Introduction

Each year many people worldwide are diagnosed with leukaemia or other fatal blood disorders. Bone marrow or stem cell transplantation offers the only possible curative treatment for many of these patients.

Bone marrow is a spongy tissue inside our bones, which makes blood cells. Stem cells born in the bone marrow develop into mature circulating red cells, white cells or platelets as the body needs. These stem cells are used for transplantation and can be collected from bone marrow, peripheral blood or placental (umbilical cord) blood.

The most suitable donor for a stem cell transplant is a fully matched (tissue typed) family member, but only about one patient in three has such a donor. If a suitable donor is not found within the immediate family a wider family search and/or unrelated donor search may be needed.

This information has been designed for patients and their families to inform them of the processes and timing involved when searching for a suitable stem cell donor.

HLA typing

What is tissue typing?

Matching of stem cell donor to a recipient is determined by comparing their tissue types, also known as their Human Leucocyte Antigen (HLA) types. An individual's HLA type is present on nearly all tissues in the body. The white cells from a blood sample are a convenient source of "tissue" that the laboratory can use to determine an individual's HLA type.

Why is HLA typing important?

HLA typing is important since the degree of HLA compatibility between donor and recipient will influence the outcome of the transplant.

The function of the immune system is to fight against foreign particles that the body sees as "non-self", such as bacteria and viruses. A stem cell transplant from an HLA mismatched donor can result in the recipient's immune system recognising the transplanted cells as "non-self" and attacking the cells as it would bacteria or viruses. This can lead to rejection of the transplanted stem cells. Likewise cells from the donor's immune system which are introduced along with the transplanted stem cells ("graft") can also recognise HLA mismatches and attack vital organs of the recipient's body ("host"). This is called graft versus host disease (GvHD).

The more compatible the donor-recipient match, the less likely it is that rejection or severe GvHD will occur.

How is HLA typing performed?

A 20-30 ml blood sample is required to perform HLA typing. The white cells are isolated from the blood and typing is performed by two different methods:

- Serological testing: where the white cells are used

- DNA testing: where DNA extracted from the white cells is used.

When DNA testing is performed there is no breach of a person's confidentiality. The DNA is not used for any reasons other than tissue typing and ethically approved research purposes, and remains the property of the tissue typing laboratory.

Preliminary tissue typing takes about 2 weeks. Further high resolution (more detailed) tissue typing performed on the patient and any potentially matched donor samples may take another 2 to 4 weeks.

How is HLA typing reported?

HLA typing is reported as a series of numbers. For example, an HLA type will appear on the report as A 3, 32; B 7, 37; DR 1, 15. Results of family members and/or unrelated donors are compiled with the patient's HLA typing results and reported directly to the clinician by the laboratory that performed the tests. The clinician will inform the patient and family of matches found and will be available to discuss the results.

Searching for a related donor

An HLA type consists of two main groups: Class I antigens (HLA-A, -B, -C) and Class II antigens (HLA-DR, -DQ, -DP). There are six HLA antigens considered most important for determining compatibility: two A antigens, two B antigens, and two DR antigens (eg: A 3, 32; B 7, 37; DR 1, 15).

We inherit a set (or haplotype) of HLA-A, B and DR antigens from each parent.

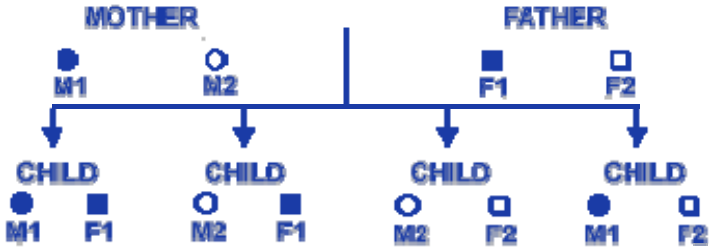


Figure 1: Inheritance of HLA type.
The differently shaded circles and squares represent the 4 familial haplotypes: M1 and M2 represent the maternal haplotypes, F1 and F2 represent the paternal haplotypes.

The two inherited haplotypes determine the HLA type of an individual consisting of two HLA-A antigens, two HLA-B antigens and two HLA-DR antigens. Since the maternal and paternal haplotypes can combine in four different ways (as shown in the figure above), there are four possible HLA types that can be inherited by the children. This means that statistically each child has a one in four chance of being HLA matched with any one sibling. HLA matching is not related to appearance or personality between family members, blood group or sex.

Typing family members

The donor search coordinator initiates a family search at the request of the patient's clinician. The coordinator will arrange for HLA typing of family members depending on their relationship to the patient. Since typing of family

members is done systematically we ask that family members do not come forward for testing without first contacting the donor search coordinator.

Immediate family

To assist us with the family search, the donor search coordinator requires the following:

- the patient or patient's representative to approach immediate family members to ascertain their willingness to be tested
- a designated contact person within the family to liaise with the donor search coordinator
- a family tree clearly showing relationship to patient, sex, age and number of children of family members willing and available for tissue typing

Extended family

An extended family search may be considered if a matched sibling is not found and the patient has at least one haplotype that is commonly found in the general population. An extended family search is done systematically, exploring the side of the family from which the least common haplotype has been inherited. The aim is to look for a person who has inherited the less common haplotype by descent but who has also inherited the more common haplotype by chance through marriage or partnerships.

Can my friends be typed?

The best chance of finding a matched donor is within the immediate family (siblings) and the chance of finding a suitable donor decreases in the extended family. The chance of an unrelated person (friend) having the same tissue type as the patient is remote. However, if a friend wishes to be tissue typed, he or she must be willing to join the Australian Bone Marrow Donor Registry and donate stem cells for any patient in need if required.

Searching for an unrelated donor

What are unrelated bone marrow donor registries and cord blood registries?

Unrelated bone marrow donor registries and cord blood registries have been developed to help the 60 - 70% of patients in need of a stem cell transplant who are unable to find a suitably matched related donor.

Over 7 million donors from more than 35 countries are listed on Bone Marrow Donors Worldwide (BMDW), an international database managed by The Netherlands. Of these, more than 90,000 are cord blood units.

What are bone marrow donor registries?

Bone marrow donor registries are registers of volunteers willing to anonymously donate stem cells for any patient worldwide in need of a stem cell transplant. On joining, donors have preliminary tissue typing performed, and the results are recorded on a computerised database. The Australian registry is called the Australian Bone Marrow Donor Registry (ABMDR).

What are cord blood registries?

Blood removed from the umbilical cord and placenta of newborns is a rich source of stem cells suitable for transplantation in some patients, especially young children. Cord blood registries record details of stored cord blood units, donated by mothers on the birth of their babies.

How are the registries searched?

If the transplant clinician considers that the patient would benefit from a transplant using an unrelated donor, a registry search is initiated. This process is performed by a team, which includes the transplant unit staff, tissue typing laboratory staff, and ABMDR coordinators. Patients do not have direct access to the registries.

The search process

A search of the BMDW website is conducted, giving an immediate overview of potential donors worldwide.

Australian Bone Marrow Donor Registry (ABMDR) search request forms are completed with details of the patient's tissue type, age, sex, ethnicity and disease. These are forwarded to the ABMDR National Office. All information collected will be handled confidentially and in accordance with the Federal Privacy Act.

The ABMDR National Office enters the patient's tissue type into the database and a computer program compares the patient's tissue type with those of all donors on the Australian registry daily. A list of potentially matched donors is produced which is usually available the next day.

The patient's tissue type is confirmed and high resolution DNA sub-typing is commenced. This can take 2 - 3 weeks.

If a potential donor is not found on the ABMDR, an international search of bone marrow donor and/or cord blood registries may be initiated.

How long does it take to identify a donor?

Because a well-matched donor or cord blood unit is crucial to the success of the transplant, and the time it takes to find a suitable match varies greatly, it is important for patients and clinicians to understand the search process.

Although the initial registry search will usually identify some potential matches, more detailed tissue typing of potential donors is usually required. The search coordinator reviews the list of potentially matched donors, and decides what further typing is needed.

Listed below are the three (3) main steps used to identify a compatible donor.

Search identifies donor matched at A and B (DR type is unknown)

Example Patient A3, 32; B7, 37; DRB1*0101, 1501

Donor A3, 32; B7, 37

DR typing is requested. The chance of a specific donor matching at HLA-DR depends on the frequency of antigens among donors on the registry and the ethnicity of the patient and donor.

If the laboratory has a stored DNA sample from the donor, this testing may take 2-3 weeks, but if another blood sample needs to be taken from the donor, then it may take 4-5 weeks.

If the donor is matched, proceed to High Resolution (HR) subtyping.

Search identifies donor matched at A, B and DR, but not sub typed

Example Patient A3, 32; B7, 37; DRB1*0101, 1501;

Donor A3, 32; B7, 37; DRB1*01XX, 15XX;

High Resolution (HR) DNA subtyping is requested. If the patient has a common DR subtype, the chance of a donor matching is good, but if the patient has an unusual DR subtype, then the chance of a full match may be slight;

If the laboratory has a stored DNA sample from the donor, this testing may take 2-3 weeks, but if another blood sample needs to be taken from the donor, then it may take 4-5 weeks.

If the donor is matched, proceed to confirmatory typing.

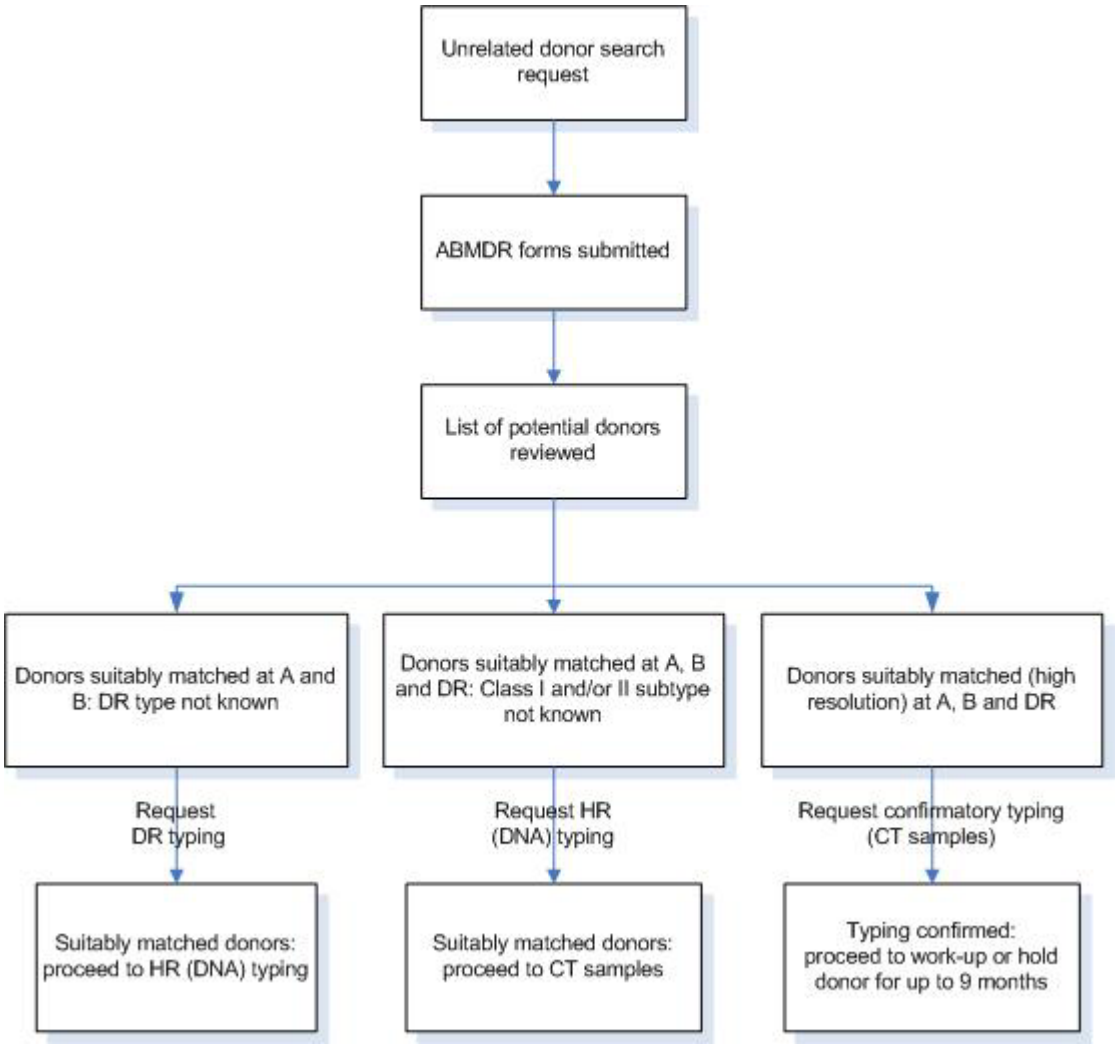
One or more fully matched sub-typed donor(s) identified.

Example: Patient A3, 32; B7, 37; DRB1*0101, 1501

Donor A3, 32; B7, 37; DRB1*0101, 1501

A confirmatory typing (CT) sample is requested from the donor/s. The donor centre coordinator contacts the donor. After checking that they are still available and willing to donate stem cells, a blood sample is taken and sent to the tissue typing laboratory affiliated with the patient's transplant centre. The laboratory types the donor sample to confirm the original typing. Further typing may also be done to define a more exact level of match, and cellular assays may be performed to further assess donor/patient compatibility.

The donor sample is also tested for infectious diseases. Allow a minimum of 4 weeks.



If a donor is identified, what happens next?

The transplant team will determine the urgency of a stem cell transplant depending on the disease of the patient and their clinical condition. If the transplant is urgent, the search coordinator will request "work up" of the compatible donor: a series of medical tests and appointments to ascertain the donor's suitability as a stem cell donor. If an unrelated donor is identified for a patient, but transplant is not indicated straight away, the donor can be reserved for that patient for up to 9 months. After that time the donor is released from the patient search and details of the donor ID, registry and tissue type are recorded in the patient file for easy recall of the donor when transplant is indicated.

Currently there are two ways a donor can donate stem cells. Details of these procedures and associated risks are outlined below. The choice will be dictated by the patient's needs and so a donor may be asked to donate either bone marrow or peripheral blood stem cells. A small percentage of people may be asked to donate both stem cells and bone marrow.

How is the donation collected?

Bone marrow donation

Bone marrow is collected under general anaesthetic from the cavities in the hipbones. Using a needle and syringe, punctures are made through the skin over each hip, and the marrow is extracted from the pelvic bone cavity. This procedure can take up to two hours. The time needed for complete recovery varies, but generally a donor can go home the next day, and resume normal activities after two or three days. Normal bone marrow will re-grow rapidly to replace the donated bone marrow.

Peripheral blood stem cell (PBSC) donation

Normally the number of stem cells circulating in the blood is low. To increase the number of blood stem cells, a hormone-like substance called G-CSF is injected under the skin daily for 4 days prior to the procedure. The stem cells are then collected by a procedure called leukapheresis. During this procedure a needle is inserted into a vein in the arm and the donor's blood passes into a cell separator machine, which selectively removes the stem cells. The remaining blood components are immediately returned to the donor. This procedure is performed at a hospital or blood bank, does not require a general anaesthetic and takes approximately 3-4 hours. After the procedure the donor may leave but subsequent donations may be necessary if insufficient cells numbers were collected.

What are the risks for the donor?

Bone marrow donation

The risks for donating bone marrow are the same as those with any general anaesthetic. The chance of a serious complication is very low but some people may experience nausea and/or local pain and discomfort for several days.

Peripheral Blood Stem Cell (PBSC) donation

G-CSF is usually well tolerated, although the donor may experience bone pain and some flu-like symptoms during the course of the injections. As yet no significant long term side effects have been observed with prolonged administration of G-CSF to patients but the long term effects of short treatments in normal donors is unknown.

How do family and friends join the ABMDR

Sometimes family and friends wish to join the ABMDR because they are made aware of the need for an unrelated donor search when no compatible family member is found for a patient needing a stem cell transplant.

Family members

Family members who have been tissue typed are not automatically registered with the ABMDR. They must complete ABMDR Consent Forms in order to join the registry. These forms can be obtained from the ABMDR Coordinator in their state to ensure that their tissue typing results are entered on to the ABMDR database.

Friends

The chance of an unrelated person matching a certain patient is so remote that if friends wish to be tissue typed, then they must be prepared to join the Australian Bone Marrow Donor Registry in order to have tissue typing performed. Each year the ABMDR searches for over 1000 patients in need of a stem cell transplant and by joining the ABMDR it is important to realise they may be selected to help any patient in need, anywhere in the world.

People wishing to join the ABMDR must read the ABMDR brochure "Offer Someone the Chance of a Lifetime" which is available from the ABMDR coordinator in your state. Volunteers must be in good health and between the ages of 18 and 40. Retirement from the registry is on their 56th birthday.

A small sample of blood is necessary for tissue typing to be performed and can usually be collected during a routine blood donation.

The ABMDR has approximately 160,000 potential donors but needs more people from different ethnic backgrounds to be able to accommodate the diverse composition of the Australian population. However, increasing the number of people on the registry does not always increase the chance of a match.