



HLA-DPB1 — an overlooked determinant of hematopoietic cell transplantation outcome?

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ABSTRACT

A statistical meta-analysis of survival data for 1347 hematopoietic cell transplants was carried out to understand more about how HLA gene mismatches influence transplantation outcome.

Mismatches of HLA-C & HLA-DPB1 alleles showed a negative effect on recipients' survival prospects under our statistical modelling assumptions.

Recently the importance of HLA-C matching has become accepted, but the importance of HLA-DPB1 matching is unproven. If other studies support our finding, it will need to be incorporated into clinical protocols for finding hematopoietic cell donors for patients.

HEMATOPOIETIC CELL TRANSPLANTATION

In various life-threatening diseases (leukæmias, lymphomas, immune system disorders) some kind of HCT (e.g. bone marrow transplantation) is often the best treatment option.

Adverse transplantation reactions are linked to disparities between donor and recipient alleles of the highly polymorphic Human Leukocyte Antigen (HLA) genes of the Major Histocompatibility Complex (MHC) on chromosome 6.

The relative importance of mismatches at different HLA genes are not understood. Transplant centres' donor matching guidelines differ.

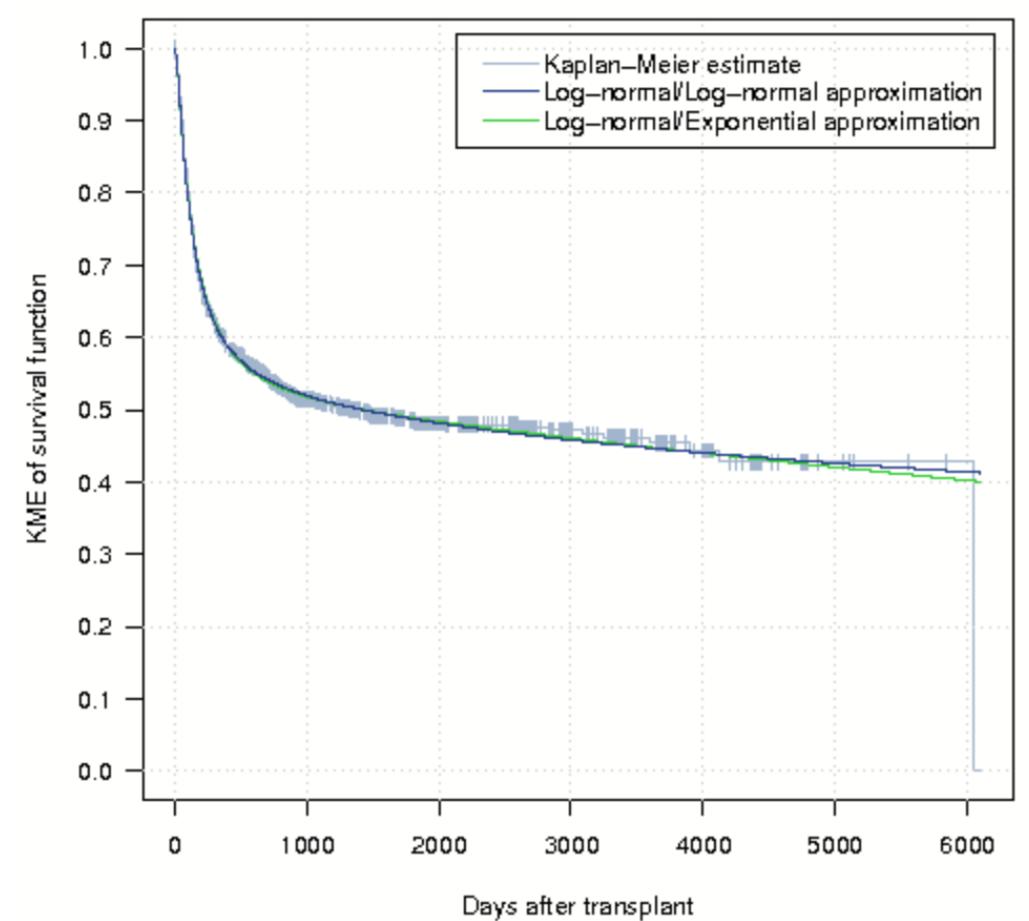
DATA

The publicly available dbMHC database of the International Histocompatibility Working Group was used.

For each recipient-donor pair the allele types (4-digit codes) of six HLA genes (HLA-A, -B, -C, -DRB1, -DQB1, -DPB1) were given. HLA-DPB1 types were available for 1050 of the 1347 pairs.

STATISTICAL MODEL

A new parametric model of survival time distributions was investigated in the maximum likelihood framework.



Under the model, recipients encounter either *early* or *late* failure. Survival time has a mixture distribution of these two.

Time to early failure is modelled by log-normal, time to late failure by log-normal or exponential distributions.

Figure shows model fit to data.

INDIVIDUAL DISPARITIES & MODEL SELECTION

Prospects of individual recipients were described by a function of the linear combination of 4-digit mismatch counts (0, 1 or 2) between donor and recipient for some HLA genes. Greater mismatch count increases the probability of early failure.

We did exhaustive variable selection cycles ($2^6 - 1$ model fitting per cycle for the six genes) with the different mixture distributions.

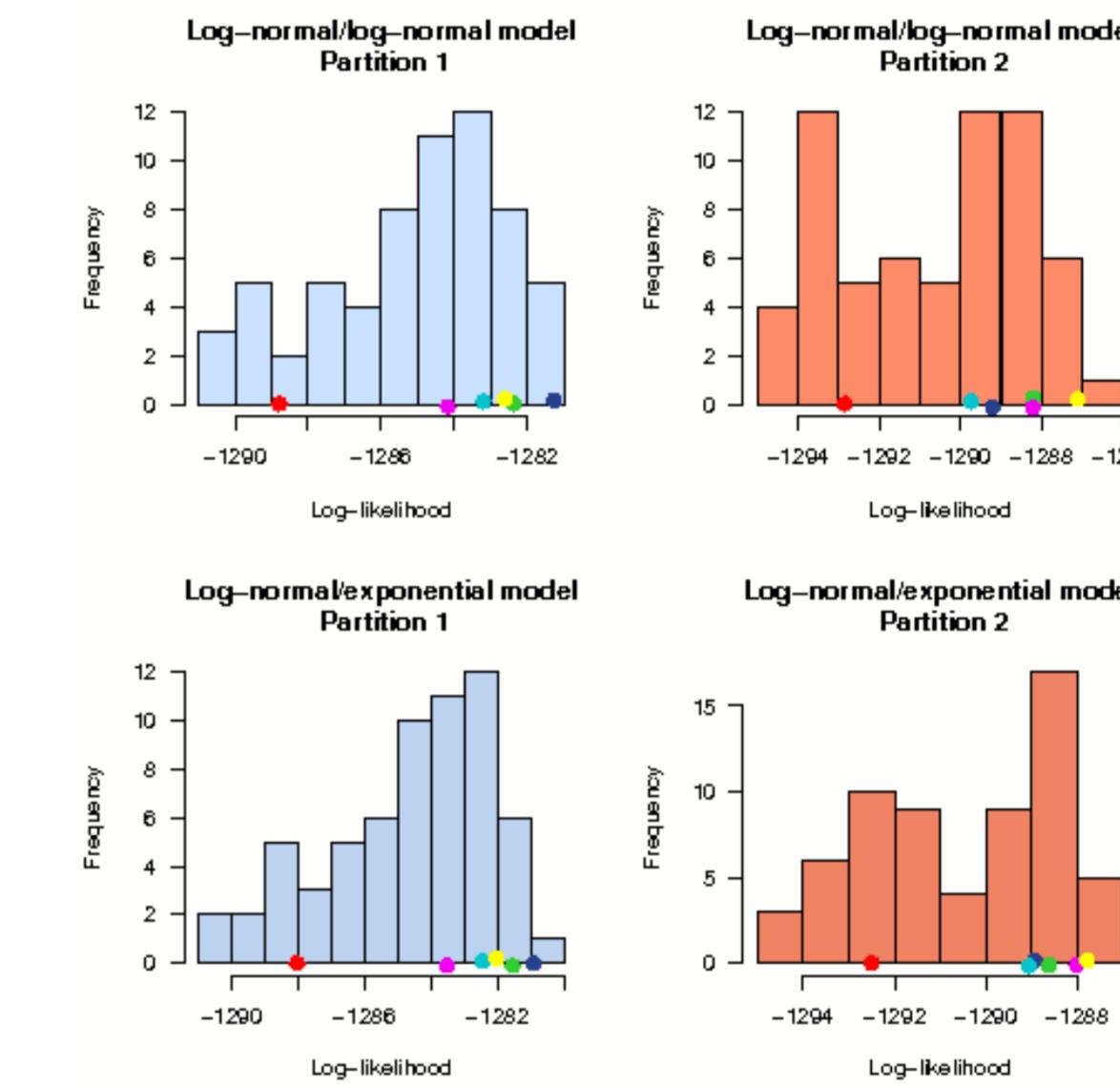
The data was partitioned into training and test sets to assess predictive power. Explanatory power of different covariate sets was compared using *likelihood ratio test* (LRT), *Akaike information criterion* (AIC) and *Bayesian information criterion* (BIC).

RESULTS

♦ Covariate sets with most explanatory and predictive power: [B,C,DRB1,DPB1], [B,C,DPB1], [B,C], [C,DPB1], [C].

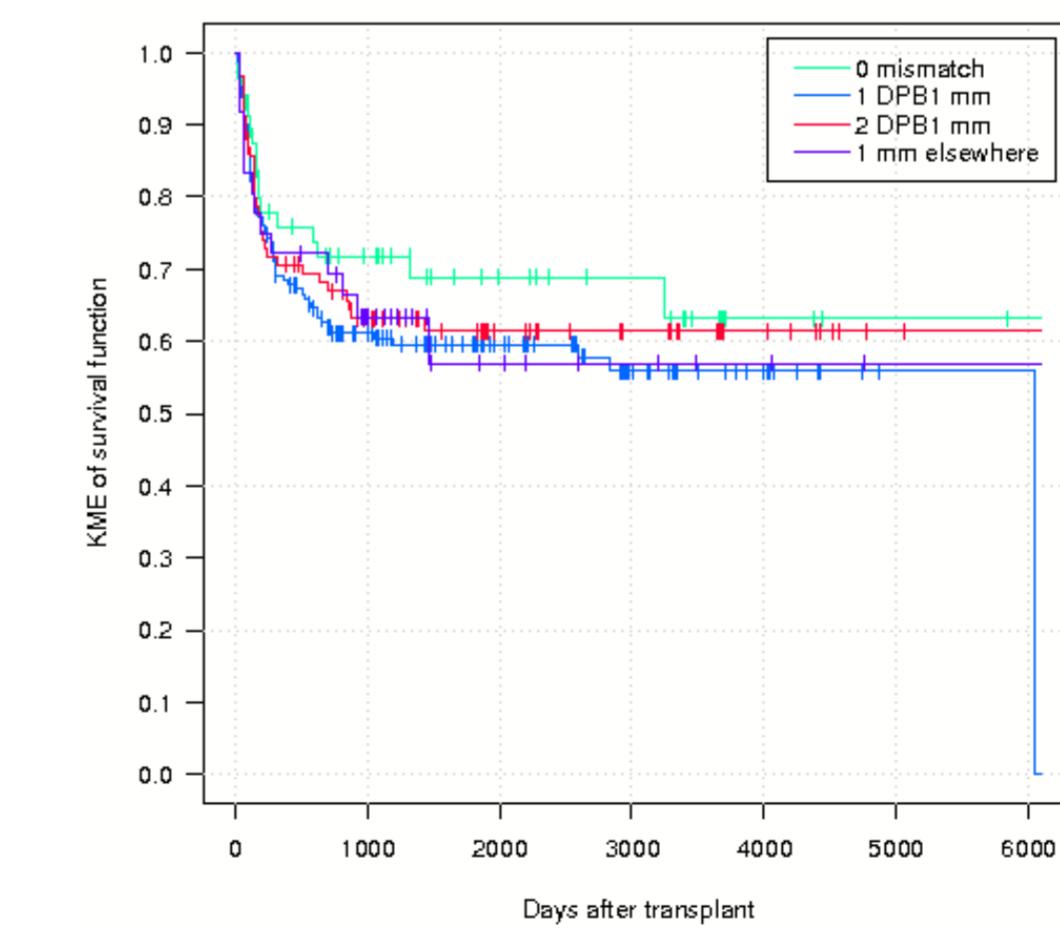
♦ [C,DPB1] is a good compromise between good fit on the training set, small number of covariates and reasonable predictive power on the test set.

Histograms of the $2^6 - 1$ log-likelihood values for the test set of all DPB1-typed recipient-donor pairs using parameter values from training. Shown for both mixture distributions and for two different partitions.



- [B,C,DRB1,DPB1]
- [B,C,DPB1]
- [B,C]
- [C,DPB1]
- [C]
- Reference: log-likelihood of the prediction without any mismatch covariates

♦ The negative effect of HLA-DPB1 mismatches can be visualised.



Probability of survival for the homogeneous cohort of the 787 HLA-DPB1-typed chronic myelogenous leukemia patients.

- 0 mismatch
- 1 DPB1 mismatch, no mismatch elsewhere
- 2 DPB1 mismatches, no mismatch elsewhere
- 1 mismatch anywhere but at DPB1

♦ Surprisingly, the study did not indicate the importance of HLA-A matching. The reason may be that HLA-A mismatched pairs were too rare.