A Family of Matched Parent-Child HLA Haplotypes: A Case Study from Bahrain

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Introduction
Bone marrow transplant (BMT) is a medical procedure performed to replace the soft, fatty bone marrow that has been damaged or destroyed by disease, infection, or chemotherapy. Most bone marrow transplants are usually performed on patients with certain blood cancers (leukemias) and other blood disorders. Cases of fully matched offspring(s) with parents are very rare and would occur when both parents share at least one haplotype which is commonly seen in several generations of consanguineous marriages [1].

The possibilities of having a perfect match is raised in family members especially siblings due to the shared alleles from the same parents. Cases of fully matched offspring(s) with parents are very rare and would occur when both parents share at least one haplotype which is commonly seen in several generations of consanguineous marriages [2].

Nuclear family members provide the best possibility of a perfectly matched donor. The probability of finding a matched parent-child is higher in consanguineous marriages [3].

The high probability is due to the cultural trend that is common in the Middle East, West Asia and North Africa where large families have high population growth, density and increased rates of consanguineous marriages. A study also in Saudi Arabia revealed that 60% of all patients had the possibility of finding a sibling being a match [4].

To check for a match, a small amount of blood is drawn and the five main HLA alleles are analyzed and compared with the other family members of with the recipient in need of the transplant.

Materials and Methods
Six DNA samples were extracted from peripheral blood using the Qiagen QIAamp DNA Mini Kit. According to manufacturer’s instructions (Qiagen, Hilden, Germany). The Qubit® 3.0 Fluorometer was then used to quantifty each of the extracted DNA sample.

A separate PCR protocol was set up for each locus to be amplified, and for each individual sample to be tested. Each run included appropriate positive control/s of known genotype, and at least one negative control for each locus being amplified. Successful amplifications were confirmed on a 1% agarose gel electrophoresis using 2µl of PCR product with 5µl loading buffer.

Sequencing of the amplified product was done using the Conexio Genomics SBT Resolver kits for High resolution Molecular HLA typing with group specific and locus specific primers.

The HLA Sequencing Based Typing (SBT) procedure used was originally developed by D. Sayer in 2001 and developed into a single tube assay in 2004 [5]. The procedure involves the initial amplification of the target sequence followed by enzymatic treatment to remove unincorporated primers and dNTPs. The amplicon is then used as a template for direct automated fluorescent DNA sequencing using customized sequencing primers and the Big Dye® Terminator sequencing kit V3.1 (Applied Biosystems, Foster City, California, USA).

The sequencing products were purified using the ethanol precipitation method and denatured with Hi-Di™ Formamide available from
Applied Biosystems™ by Life Technologies™. The purified fragments were sequenced using the ABI 3130XL Genetic Analyzer (Applied Biosystems). The data generated was then analyzed and the results were interpreted according to the manufacturer’s guidelines using the CareDx Pty Ltd’s ASSIGN™ SBT software from CareDx Pty Ltd3-5. (CareDx Pty Ltd’s OLERUP SBT™ HLA SBT kits) used for typing of HLA Class I and Class II genes from genomic DNA. The sequencing products were purified using the ethanol precipitation method and denatured with Hi-Di™ Formamide available from Applied Biosystems™ by Life Technologies™. The purified fragments were sequenced using the ABI 3130XL Genetic Analyzer (Applied Biosystems). The data generated was then analyzed and the results were interpreted according to the manufacturer’s guidelines using the CareDx Pty Ltd’s ASSIGN™ SBT software from CareDx Pty Ltd3-5. (CareDx Pty Ltd’s OLERUP SBT™ HLA SBT kits) used for typing of HLA Class I and Class II genes from genomic DNA.

Results
Our experience of HLA typing show the known 50% match between parent and child. However, in this case, and due to the consanguineous marriages seen within generations in the family (figure 1), we observed a shared haplotype in both parents (figure 2) leading to children being a 100% match to either one of the parents.

Figure 1: Extended family pedigree showing consanguineous marriages seen within generations in the family

Figure 2: Son 1 – 50% matched with the father and 100% matched with the mother
Daughter 1 – 50% matched with the mother and 100% matched with the father
Son 2 – 50% matched with the father and 100% matched with the mother
Daughter 2 – 50% matched with the mother and 50% matched with the father
There were very strikingly matched allele patterns seen in the children tested for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 (Figure 2).

Due to the high number of shared alleles between the parents, both sons were a 100% match with the mother, while one of the two daughters (daughter 1) was a 100% match with the father. Daughter 2 inherited the two HLA haplotypes that were not shared by the parents. Son 1 was a 100% match with son 2. He was also a 50% match with both his sisters (daughter 1 & 2). Both daughters were a 50% match with each other.

Discussion

Following the normal inheritance pattern, a biologic child usually is a 50% match with his or her parent because each child receives half of the HLA genes from each parent. Reported findings in a Saudi population study revealed that, patients in need of HCT have a greater chance of finding an HLA-matching sibling than is reported in most Western countries [4]. There was a 43% chance of finding a matching sibling in patients aged 0 to 5 years, this percentage increased to 68% in patients aged 20 and above. The change in pattern observed in contrast to that in the western world in the Saudi population is mainly because of the larger number of siblings in most Saudi families [4]. However, among communities where the parents are related, the probability of matched parent-child as well as matched siblings are higher [2].

It has been reported in the literature from previous studies in Saudi Arabia and Turkey that the chances of finding a parent-child match is relatively high [2]. In these countries the probability for all patients to have a matched sibling due to consanguineous marriages is reported to be 60% [4]. There has been no such incidences reported yet in Bahrain. This pattern of occurrence would be expected to be seen in significantly higher percentages due to the similar marriage culture that prevails in the gulf region and North Africa.

Though our case becomes uniquely different with very closely matched parent and children having a high degree of compatibility. Further studies are suggested to come to a broader conclusion whether this is an isolated case or more of such cases would be found to be a trend in the Bahraini population.

References

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