The Probability of Finding a Suitable Related Donor for Bone Marrow Transplantation in Extended Families

By R.F. Schipper, J. D’Amaro, and M. Oudshoorn

In bone marrow transplantation, the advantages of family donors over unrelated donors are threefold. (1) Family donors are better matched because they share complete haplotypes. (2) The time between the start of the search and the actual transplantation can be much shorter than for unrelated donors. (3) Related bone marrow transplantation is cheaper. We developed a procedure for calculating the probability of finding a suitable donor among cousins and blood-related aunts and uncles (the extended family). The procedure calculates the following probabilities \( P \): (1) \( P \) that any blood-related uncle or aunt is a suitable donor, (2) \( P \) that a suitable donor exists in all blood-related uncles/aunts (from one recently described by Kaufman (Bone Marrow Transplant 15:279, 1995).

Materials and Methods

Description of the procedure. We follow the convention of labeling the haplotype that the patient inherited from his father as A and the haplotype that he inherited from his mother as C. The frequencies (HF) of those haplotypes are used to calculate the probability that an extended family member exists with haplotypes A and C. The haplotypes B and D, which are not inherited by the patient, are assumed to be any haplotype that is neither A nor C. The special case in which any parent of the patient is homozygous is discussed in the section on homozygosity. The procedure has two parts, i.e., phase I for uncles and aunts and phase II for cousins.

Phase I: uncles and aunts. This phase calculates the probability of an identical family member among the blood-related uncles and aunts of the patient. The calculation consists of three parts.

Part 1 consists of the calculation of the probability \( P \) that a sister or brother of the father is AC, using the fact that the father inherited A from one grandparent of the patient and B from the other grandparent of the patient and that the two other haplotypes of the father’s parents are unknown. AC individuals can therefore result from several grandparental mating types, as shown in Table 1 (where N is not A and not C). \( P \) is therefore calculated using the equation: \( P = 0.25 \times H_{FA} + 0.5 \times H_{FC} \times H_{FC} \). Part 2 consists of the calculation of the probability \( P \) that a sister or brother of the mother is AC: \( P = 0.25 \times H_{FA} + 0.5 \times H_{FC} \times H_{FC} \). Part 3 consists of the combination of \( P \) and \( P \) into a combined probability for all blood-related uncles and aunts as follows: \( P = (1 - P)^2 \times (1 - P)^2 \) (equation 1), where \( N_1 \) and \( N_2 \) are the number of brothers/sisters of the father and mother, respectively.

Phase II: cousins. The second phase calculates the probability of finding a cousin with the same haplotypes as the patient. Table 2 gives the different mating types of cousins and aunts that can result in AC cousins of the patient and the percentage of expected AC offspring. N again denotes any haplotype but A or C. The chances of the occurrence of the five haplogetic combinations AN, AA, AC, CC, and CN are different for the uncle/aunt that is non-blood-related to the patient and the uncle/aunt that is blood-related to the patient. For the non-blood-related uncle/aunt, these probabilities equal the product of the haplotype frequencies: \( P_{AN} = 0.25 \times H_{FA} \times H_{FC} \), where \( H_{FA} = (1 - H_{FA} - H_{FC}) \); \( H_{AA} = H_{FA} \); \( P_{AC} = 0.25 \times H_{FA} \times H_{FC} \); \( H_{CC} = H_{FA} \); \( H_{CN} = 0.25 \times H_{FA} \times H_{FC} \). For the blood-related uncle/aunt on the father’s side, these probabilities are calculated as follows: \( P_{AN} = 0.25 \times H_{FA} + 0.25 \times H_{FA} \times H_{FC} \). For the blood-related uncle/aunt on the mother’s side, these probabilities are calculated as follows: \( P_{AN} = 0.25 \times H_{FA} + 0.25 \times H_{FA} \times H_{FC} \). These differ from the non-blood-related side because one of the grandparents must have a A (we will call this the first grandparent) and the other B (the second grandparent). We will explain the

Definitions

The nuclear family consists of the parents and siblings of the patient. The extended family consists of first cousins and blood-related uncles and aunts of the patient. An identical family member is one who shares one HLA-haplotype with the patient and one extended haplotype. An extended haplotype is a specific combination of alleles from different loci that are in significant linkage disequilibrium in chromosomes of unrelated individuals.1

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most complex one, \( P_{AN} \) (also see the pedigree in Fig 1): .25 because the first grandparent must have A (at least once) and the second must have B (at least once), resulting in a 25% probability of AB offspring. \( .25 \times \text{HF}_A \) because the homozygous combination AA (with a probability of \( \text{HF}_A \)) in the first grandparent combined with BX (B with any other haplotype) in the second adds a 25% probability of AB offspring; \( .25 \times \text{HF}_N \) because the (homozygous NN) combination BN in the second grandparent combined with AX in the first, adds a 25% probability of AB offspring; \( .25 \times \text{HF}_A \times \text{HF}_N \) because the homozygous combination AA in the first grandparent, combined with BN in the second grandparent, adds a 25% probability of AN offspring; \( .25 \times \text{HF}_A \times \text{HF}_N \) because the homozygous combination AA in the first grandparent, combined with BN in the second grandparent, adds a 25% probability of AN offspring.

Table 1. The Percentage AC Offspring for the Grandparental Mating Types on the Father’s Side

<table>
<thead>
<tr>
<th>Known Haplotype</th>
<th>( \text{B} )</th>
<th>( \text{B} )</th>
<th>( \text{B} )</th>
<th>( \text{B} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{A} )</td>
<td>( \text{A} )</td>
<td>( .5 )</td>
<td>( .5 )</td>
<td>( .5 )</td>
</tr>
<tr>
<td>( \text{A} )</td>
<td>( \text{C} )</td>
<td>( .25 )</td>
<td>( .25 )</td>
<td>( .25 )</td>
</tr>
<tr>
<td>( \text{A} )</td>
<td>( \text{N} )</td>
<td>( .25 )</td>
<td>( .25 )</td>
<td>( .25 )</td>
</tr>
</tbody>
</table>

Column totals: \( .25 \text{HF}_A \times \text{HF}_C \) + \( .25 \text{HF}_C \times \text{HF}_A \)

HFA; \( P_{AN} = .25 \times \text{HF}_A ^2 \); \( P_{AC} = .25 \times \text{HF}_A \times .5 \times \text{HF}_A \times \text{HF}_C \); \( P_{AC} = .25 \times \text{HF}_A \times .25 \times \text{HF}_C \); \( P_{AN} = .25 \times .25 \times \text{HF}_A \times .25 \times \text{HF}_C \times .25 \times \text{HF}_C \times .25 \times .25 \times \text{HF}_A \times \text{HF}_C \times \text{HF}_A \times \text{HF}_C \). The haplotypic combinations and their corresponding percentages in the offspring are set out in Table 4. To illustrate these calculations, we give an example: if the frequencies of A, C, and N are .1, .1, and .8, respectively, then, for mating type AN \( \times \) AN on the father’s side, the frequency of AN \( \times \) AN is .25 \( \times \) AN \( \times \) AN = .16 for the non-blood-related uncle/aunt and .25 \( \times \) .1 \( \times \) .8 \( \times \) .25 \( \times \) .1 \( \times \) .25 \( \times \) .8 = .515 for the blood-related uncle/aunt; but, naturally, the percentage of AC offspring from that mating type = 0, making the contribution to the overall single cousin probability = 0. Mating type AN \( \times \) AN on the mother’s side, with AN \( P = \text{HF}_A \times \text{HF}_N = .08 \) as non-blood-related and CC \( P = .25 \times \text{HF}_A \times .25 \times \text{HF}_C ^2 = .0275 \) as blood-related combination and a 50% probability of AC offspring, contributes .08 \( \times \) .0275 \( \times \) .5 = .0011 to the overall single cousin probability.

Because the match possibilities of cousins from the same parents are dependent, the chance of finding a matched cousin in a particular family has to be calculated first. If \( P_{j} \) is the probability of the occurrence of mating type \( j \) and \( P_{j} \) is the percentage of AC offspring of that mating type, then for mating type \( j \) in family \( i \) with \( N \) cousins, the probability of a matched cousin is as follows: \( M_{ij} = P_{j} \times (1 - (1 - P_{j})^{N}) \) (equation 2).

In the total of \( J \) (\( n = 25 \)) mating types, the probability of a matched cousin in family is as follows: \( M = \sum_{j=1}^{J} P_{j} \times (1 - (1 - P_{j})^{N}) \) (equation 3).

The overall probability of a matched cousin in all families is then calculated as follows: \( M = 1 - \prod_{j=1}^{J} (1 - M_{i, j}) \) (equation 4). These probabilities are calculated for the father’s and the mother’s side of the family separately because of the difference in mating types (see Tables 3 and 4, respectively) and the probabilities that they occur. The probability \( M_{i} \) on the father’s side and \( M_{m} \) on the mother’s side are combined into the overall probability \( P_{a} \) of finding an identical cousin using equation 5: \( P_{a} = 1 - (1 - M_{i}) \times (1 - M_{m}) \) (equation 5).

Overall probability. The final calculation yields the combined probability of finding an identical family member in uncles or aunts.
The probability of finding a matched extended family member changes accordingly. If the father has haplotypes AA, then Table 1 changes to Table 5. If both grandparents have haplotype A, an extra factor of \( .25 \times H_F C \) has to be added to the probability that a blood-related uncle or aunt on the father's side is AC, being the probability of AC offspring from the combination of a possible haplotype C in the first grandparent and the known haplotype A in the second grandparent. This extra factor is placed at the right margin of Table 5. Similarly, the probability that a blood-related uncle or aunt on the mother's side is AC increases by a factor \( .25 \times H_F C \).

The equations for \( P_1 \) and \( P_2 \) change to the following: \( P_1 = .5 \times H_F C + .5 \times H_F A \times H_F C \); \( P_2 = .5 \times H_F A + .5 \times H_F A \times H_F C \).

The probability that a first cousin is AC when the father of the patient is homozygous changes, because the probabilities of the occurrence of five haplotype combinations AN, AA, AC, CC, and CN change to the following: \( P_{AN} = .5 \times H_F N + .5 \times H_F A \times H_F N \); \( P_{AA} = .25 \times .5 \times H_F A + .25 \times H_F A \times H_F C \); \( P_{AC} = .5 \times H_F C + .5 \times H_F A \times H_F C \); \( P_{CC} = .25 \times H_F C \); \( P_{CN} = .5 \times H_F C + .5 \times H_F N \times H_F C \).

\( P_{AN} \) and \( P_{AC} \) increase, whereas \( P_{CN} \) decreases. \( P_{AN} \) can either increase or decrease, depending on the frequencies of the haplotypes involved. \( P_{AC} \) does not change. In general, the chance of inheriting A via the blood-line increases, whereas that of inheriting C via the blood-line decreases. The probability that a first cousin is AC when the mother of the patient is homozygous changes accordingly, as follows: \( P_{AN} = .5 \times H_F N + .5 \times H_F A \times H_F N \); \( P_{AA} = .25 \times H_F A \times H_F C \); \( P_{AC} = .5 \times H_F A + .5 \times H_F A \times H_F C \); \( P_{CC} = .25 \times H_F C \); \( P_{CN} = .5 \times H_F C + .5 \times H_F C \times H_F C \).

\( P_{AN} \) can either increase or decrease, depending on the frequencies of the haplotypes involved. \( P_{AC} \) does not change. In general, the chance of inheriting A via the blood-line increases, whereas that of inheriting C via the blood-line decreases. The probability that a first cousin is AC when the mother of the patient is homozygous changes accordingly, as follows: \( P_{AN} = .5 \times H_F N + .5 \times H_F A \times H_F N \); \( P_{AA} = .25 \times H_F A \times H_F C \); \( P_{AC} = .5 \times H_F A + .5 \times H_F A \times H_F C \); \( P_{CC} = .25 \times H_F C \); \( P_{CN} = .5 \times H_F C + .5 \times H_F C \times H_F C \).

### RESULTS

Figure 2 shows an example of the output of the program based on a patient with one very frequent haplotype (HLA-A1, -B8, -DR3) and one less frequent haplotype (HLA-A2, -B44, -DR7). The first section (Patient data) shows a summary of the input data with the haplotype frequencies. The second section (Uncles/aunts) shows the probability \( P_1 \) of finding a suitable donor among the blood-related uncles and aunts. The third section (Cousins) shows the results of calculating the probability \( P_2 \) of a first cousin with haplotypes A and C. The last section (Total) shows the overall probability of finding a suitable donor in the extended family. Note that the combined probabilities in the second, third, and last section are not the sum of the individual chances, but have been calculated using equations 1, 5, and 6.

The higher frequency of haplotype A in this example results in a higher probability of finding a suitable donor in the mother's side of the family, where the less frequent haplotype C is inherited via the blood-line, whereas the probability that haplotype A is inherited by chance is quite high.

To illustrate the effectiveness of searching for extended family donors, we looked at 20 donor searches that had been performed for Dutch patients by the Europdonor Foundation. Table 6 summarizes the results of these searches. Fourteen of these patients had one HLA-A, -B, -DR haplotype, with a high frequency in the Dutch Caucasian population; the remaining 6 had one HLA-A, -B or HLA-B, -DR haplotype with a high frequency. In all cases, the family lineage with the least common haplotype was searched first. The second family lineage was only searched in one case, in which both haplotypes were rather common. In the remaining cases, an unrelated donor was searched instead. All donors were found in the lineage with the least common haplotype.
FINDING SUITABLE DONORS IN EXTENDED FAMILIES

Table 6. Results of Searching for Donors in the Extended Families of 20 Dutch Caucasoid Patients

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>No. of Patients</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>for Whom an One HLA Antigen Mismatched Donor Was Found</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Patients with one frequent HLA-A, -B, -DR haplotype</td>
<td>14</td>
<td>6.4</td>
</tr>
<tr>
<td>B. Patients with one frequent HLA-A, -B, or -B, -DR haplotype</td>
<td>6</td>
<td>9.3</td>
</tr>
</tbody>
</table>

For the 14 patients with a frequent HLA-A, -B, -DR haplotype, an average of 6.4 family members were typed per patient. For 3 of these patients, an identical donor was found; for 6 of these patients, a donor with one HLA mismatch was found. For the 6 patients with a frequent HLA-A, -B or -B, -DR haplotype, more family members had to be typed (an average of 9.3 per patient). Although no identical donors were found for them, a donor with one HLA mismatch was found for 3 of them.

DISCUSSION

HLA-matched related donors are preferable to unrelated donors because unrelated donors are merely matched at the phenotypic level. Moreover, their phenotypes are usually determined by serology, showing only part of the genetic polymorphism. However, a related donor shares haplotypes with the patient. A haplotype that is shared via the blood line is completely identical for the HLA region, whereas extended haplotypes are very likely to be completely identical. Also, family donors may be better matched for other factors that are not routinely tested for, such as antigens from minor histocompatibility loci. Additionally, the motivation of family members to act as donors is usually high, so the availability of matched family donors probably exceeds that of unrelated donors.

It is quite a common procedure to start searching for unrelated donors when no identical family member has been found in the nuclear family. The procedure described here can be a motivating factor for the patient's physician to consider recruiting donors in the patient's extended family. In general, the larger the size of the extended family, the more useful the search for identical related donors will be, although the probability of finding one depends largely on the frequencies of the haplotypes involved.

Our procedure is also usable for calculating the probability that an extended family member exists that is mismatched with the patient at one of the HLA loci. This can be performed by replacing the frequency of one of the haplotypes by the frequency of the corresponding haplotype with one locus less, leaving out the locus for which a mismatch is allowed. For example, if one of the patient's haplotypes is HLA-A66, -B8, -DR3, then the calculation of the probability of finding an extended family member with a possible mismatch for HLA-A on that haplotype can be made by using the frequency of the HLA-B8, -DR3 haplotype in the general population. The survival of a patient who received marrow from a family donor who has only one antigen mismatch with the patient may be equal to that of patients who received marrow from an HLA-identical sibling or from a phenotypically matched unrelated donor.

The increased probability of finding identical related donors as compared with identical unrelated donors is most striking when one of the patient's haplotypes has a very low frequency in the population and the other haplotype has a high frequency. Table 7 shows the probability of finding an identical family member when one haplotype frequency is less then 1 in 10,000, whereas the other haplotype is one of the five most frequent haplotypes in the Dutch caucasoid population and for a hypothetical situation of exactly three children per household (16 extended family members). Note that the contribution to the overall probability of the family lineage that inherited the common haplotype is negligible. The probabilities in Table 7 are established entirely through the family lineage that inherited the uncommon haplotype.

The side of the family that contributes most to the overall probability is the side one should start examining. Any family members that are either too old or too young to act as bone marrow donors should be left out of the calculations by simply reducing the number of their category in the procedure.

It is imperative that haplotype frequency estimates are derived in the same population, ie, ethnic group, that the patient's family belongs to. For haplotype frequencies to be used in this manner, the genes in the different HLA loci in that population naturally should be in Hardy-Weinberg equilibrium.

The method recently described by Kaufman is different from ours in several aspects. His model predicts only the probability of finding a matched extended family member who inherited one matching haplotype (A or C) from the common grandparent. In the appendix of his report, Kaufman makes two assumptions that exclude from his model the probability that the other haplotype of a grandparent is A or C, leading to extra matched extended family members. This assumption is reasonable, but even if HFC is low (<1%), the contribution to the overall probability can be more than negligible, especially when many extended family members are available. Also, Kaufman's model does not take into account the possibility that either parent of the

Table 7. Minimal Probability of Finding an Identical Family Member for the Five Most Frequent Haplotypes in the Dutch Caucasoid Population Based on Three Children per Household

<table>
<thead>
<tr>
<th>Haplotype Frequency</th>
<th>Probability of an Identical Family Member</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 B8 DR3</td>
<td>0.0720</td>
</tr>
<tr>
<td>A3 B7 DR2</td>
<td>0.0470</td>
</tr>
<tr>
<td>A2 B7 DR2</td>
<td>0.0238</td>
</tr>
<tr>
<td>A2 B80 DR13</td>
<td>0.0237</td>
</tr>
<tr>
<td>A3 B36 DR1</td>
<td>0.0214</td>
</tr>
</tbody>
</table>
patient may be homozygous, which considerably changes the probability of finding an identical extended family member. Finally, it would have been quite useful if the model described by Kaufman had been built into a computer program, making the calculations much easier than performing them by hand.

The procedure we describe is very efficient. After identifying the haplotypes in the nuclear family and examining the structure of the extended family, calculation is performed in a matter of minutes. We plan to extend the procedure to include nephews and nieces of the patient. We developed a Personal Computer program, EXTFAM, that calculates the probability that at least one identical family member exists in the extended family of a patient. The program is available on request to the corresponding author.

In conclusion, we describe a method for calculating the probability of finding a haplotype-matched related donor among the blood-related uncles, aunts, and first cousins of a patient and provide a computer program that calculates such probabilities for any combination of haplotype frequencies and family compositions. The use of family donors avoids lengthy matching procedures and provides patients with donors who are not only identical for determinants in the matched loci but also for others in the unexamined loci.

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The probability of finding a suitable related donor for bone marrow transplantation in extended families [see comments]

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