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Human leukocyte antigen loss as a mechanism of immune escape after allogeneic stem cell transplantation in a patient with mycosis fungoides

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All data can be provided to researchers on individual request.

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Competing Interests

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Case Report

Allogeneic stem-cell transplantation (allo-SCT) represents a potentially curative treatment for advanced-stage mycosis fungoides (MF) or patients with Sézary syndrome (SS), two entities belonging to the group of cutaneous T-cell lymphoma (CTCL). However, relapse still represents the major cause of treatment failure as it occurs in approximately half of the patients after a median of 8 months posttransplant [1–3]. For relapsed patients, there are few treatment options, including chemotherapy or targeted approaches followed by a cell-based consolidation either with a 2nd transplant or with donor lymphocyte infusions (DLI). A recent meta-analysis reported complete remission (CR) rate of 46% after DLI, underlining the importance of a graft-versus-lymphoma (GvL) effect in allo-SCT for MF and SS [4]. Nevertheless, more than half of the patients did not experience CR after DLI, suggesting potential mechanisms of immune escape in this setting. In posttransplant relapse of of myeloid malignancies, a well-described immune escape mechanism is represented by genomic alterations resulting in the specific loss of human leukocyte antigens (HLA) mismatched between patient and donor, henceforth referred to as HLA-Loss. The mechanism of HLA-Loss is the deletion of one HLA haplotype (loss of heterozygosity, LOH), followed by duplication of the other (uniparental disomy, UPD). Consequently, HLA-Loss relapses no longer express mismatched HLA and therefore become invisible to alloreactive donor T-cells after allo-SCT [3,4]. Consequently, application of DLI or a 2nd transplant from the same donor lose therapeutic GvL efficacy in this setting, but are still associated with a relevant risk for graft-versus-host disease (GvHD). Whether HLA-Loss can also be a driver of relapse in patients with CTCL, is currently unknown. Here, we investigated this in a patient with cutaneous relapse after mismatched unrelated donor allo-SCT for MF. This work was approved by the committee of the University Hospital Essen (approval number: 22-101708-BO).

A 40-year old female patient was diagnosed with stage IB MF in 2010, with no evidence of systemic disease (**Figure 1**). Upon multimodal treatment approaches comprising topical steroids, Psoralen plus Ultraviolet A (PUVA) therapy, bexarotene and methotrexate, the patient developed progressive stage IIB disease in 2018. Brentuximab vedotin initial led to disease stabilization in 2019, which however progressed after a side effect-motivated switch to mogamulizumab in 2021. After treatment by extracorporal photopheresis, psoralen plus ultraviolet A (PUVA) and intermittent interferon therapy, the patient received an allo-SCT in 2023 while being in partial remission (PR) induced by total skin electron beam therapy (TSEBT) and gemcitabine. The donor was a 19-year old unrelated female with antigen mismatches in HLA-A and -DPB1. Conditioning was based on fludarabine and treosulfan, with immunosuppression by tacrolimus, mycophenolat mofetil (MMF) and posttransplant cyclophosphamide (Pt-Cy) (**Figure 1**). After positron emission tomography (PET)-based CR on d+100 after transplantation, the patient experienced progressive cutaneous relapse on d+187. TSEBT, followed by 2 rounds of DLI without GvHD was able to induce an intermittent PR, which was rapidly followed by next progression of the skin lesions from d+330 onwards. A diagnostic skin biopsy ruled out transformation to an aggressive T-cell lymphoma, but suggested a partial loss of the HLA haplotype carrying the mismatched HLA-A and -DPB1 alleles (**Figure 2**). Briefly, qPCR-based chimerism analysis revealed an infiltration of the biopsy by 10% donor cells, while the remaining cells were of patient origin (data not shown). The relative percentage of patient- and donor-derived reads for the mismatched HLA-A and -DPB1 alleles was determined by next-generation-sequencing (NGS). This revealed a striking reduction of the reads for the patient-specific alleles from the expected 45% in the absence of UPD, to 18.6% and 13.3% for HLA-A and HLA-DPB1, respectively (**Figure 2a**). Importantly, also the relative read counts for the two alleles at the matched HLA-B, -C,

-DRB1, and -DQB1 loci (expected to be present at 50% each in the absence of UPD), were shifted to 25% vs 75%, with alleles expected to be in linkage having similarly reduced percentages (not shown). Taken together, these data are compatible with UPD encompassing loss of the entire haplotype carrying mismatched HLA and duplication of the other. Of note, the residual signals for the patient-specific alleles in the biopsy suggest either the presence of normal patient-derived skin cells (which do not carry HLA-Loss), and/or the absence of HLA-Loss in a limited fraction of tumor cells. To determine whether HLA-Loss had already been present prior to first allo-SCT, paraffin embedded (FFPE) tumor tissue obtained in 2018 (**Figure 2b**) was analyzed for imbalance between heterozygous HLA-A and -DPB1 alleles. Since FFPE material is not suitable for NGS-based HLA-loss diagnostics, we used a reverse Sequence-Specific Oligonucleotide (rSSO) HLA typing method as previously described [5]. This analysis suggested partial LOH in the tumor cells prior to allo-SCT, which was markedly increased after transplantation (**Figure 2c**). Disease progression at d+330 was treated by 4 cyles of gemcitabine inducing a rapid response. This was followed in 2025 (more than 2 years after the first transplant) by a second allo-SCT from an alternative unrelated donor mismatched for the duplicated HLA-A*26:01 and -DPB1*03:01 (**Figure 1**). After PET-based evidence of CR at d+60 after the 2nd allo-SCT, the patient relapsed again on d+120 and did not achieve a stringent response despite occurrence of acute cutaneous GvHD after tapering of immunosuppression, treatment with DLI, mogamulizumab and extracorporal photopheresis. She further received best supportive care and a palliative radiation and died on d+502 after second allo-SCT.

In recent years, huge efforts have been made to elucidate posttransplant relapse mechanisms, especially for myeloid neoplasms. Amongst them, HLA-Loss by UPD has been reported predominantly after allo-SCT from haploidentical family donors and, to

a lesser extent, from unrelated donors [6], including the increasingly used Pt-Cy based platforms [7–10]. While most studies investigated bone marrow relapse, two cases of HLA-Loss were also reported in extramedullary relapse of acute myeloid leukemia after allo-SCT [11]. To our best knowledge, we here describe for the first time HLA-Loss as a posttransplant relapse mechanism also in CTCL. Of note, we identify UPD as the genomic mechanism also in this case with important consequences for second donor selection, which should be tailored to carry mismatches against any of the HLA alleles on the haplotype retained by leukemia, while being matched for the other. Our findings align well with recent data demonstrating that genetic alterations affecting HLA-class I genes, including LOH of alleles with high predicted neoantigen presentation capacity, occur in up to 40% of patients with advanced-stage MF and SS outside the context of allo-SCT [12]. Notably, these changes were frequently allele-specific, subclonal and dynamically regulated, which may explain why in patients with CTCL, initial responses to immunotherapy or transplant can be followed by overt relapse and refractoriness towards further cell- and/or immunotherapy. In line with these observations, our findings are compatible with the presence of HLA-Loss in a small proportion of tumor cells already prior to allo-SCT, which increased dynamically thereafter, supporting a selective advantage of these cells for escape from donor T-cell alloreactivity, and explaining the failure to respond to dose-escalating DLI from the original donor. Given the reported high frequency of LOH in CTCL, our findings also support the potential utility of HLA-Loss diagnostics even prior to a first allo-SCT, to enable the adaptation of donor search in case of a pre-existing HLA-loss.

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Figure Legends

Figure 1. Clinical Course of a MF Patient over a 15-year Period.

Diagram depicting the clinical course of a patient covering the time from initial diagnosis of mycosis fungoides (MF) until the early posttransplant phase after second allografting. The 40-year old female patient presented initially with patches and plaques (stage IB) in 2010. Initial staging examination and repetitive patient monitoring according to national guidelines did not show any evidence of systemic disease. Upon different multimodal treatment approaches comprising topical steroids, PUVA therapy, bexarotene and methotrexate the patient showed progressive skin disease and finally developed additional tumors (stage IIB) in 2018. Since skin biopsy revealed CD30-expression with large cell transformation, brentuximab vedotin was initiated in 2019. After initial disease stabilization, brentuximab vedotin was switched to mogamulizumab in 2021 due to severe side effects (peripheral neuropathy grade 3) and progressive skin disease, which was treated by ECP, systemic PUVA, intermittent interferon therapy and TSEBT (2 days with 4 Gy each to cumulative 8 Gy in 12 fields) followed by gemcitabine. In 2023 allo-SCT was performed in partial remission from a 19-year old female MMUD after conditioning with fludarabine (30mg/m^2, d-6 to -2) and treosulfan (10mg/m^2, d-4 to -2). Posttransplant immunosuppression was based on tacrolimus, mycophenolat mofetil (MMF) and posttransplant cyclophosphamide (Pt-Cy, 50mg/kg body weight d+3 and d+4). On d+187 cutaneous relapse was diagnosed by skin biopsy and treated by another TSEBT and DLI (0,5 and 1x10^6 CD3+ T-cell/kg bodyweight on d+261 and d+293). An initial PR was rapidly followed by renewed disease progression and another biopsy was taken for HLA-Loss diagnostics on d+330 (Figure 2). HLA-loss was diagnosed and therefore a 2nd allo-SCT from an alternative donor mismatched for the duplicated haplotype (bearing HLA-A*26:01), but matched for the lost haplotype (bearing HLA-A*23:01) was planned. After achieving another

partial remission after gemcitabine, 2nd allo-SCT was performed at the beginning of 2025, but again was followed by disease progression at d+120. After rapid tapering of immunosuppression, cutaneous GvHD ensued, but this was resolved after local and systemic steroid therapy. Despite GvHD, the disease showed further progression and therefore treatment with DLI and mogamulizumab was initiated, albeit without achievement of a stringent response. The patient received palliative care and died on day +502 after second allo-SCT.

Abbreviations: allo-SCT, allogeneic stem cell transplantation; CMV: cytomegalie virus; ECP: extracorporal photopheresis; DLI: donor-lymphocyte infusion; GvHD: Graft-versus-Host Disease; Gy, Gray; HLA, human-leukocyte antigen; LN: lymph node; MMF, mycophenolate mofetil; MMUD: mismatched unrelated donor; NGS: next-generation sequencing; Pt-Cy: post-transplant cyclophosphamide; PUVA: Psoralen plus Ultraviolet A; TBI: total-body irradiation; TSEBT: low-dose total skin electron beam therapy

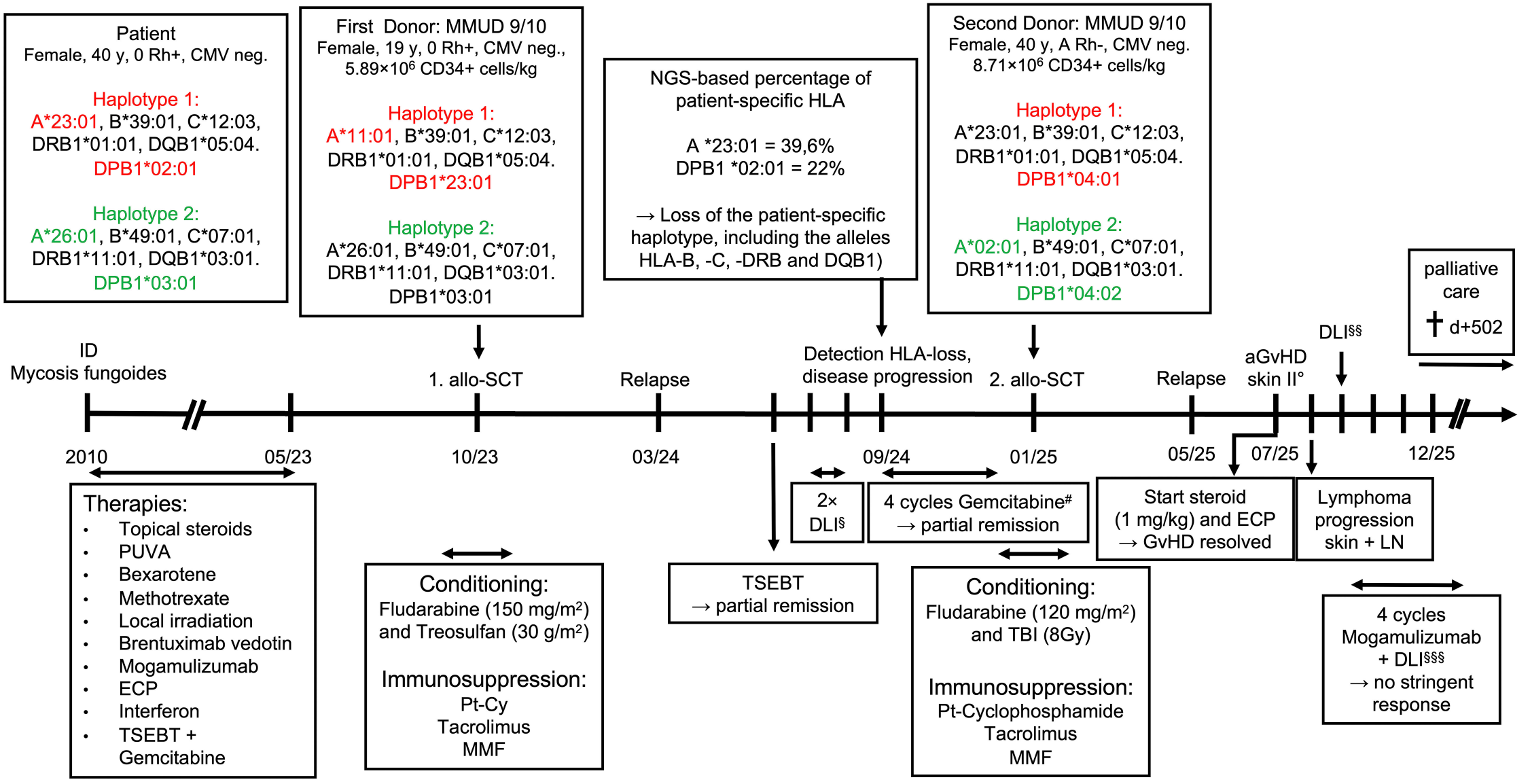
Figure 2. HLA-Loss diagnostics pre- and post-transplant.

Shown are the results of NGS- or rSSO-based HLA-Loss diagnostics on a tumor biopsy from d+330 after first allo-SCT or on FFPE material from 2018, prior to the first allo-SCT (**Figure 1**). **a)** HLA-Loss diagnostics on genomic DNA of the d+330 biopsy was performed by NGS of the HLA-A and -DPB1 loci on the Illumina iSeq100 platform using the NGSgo AmpX v2 kit (GenDx, Utrecht, Netherlands). The number of reads for the patient-specific, donor-specific, and the shared allele were quantified and compared using the NGSengine software (GenDx, Utrecht, Netherlands). Shown are the exemplary basevariants (%) for the NGS of the HLA-A locus. Heterozygous positions corresponding to the HLA allele with the higher average basevariant percentage are marked with a bold blue X (shared HLA-A*26:01 allele), and for the

allele with the lower average basevariant percentage with a bold red X (recipient-specific HLA-A*23:01 allele). Unassigned basevariants (i.e., noise) are marked with a small red x. Highlighted in the green bar is the dotted line of HLA-A*11:01 allele-specific SNPs (donor-derived), unassigned by the analysis software. Below the graph are shown the number of single nucleotide polymorphisms (SNP) analyzed for shared, patient- and donor-specific HLA-A and -DPB1 alleles and the observed, as well as the expected percentage of reads, based on the underlying chimerism of 90% patient cells (10% donor cell infiltrate, see text). The median read depth for the analysed regions was 968 for the HLA-A locus and 1382 for the HLA-DPB1 locus. The recipient chimerism is composed of predominantly malignant cells, with an undefined proportion of benign cells (e.g., stroma). **b)** Dominant skin lesion from which a biopsy was taken in 2018 prior to first allo-SCT, showing a representative area with a dense infiltration by small, mature-appearing lymphoid cells (H&E staining in 10x and 40x magnification). **c)** rSSO-based analysis of the relative balance between the two heterozygous HLA-A and -DPB1 alleles in the patient prior to first allo-SCT. The number of allele-specific probes was 6 for each of the two HLA-A alleles and 4 for each of the two HLA-DPB1 alleles. Shown are the normalized ratios of allele-specific rSSO signals for HLA-A*23:01 vs. A*26:01 (blue) and for HLA-DPB1*02:01 vs DPB1*03:01 (green) in the patient‘s pre-transplant peripheral blood (pB), the tumor biopsy pre-transplant (panel b) or the tumor biopsy at d+330 posttransplant (the latter with NGS-ascertained HLA-Loss). In the absence of LOH, the ratio between the signals for the two alleles is close to 100%. When LOH is present, the ratio is lower due to the imbalance between the two alleles. Note that the shifts in rSSO signal ratios were consistent between the pretransplant and posttransplant biopsies, compatible with a partial loss of HLA-A*23:01 and -DPB1*02:01 prior to first allo-SCT, which was accentuated after transplantation mismatched for these two alleles.

Abbreviations: allo-SCT, allogeneic stem cell transplantation; DNA, deoxyribonucleic acid; FFPE, formalin-fixed paraffin-ebmedded; HLA, human leukocyte antigen; LOH, loss of heterozygosity; NGS, next generation sequencing; pB, peripheral blood; rSSO, reverse Sequence-Specific Oligonucleotide; SNP, single nucleotide polymorphisms; Tx, transplant

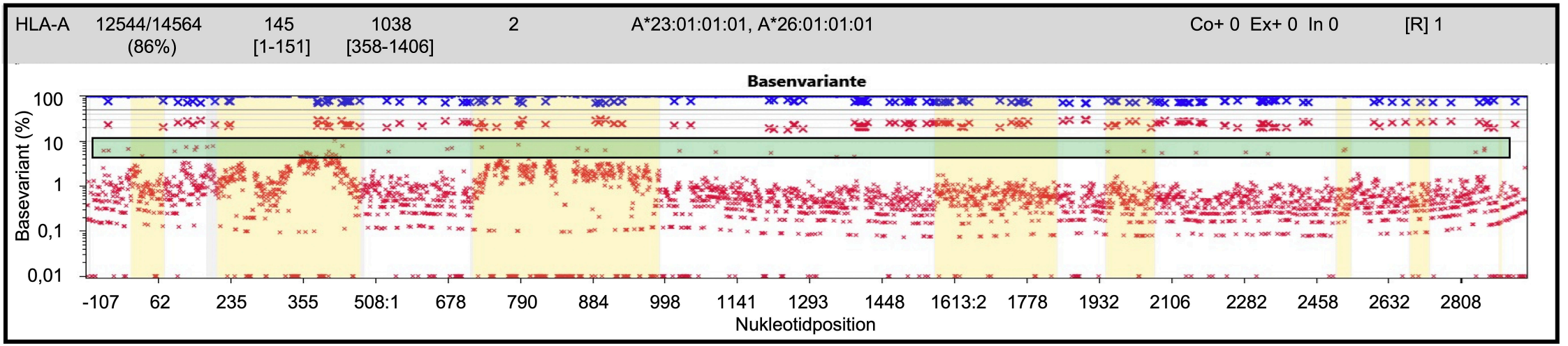
Figure 1.



§ = 1. DLI: 0.5×10^6 CD3+/kg bw, 2. DLI: 1×10^6/kg bw
# = dose reduction due to cytopenia
§§ = 3. DLI: 1×10^6 CD3+/kg bw
§§§ = 4. DLI: 2.8×10^6 CD3+/kg bw

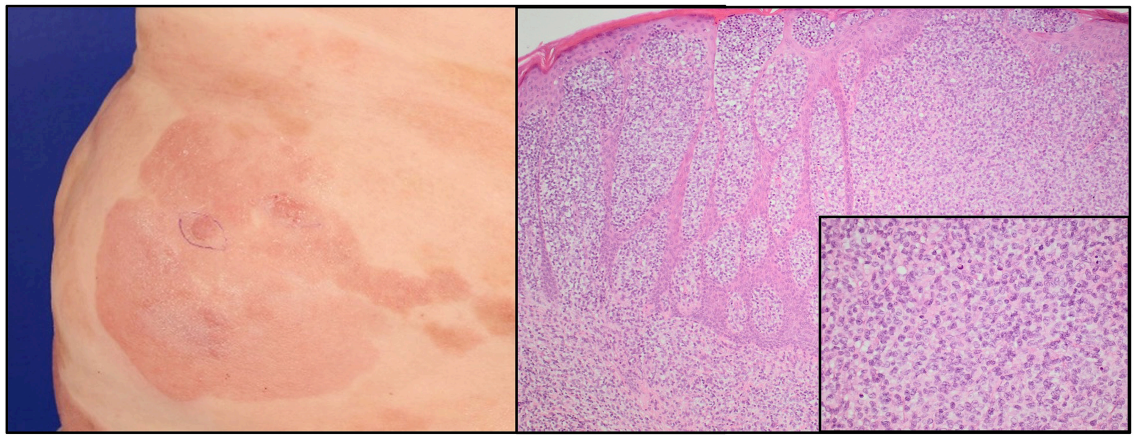
Figure 2.

a



Assignment	A-Locus	N SNPs	% reads measured	% reads expected	DBP1-Locus	N SNPs	% reads measured	% reads expected
shared	A*26:01	5	73,7	50	DPB1*03:01	5	82,1	50
recipient	A*23:01	5	18,6	45	DPB1*02:01	5	13,3	45
donor	A*11:01	5	7,7	5	DPB1*23:01	5	4,6	5

b



c

