
بسم الله الرحمن الرحیم

Genetically donor selection for non-malignant hematologic disease

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Donor Selection

- Best choose:

HLA-identical sibling donor

MUD

Alternative HSCTs (MMURD, CB, haplo family donors)

Primary Immunodeficiencies (PID)

- Overall guidelines for HSCT for **SCID and non-SCID** diseases together with detailed protocols have been produced by the EBMT Inborn Errors Working Party (EBMT IEWP) and can be found online at https://www.ebmt.org/sites/default/files/migration_legacy_files/document/Inborn%20Errors%20Working%20Party%20ESID%20EBMT%20HSCT%20Guidelines%202017.pdf.

- Haplo: T cell dep.

Fanconi's Anemia and Other Hereditary Bone Marrow Failure Syndromes

Donor:

-The best donor is MSD.

-Consider MUD in case of no appropriate MSD

-Mismatched related and UD and unrelated CB only in experienced centers and preferentially in clinical trials

Source of stem cells:

BM is the best source of stem cells

Matched related CB is a good option

PB is associated with higher risk of cGVHD and should be avoided

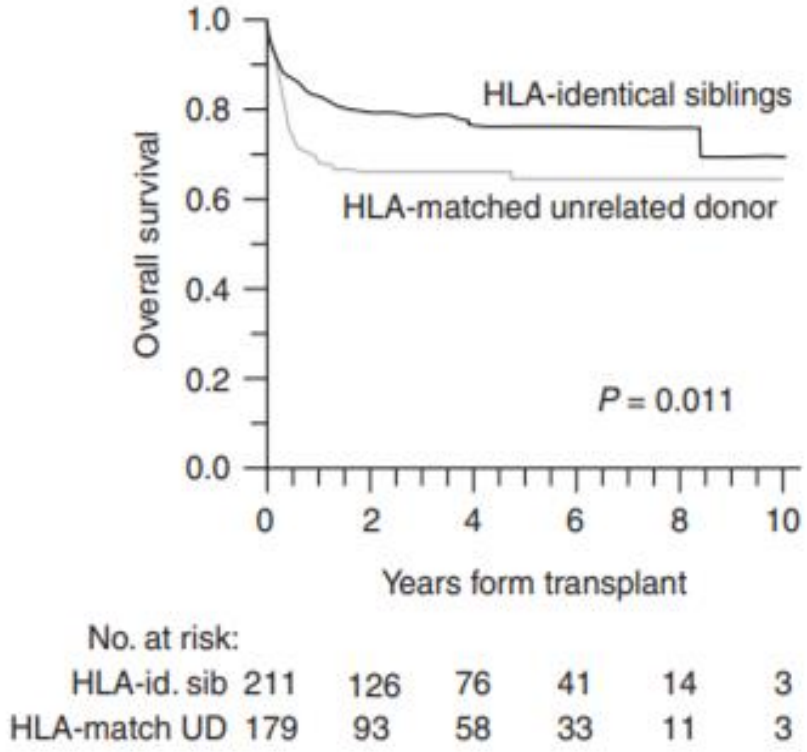
Cell dose

It is important for graft failure prevention:

NC > 3 × 108 /kg recipient bw for BM

NC > 3 × 107 /kg recipient bw for related CB

NC > 4 × 107 /kg recipient bw for unrelated CB



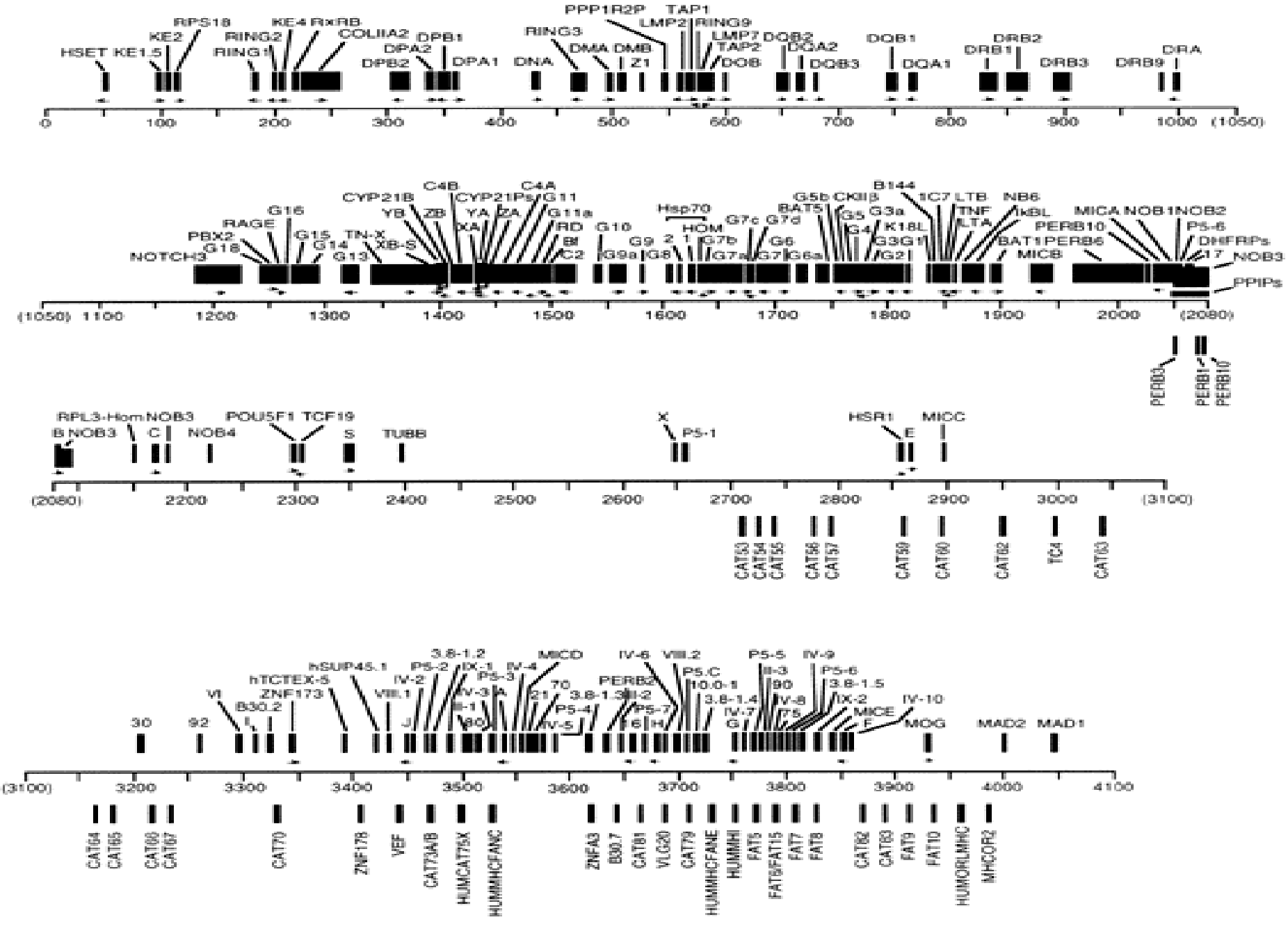
OS for Fanconi's anemia according to the type of donor: transplant period 2000–2009. The EBMT experience. Peffault de Latour R. Blood 2013; 122: 4279–86

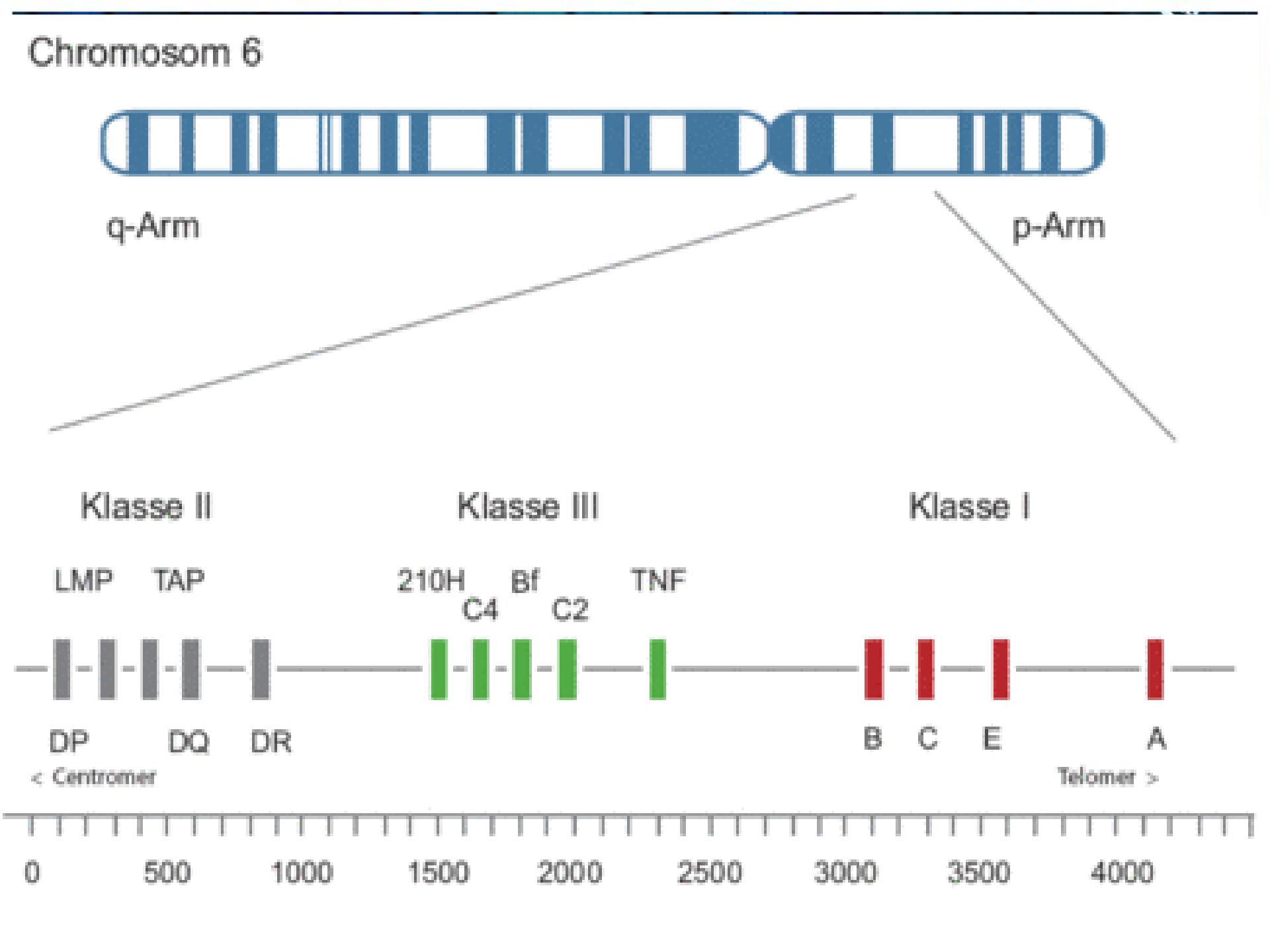
Leukocyte adhesion deficiency (LAD)

- HLA-matched sibling is strongly advocated for donor selection in allogenic HSCT of LAD patients.
- without an HLA-matched sibling donor, we also investigated HSCT from other matched related donors or MUD
- Unrelated cord blood stem cell or haplo-identical parent was considered as the **last option** for the treatment of LAD-I patients

- Low-resolution molecular typing for HLA-A and -B and -DRB1 were carried out for patients and their sibling. Moreover, high-resolution typing for class-I and II alleles was performed for recipient/ other related donor pairs. Unrelated cord blood stem cell or haplo-identical parent was considered as the last option for the treatment of LAD patients

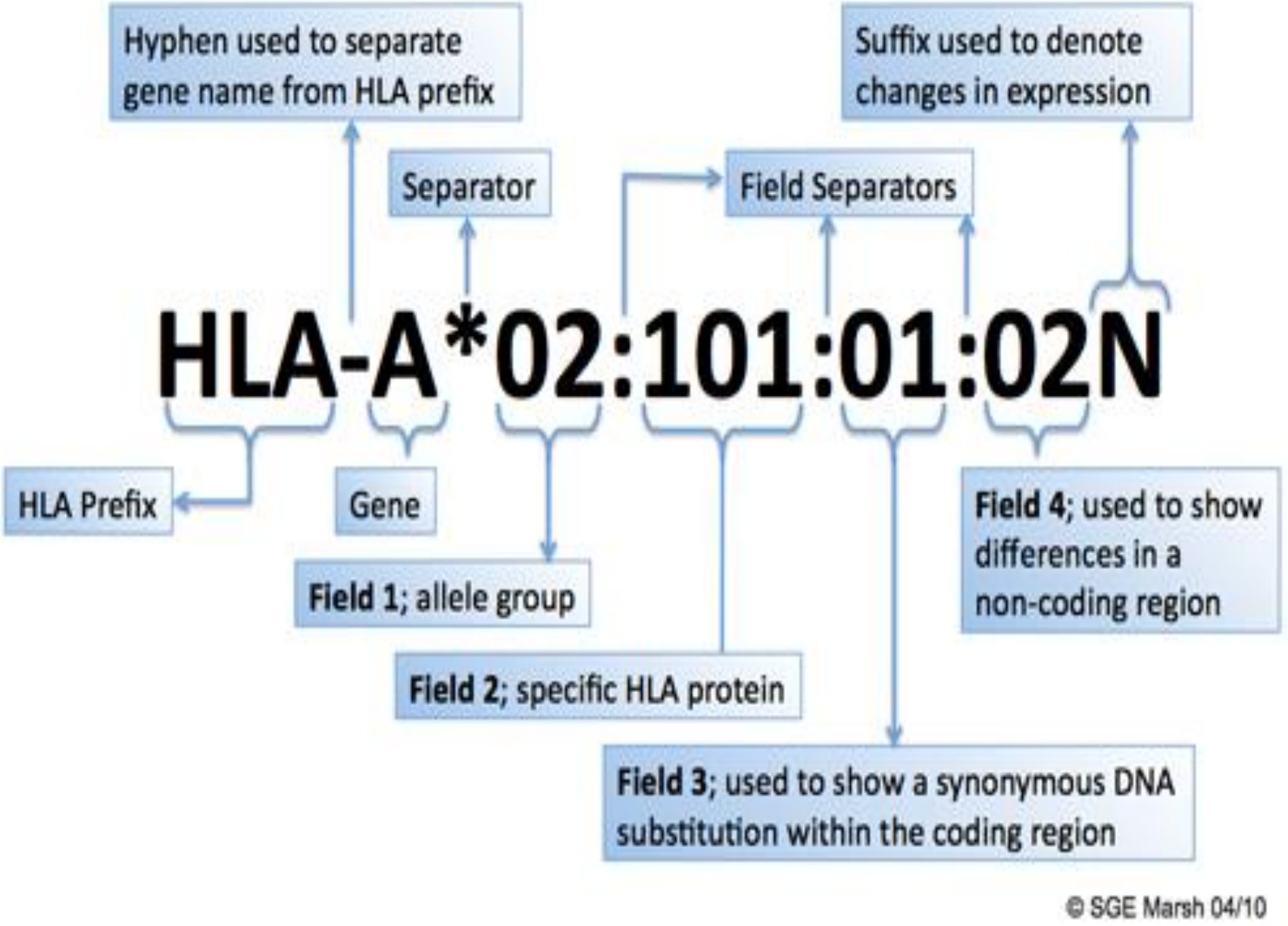

HLA
HLA


HSET KE1.5 KE2 RPS18 RING2 RING1 KE4 RxRB COLIIA2 DPB2 DPA2 DPB1 DPA1 DNA RING3 DMA DMB Z1 PPP1R2P TAP1 LMP2 RING9 LMP7 TAP2 DOB DOB2 DOA2 DOB3 DOB1 DOA1 DRB2 DRB1 DRB3 DRB9 DRA
0 100 200 300 400 500 600 700 800 900 1000 (1050)
NOTCH3 G18 PBX2 RAGE G16 G15 G14 G13 TN-X XB-S CYP21B YB C4B ZB CYP21Ps YA C4A ZA G11 G11a RD C2 G10 G9a G9 G8 Hsp70 2 1 HOM G7c G7b G7a G7d G7 G6 G6a BAT5 G5b CKIIβ G5 G4 G3a G3G1 G2 K18L B144 tC7 LTB TNF LTA NB6 kBL MICB MICA NOB1 NOB2 PERB10 PERB6 BAT1 P5-6 DHFRPs 17 NOB3 PPIPs
(1050) 1100 1200 1300 1400 1500 1600 1700 1800 1900 2000 (2080)
PERB3 PERB11 PERB10
RPL3-Hom B NOB3 NOB3 C NOB4 POU5F1 TCF19 S TUBB X P5-1 HSR1 E MICC
(2080) 2200 2300 2400 2500 2600 2700 2800 2900 3000 (3100)
CAT53 CAT54 CAT55 CAT56 CAT57 CAT59 CAT60 CAT62 TC4 CAT63
hTCTEX-5 ZNF173 VI B30.2 30 92 hSUP45.1 VIII.1 3.8-1.2 P5-2 IV-2 IX-1 P5-3 IV-3 III-1 IV-4 MICD 70 21 PERB2 3.8-1.3 P5-4 IV-5 P5-7 IV-6 VIII.2 P5.C 10.0-1 3.8-1.4 P5-5 III-3 90 IV-8 75 IV-7 IV-9 P5-6 3.8-1.5 IX-2 MICE IV-10 MOG MAD2 MAD1
(3100) 3200 3300 3400 3500 3600 3700 3800 3900 4000 4100
CAT64 CAT65 CAT66 CAT67 CAT70 ZNF178 VEF CAT73A/B HUMCAT75X HUMMHCFANC ZNFA3 B30.7 CAT81 VLG20 CAT79 HUMMHCFANE HUMMHI FAT5 FAT5/FAT15 FAT7 FAT8 CAT82 CAT83 FAT9 FAT10 HUMORLMHC MHCOR2


Chromosom 6
q-Arm
p-Arm
Klasse II
Klasse III
Klasse I
LMP
TAP
210H
C4
Bf
C2
TNF
DP
DQ
DR
B
C
E
A
< Centromer
Telomer >
0
500
1000
1500
2000
2500
3000
3500
4000

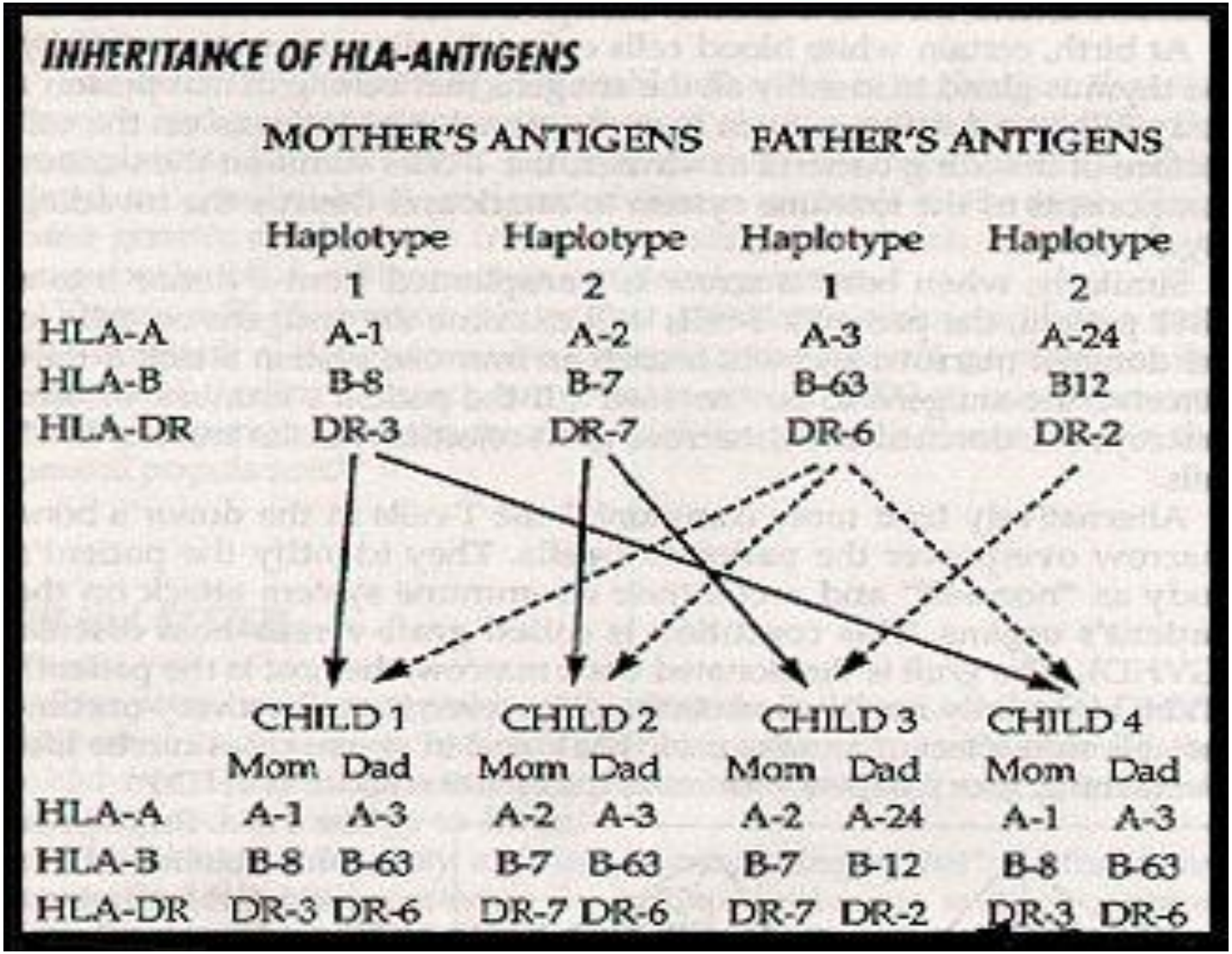
HLA Alleles Numbers

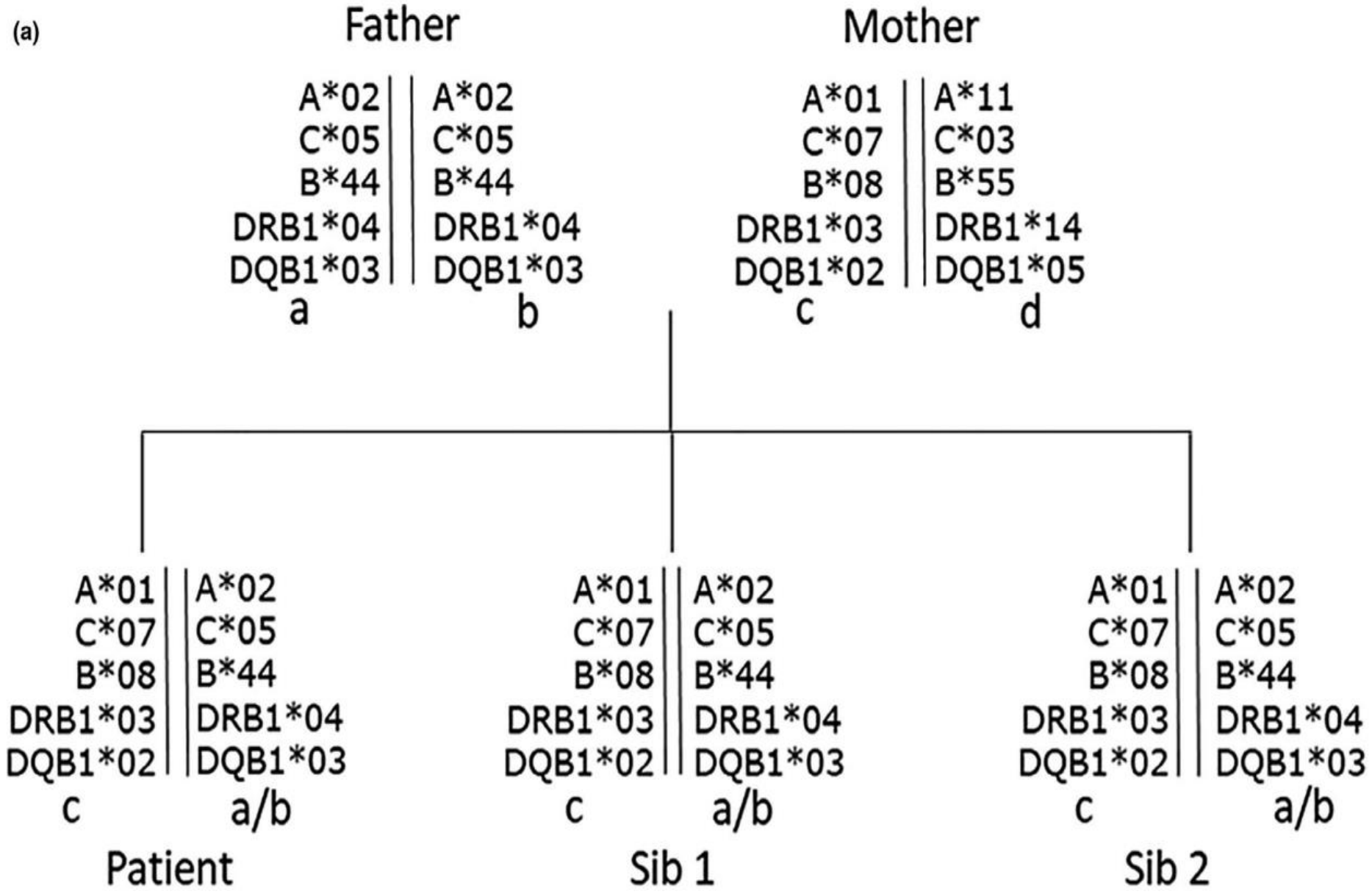
Numbers of HLA Alleles	
HLA Class I Alleles	25,019
HLA Class II Alleles	10,201
HLA Alleles	35,220
Other non-HLA Alleles	796

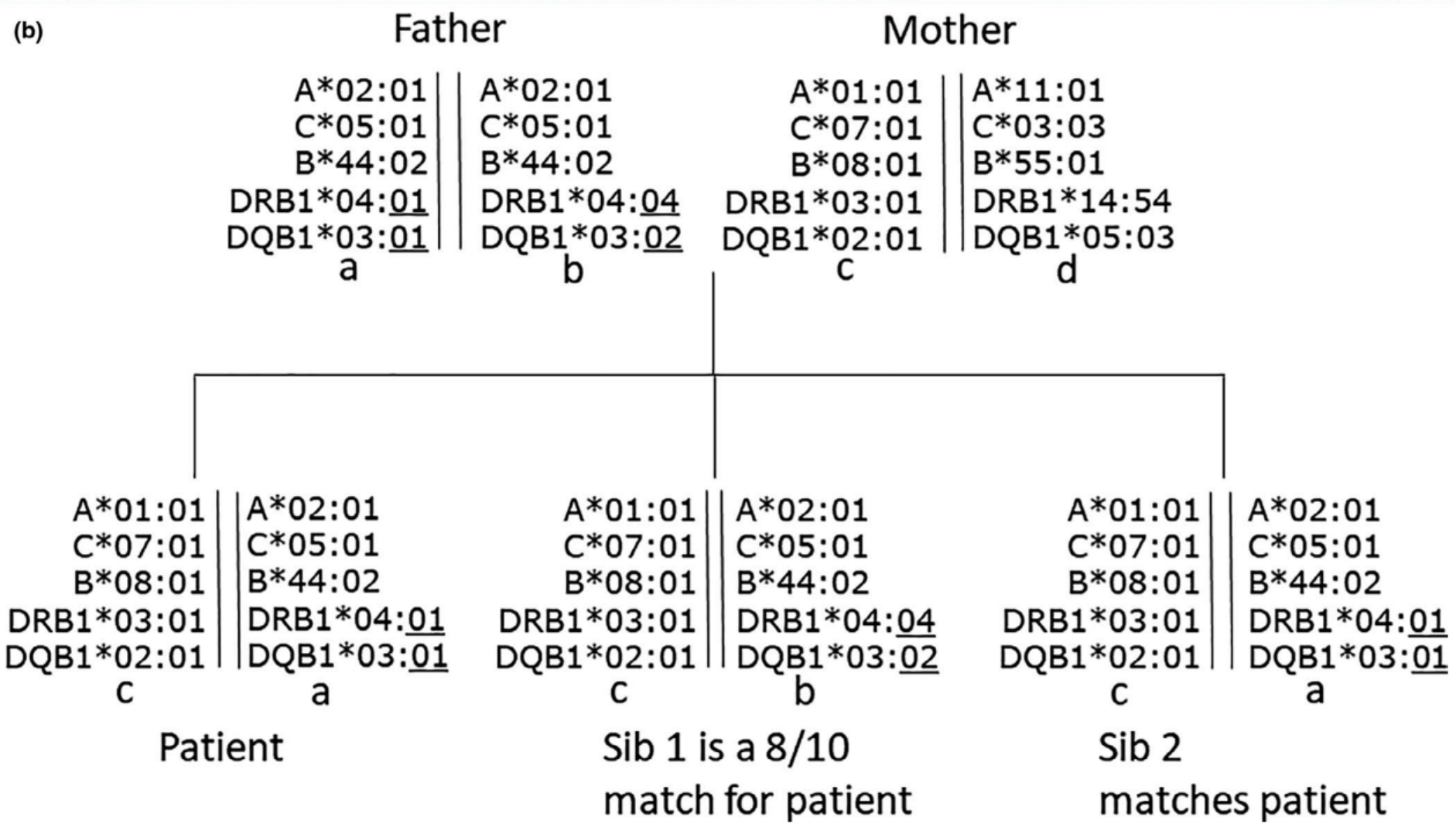

Hyphen used to separate gene name from HLA prefix
Suffix used to denote changes in expression
Separator
Field Separators
HLA-A*02:101:01:02N
HLA Prefix
Gene
Field 1; allele group
Field 2; specific HLA protein
Field 3; used to show a synonymous DNA substitution within the coding region
Field 4; used to show differences in a non-coding region
© SGE Marsh 04/10

HLA TYPING TECHNIQUE

Haplotypes


INHERITANCE OF HLA-ANTIGENS
MOTHER'S ANTIGENS
FATHER'S ANTIGENS
Haplotype 1
Haplotype 2
Haplotype 1
Haplotype 2
HLA-A A-1 A-2 A-3 A-24
HLA-B B-8 B-7 B-63 B12
HLA-DR DR-3 DR-7 DR-6 DR-2
CHILD 1
CHILD 2
CHILD 3
CHILD 4
Mom Dad Mom Dad Mom Dad Mom Dad
HLA-A A-1 A-3 A-2 A-3 A-2 A-24 A-1 A-3
HLA-B B-8 B-63 B-7 B-63 B-7 B-12 B-8 B-63
HLA-DR DR-3 DR-6 DR-7 DR-6 DR-7 DR-2 DR-3 DR-6


(a)
Father
A*02 A*02
C*05 C*05
B*44 B*44
DRB1*04 DRB1*04
DQB1*03 DQB1*03
a b
Mother
A*01 A*11
C*07 C*03
B*08 B*55
DRB1*03 DRB1*14
DQB1*02 DQB1*05
c d
A*01 A*02
C*07 C*05
B*08 B*44
DRB1*03 DRB1*04
DQB1*02 DQB1*03
c a/b
Patient
A*01 A*02
C*07 C*05
B*08 B*44
DRB1*03 DRB1*04
DQB1*02 DQB1*03
c a/b
Sib 1
A*01 A*02
C*07 C*05
B*08 B*44
DRB1*03 DRB1*04
DQB1*02 DQB1*03
c a/b
Sib 2


(b)
Father
Mother
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
A*02:01
C*05:01
B*44:02
DRB1*04:04
DQB1*03:02
b
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*11:01
C*03:03
B*55:01
DRB1*14:54
DQB1*05:03
d
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
Patient
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:04
DQB1*03:02
b
Sib 1 is a 8/10 match for patient
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
Sib 2 matches patient

Donor–recipient HLA match

- 10/10 , 9/10, haplo in HLA-A, -B, -C, -DRB1, -DQB1 (DPB1)

- CB:

Minimum of 8 high-resolution (HLA-A, HLA-B, HLA-C, and HLA-DRB1) for both patient and CB unit

>4/6 HLA-A and HLA-B antigen, HLA-DRB1 high-resolution (traditional match), and >4/8 high-resolution match (some centers investigating use of 4/6 and 3/8 units if adequate dose)

EBMT guidline

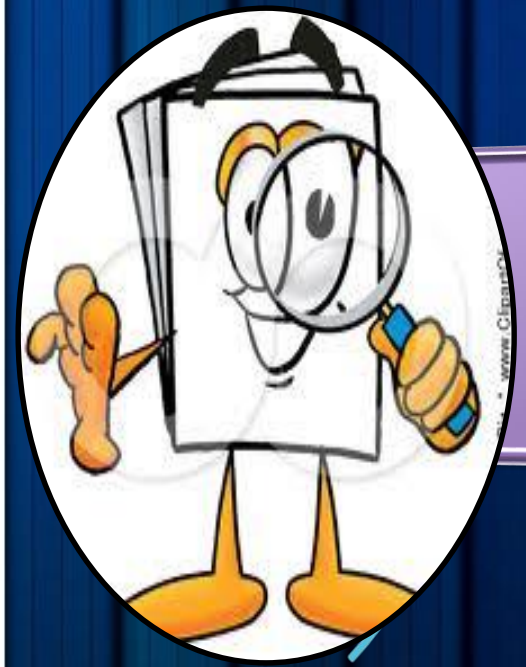
	Volume collected	Med CD34 content	Med CD3 content	Target cell dose
Bone marrow	10–20 mL/kg	$2–3 \times 10^6$/kg[a]	25×10^6/kg	$>2 \times 10^8$ TNC/kg
Peripheral blood	150–400 mL	8×10^6/kg	250×10^6/kg	$5–10 \times 10^6$ CD34+/kg
Umbilical cord blood	80–160 mL	0.2×10^6/kg	2.5×10^6/kg	$>3 \times 10^7$ TNC/kg

[a]Per kg recipient body weight

CB guidelines from the NMDP/CIBMTR:

TNC >2.5 * 107 /kg and CD34 cells >1.5 * 105 /kg

- For prioritization of **cell dose vs HLA match** (applies to single- and double-unit transplants), cell dose frequently needs to take priority over HLA match for adult and larger pediatric patients. HLA-match can take priority in children or smaller adults or those with common HLA typing who have multiple units with high cell dose. Optimizing HLA-match is very important in CB transplant for nonmalignant diagnoses. **In children with nonmalignant diagnoses, higher cell doses (>5 * 107 /kg)** should be selected. Further data are required as to how to balance cell dose against HLA match. A current guidance for consideration is as follows: **if high doses (eg, TNC >3 * 107 /kg and CD34 >2 * 105 /kg), consider optimizing high-resolution HLA match over cell dose**; if lower TNC and CD341 doses, optimize dose first and high-resolution HLA match second; and if units have similar cell doses, optimize high-resolution HLA match.



Severe aplastic anemia (SAA)

- The preferred treatment of SAA is HSCT from HLA-identical sibling donor. Transplantation from a MUD may be considered for patients without a sibling donor after failure of IS therapy or up front in younger ≤20 years if feasible in 2–3 months since diagnosis.
- Currently a North American study aims to compare outcomes of children with SAA treated de novo with IST vs MUD HSCT (ClinicalTrials. gov number NCT02845596). While waiting the results of this trial, if a 10/10 MUD is available and the transplant appears feasible within 2–3 months since diagnosis, this type of HSCT has become a reasonable frontline option for young patients in many centers. Another option is to perform MUD HSCT early after failure of frontline IST within 4–6 months since diagnosis. This is why MUD donor search should be started at diagnosis in young patients who lack a MRD.

SAA

- Alternative HSCTs (MMURD, CB, and haplo family donors) are possible for individuals with no suitable MUD. Alternative HSCTs may be curative, but the risks of graft rejection, infectious complications, and GVHD are higher than those for MRD or MUD HSCT

Diamond-Blackfan Anemia

- Diamond-Blackfan anemia (DBA) is a rare IBMFS caused by heterozygous mutations in ribosomal genes. No genetic aberration is identified in approximately 30% of patients. Patients usually present with transfusion-dependent macrocytic anemia at birth or in early infancy. Mild neutropenia and progressive thrombocytopenia have been observed in the course of the disease. Despite various possible physical abnormalities (short stature, abnormal thumbs, cleft palate, heart defects, urogenital malformations), the non-hematologic phenotype is usually rather subtle in around 50% of patients. Patients with DBA are at increased risk of developing hematologic (AML/MDS) and non-hematologic malignancies (osteosarcoma, colon cancer).
- HSCT from a MSD including cord blood has resulted in OS >80% and is recommended for all indications. Sibling donors should be carefully assessed to rule out silent carrier status. Recent reports described improved outcome of MUD HSCT with OS ranging from 70 to 85% (Strahm, EBMT abstract 2018). By contrast, data supporting HSCT from mismatched donors as standard procedure are insufficient.

- The most common form (60%) of genetic neutropenia is due to mutations in the ELANE gene. Shwachman-Diamond syndrome (SDS) caused by a mutation of SDSB gene is the most common form of neutropenia associated with extra-hematologic features (exocrine pancreas deficiency, metaphyseal dysplasia, mental retardation, cardiomyopathy, and immune dysfunction).
- Diamond-Blackfan anemia (DBA) is a rare IBMFS caused by heterozygous mutations in ribosomal genes. No genetic aberration is identified in approximately 30% of patient