per-locus.</li> </ul>

## 13.3 Locus match probabilities in Hap-E and ATLAS search

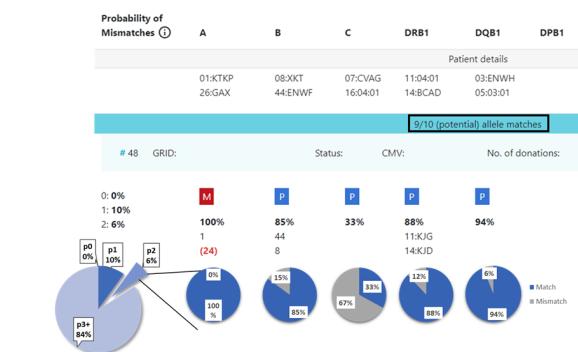
### Example 1: Hap-E



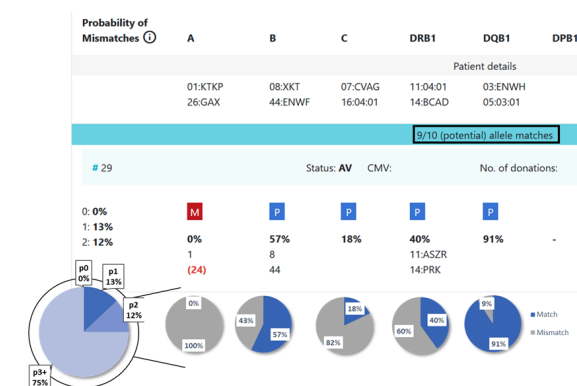
### Example 1: ATLAS



### Example 2: Hap-E

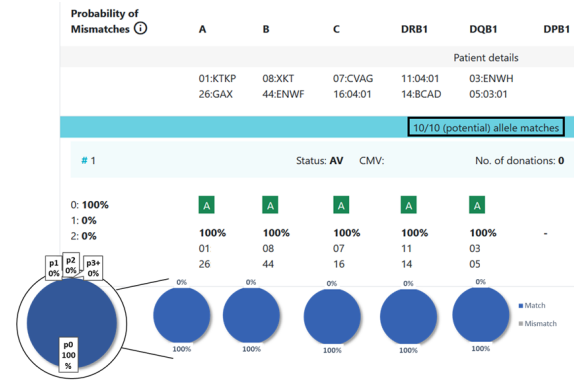
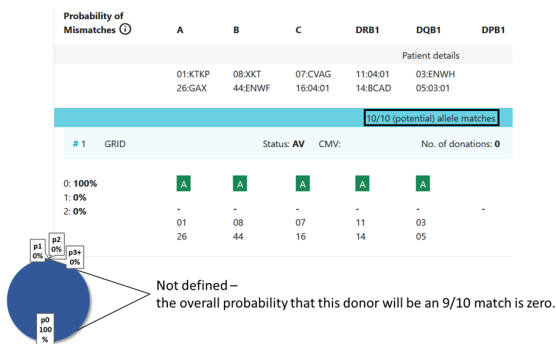


### Example 2: ATLAS

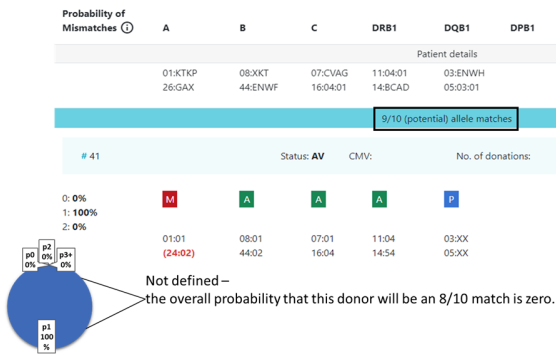


### Example 3: Hap-E

Example 3: ATLAS



Example 4: Hap-E



Example 4: ATLAS

