Probabilities of trans-located mismatches for HLA-loss relapse risks after HCT: Introducing the HLA Haplotype Match Calculator

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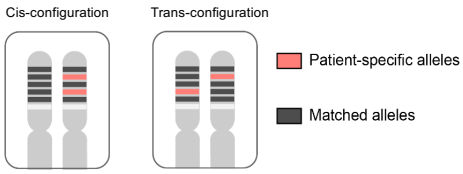
Introduction

After transplantation of hematopoietic cells (HCT) from a mismatched donor, a haplotype carrying human leukocyte antigen (HLA) graft-versus-host mismatches can be lost in the tumor cells, thereby eliminating mismatches relevant for graft-versus-leukemia effects. Malignant cells that carry this phenomenon, referred to as "HLA loss", can evade detection by donor T cells and give rise to relapse. This mechanism occurs in up to 25% of myeloid leukemia relapse after HCT from haploidentical family donors (Tameni, Blood 2024), where all HLA mismatches are located on the same haplotype.
To reduce the risk of HLA loss, it can consequently be preferable in certain scenarios to select a mismatched unrelated donor with at least two mismatched HLA alleles located in a trans-configuration, i.e., not all mismatches originating from the same haplotype.



Methods

HLA genotyping for HCT often lacks phasing information, making it difficult to determine the haplotype configuration of patients and unrelated donors. However, using known population-specific haplotype frequency distributions, the probability of mismatches in trans-configuration can be calculated for a specific patient-donor pair.

To simplify manual calculations, we developed a web-based tool that calculates the probability of trans-located mismatches in patients compared to donors (Figures 1-4).
Available haplotype frequencies based on DKMS donors' self-assigned ethnic background:

- African-American (n=200,000)
- German (n=4,500,000)
- Turkish (n=200,000)

Frequencies have been obtained using our in-house software Hapl-o-Mat, which is available from https://github.com/DKMS/Hapl-o-Mat .

- For requests with **two** or more patient specific mismatches, the tool determines possible diplotypes given the selected ethnicity's haplotype frequency distribution and evaluates mismatch locations.
  The probability of trans-located mismatches is then obtained by summing over respective haplotype frequency products (Figure 3).
- For requests with **one** patient specific mismatch, the probability of a haplotype match between patient and donor is reported.
- For requests with **no** mismatches between patient and donor are identified, the tool computes the probability of a diplotype match.

On request, the tool provides additional details (Figure 4):

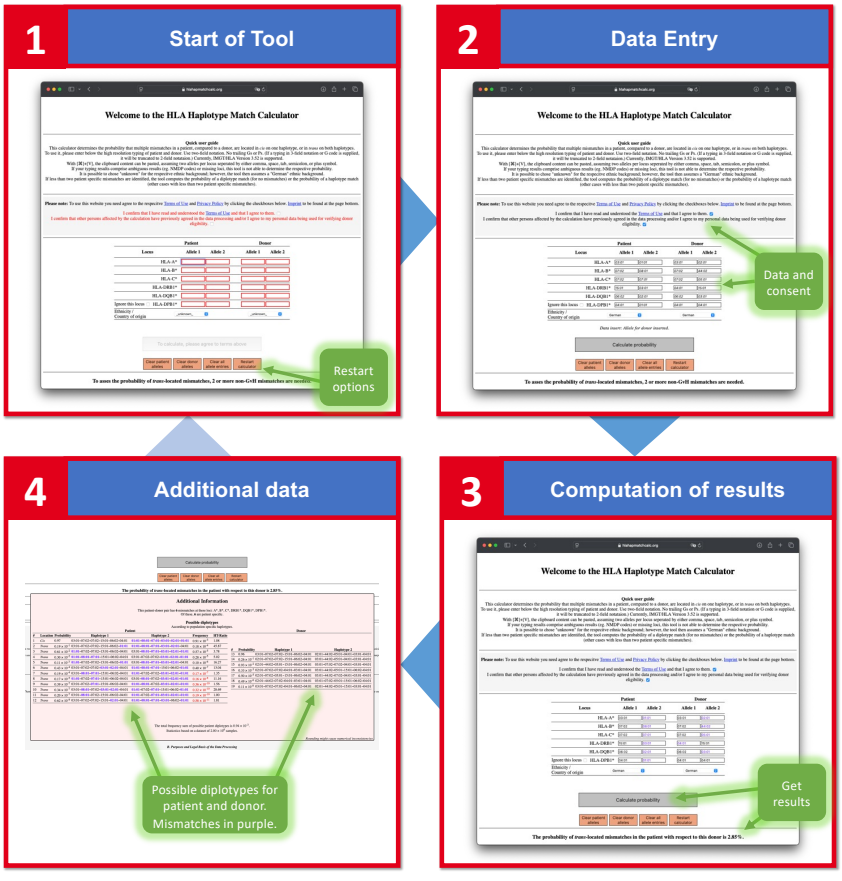
- involved diplotypes,
- highlighting of mismatch locations,
- and frequencies.

The HLA Haplotype Match Calculator

We developed an online webtool for the prediction of haplotype phasing of multiple HLA mismatches in HCT donor selection.
The online tool can process both, a 5- or 6-locus genotype (optional HLA-DPB1) for patient and donor. The tool determines possible diplotypes given the selected ethnicity's haplotype frequency distribution and evaluates mismatch locations.

Use free of charge

hlahapmatchcalc.org



Conclusion

Our online haplotype phasing tool allows users to estimate the likelihood that in HCT scenarios with two or more mismatched HLA alleles in the patient compared to the donor, these alleles are present in a trans-configuration. By selecting a donor with a higher probability for trans-located mismatches, HLA loss can potentially be mitigated, reducing the risk of a relevant mechanism of post-transplantation leukemia immune escape.

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