HLA-Matching in Solid Organ Transplantation

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16 – 18 September 2013
Changing HLA typing strategies in organ transplantation

- Still HLA typing?
- How, when and why?
<table>
<thead>
<tr>
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The DNA sequence and analysis of human chromosome 6

The present manuscript describes the complete sequence of human chromosome 6 as determined by the Human Genome Project. The chromosome is divided into 869 segments, each containing a single nucleotide, and the total sequence is 253,832,587 nucleotides long. The sequence was obtained by a combination of direct sequencing and comparison with the sequences of other human chromosomes. The sequence is presented in a linear format, with the order of the segments determined using the Map of the Human Genome Project. The sequence is available for download from the project's website.
HLA genomic typing

RFLP & Southern blotting

PCR-SSP

HLA-DQA1: Reverse dot-blot

Sequencing
How much does HLA compatibility influence organ transplantation?

- Considering the transplanted organ
  - Kidney
  - Liver
  - Heart
  - Lung

- Considering the analyzed HLA loci
  - HLA-DQ
  - HLA-DP

- Considering the typing technique
HLA-A+B+DR Mismatches
Deceased Donor, First Kidney Transplants 1985-2010
PRA > 50 %

% Graft Survival

Years

0 MM n= 684
1 MM n= 878
2 MM n=1,568
3 MM n=1,871
4 MM n=1,335
6 MM n= 208
5 MM n= 648

CTS Collaborative Transplant Study
HLA-A+B+DR Mismatches
Deceased Donor Kidney Retransplants 1985-2010
PRA > 50 %

% Graft Survival

Years

0 MM n=1,376
1 MM n=1,616
2 MM n=2,641
3 MM n=2,742
4 MM n=1,630
5 MM n= 699
6 MM n= 188

CTS Collaborative Transplant Study
HLA-A+B+DR Mismatches
Deceased Donor, First Kidney Transplants 2000-2010

% Graft Survival

Years

CTS Collaborative Transplant Study
HLA-A+B+DR Mismatches
First Orthotopic Heart Transplants 1985-2010

% Graft Survival

0-2 MM n=1,663
3 MM n=4,408
4 MM n=8,628
5 MM n=9,967
6 MM n=4,745

Years

CTS Collaborative Transplant Study
HLA-A+B+DR Mismatches
Lung Transplants 1988-2010

% Graft Survival

Years

1 MM n= 99
2 MM n= 548
3 MM n= 1,605
0 MM n= 32
4 MM n= 2,778
5 MM n= 2,788
6 MM n= 1,231

CTS Collaborative Transplant Study
HLA-A+B+DR Mismatches
Deceased Donor, First Liver Transplants 1988-2010

% Graft Survival

Years

3-4 MM  n= 9,003
5-6 MM  n= 10,207
0-2 MM  n= 1,065

CTS Collaborative Transplant Study
Can the HLA compatibility effect be seen in multicenter studies of large cohorts?
HLA-A,-B,-DR MATCHES

2881 first kidney transplants (1981-2011)

\[ p = 0.00005 \]

4-6 M  (870)
1-3 M  (2011)
HLA-A,-B,-DR MATCHES
488 first heart transplants (1990-2012)

p=0.015
HLA-A,-B,-DR MATCHES

176 first lung transplants (1993-2012)

- 2-5 HLA-A,-B,-DR M (73)
- 1 HLA-A,-B,-DR M (63)
- 0 HLA-A,-B,-DR M (40)

p=0.163

i=0.163
HLA-A,-B,-DR MISMATCHES

1013 first liver transplants (2000-2010)

% graft survival

p=0.708

- 0-2 MM (43)
- 3-4 MM (450)
- 5-6 MM (520)

time (years)
HLA-A,-B,-DR MISMATCHES

First liver transplants (2000-2010)

HCV neg (619 tx)

HCV pos (394 tx)

% graft survival

time (years)

p=0.405

p=0.517
Is DNA typing useful?

What is the compatibility effect of the HLA-DQ and DP loci?
HLA-DR Mismatches
Kidney Transplants 1985-2010

% Graft Survival

0 MM n=121,802
1 MM n=152,961
2 MM n=38,201

Years
DNA Typing HLA-DRB Mismatches

Deceased Donor Kidney Transplants 1985-2010
0 Mismatch HLA-DR Serology

DNA: DRB MM=0  n=10,210
DNA: DRB MM>0  n=1,610
DNA Typing HLA-DQB Mismatches
Deceased Donor, First Kidney Transplants 1985-2010

% Graft Survival

0 MM  n=11,002
1 MM  n=13,520
2 MM  n= 2,372

Years
DNA Typing HLA-DQB Mismatches
Deceased Donor, First Kidney Transplants 1985-2010
> 50 % PRA

% Graft Survival vs Years

0 MM, n=651
1 MM, n=806
2 MM, n=130

CTS Collaborative Transplant Study
R-21811-0812
DNA Typing HLA-DP Mismatches
Deceased Donor, First Kidney Transplants 1985-2010

% Graft Survival

Years

0 MM n=1,471
2 MM n=1,410
1 MM n=3,043

CTS Collaborative Transplant Study

R-22001-0812
DNA Typing HLA-DP Mismatches
Deceased Donor Kidney Retransplants 1985-2010

% Graft Survival

Years

0 MM n = 486
1 MM n = 1,039
2 MM n = 423

CTS  Collaborative Transplant Study
R-22101-0812
DNA Typing HLA-DP Mismatches

Deceased Donor Kidney Retransplants 1985-2010

> 50% PRA

% Graft Survival

0 MM  n=176
1 MM  n=346
2 MM  n=123

Years
Is it useful to HLA type donor-recipient pairs?

- The effect of compatibility for HLA-A,B,DR is evident for all types of organ transplants with the exception of the liver.
- 10% improvement at 10 years for more compatible grafts compared to less compatible grafts (= 100 additional functioning grafts every 1000 transplants).
- This parameter is still the most effective.
- And its effect is still the mainstay in recent years, superior to the effect determined by ischemia.
- Also compatibility for HLA-DQ and DP exerts a beneficial effect, at least in kidney transplant recipients but, above all, in retransplanted and immunized patients.
Is HLA typing of donor-recipient pairs still worthwhile?

- Retrospectively, it could serve as a guide to immunosuppressive therapy for heart and lung transplantation
- In clinical practice, HLA-A, B, DR typing is employed
- Many Centers have introduced DNA-based methods
- DQ typing becomes essential in transplant programs for hyperimmununized patients
- DP typing is performed retrospectively to clarify whether an anti-DP antibody is an anti-DSA (donor specific antibody)