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Preimplantation HLA Typing

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1. Introduction

It has been more than ten years since the first Human Leukocyte Antigen (HLA) matching for Fanconi anemia was reported, allowing successful haemopoietic reconstitution in affected sibling by transplantation of stem cells obtained from HLA-matched offspring (Verlinsky et al., 2000; Verlinsky et al., 2001). Preimplantation Genetic Diagnosis (PGD) in combination with HLA matching is being used to detect a particular gene mutation in an unaffected child who can be an HLA donor for its' sibling. HLA typing without mutation analysis has also been used for acquired diseases (Verlinsky et al., 2004), such as acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL), which require allogenic haemopoietic stem cell transplantation (HSCT) from an HLA identical donor for the cure of the disease. Stem cells in the cord blood from an HLA identical sibling can be used with a much higher success rate than a transplant from alternative donors (Gaziev et al., 2000; Orofino et al., 2003) and are therefore of great therapeutic value for hematopoietic and other life-threatening diseases (Fiorentino et al., 2006; Kahraman et al., 2004, 2007; Verlinsky et al., 2001, 2004; Van de Velde et al., 2004, 2009).

In particular for blood-borne disorders, hematopoietic stem cells (HSC) from HLA-identical siblings provide the highest success rate and current results indicate that about 90% of the cases can be cured successfully after HSC transplantation (Gaziev et al., 2005). Use of cord blood as a stem cell source also results in reduced incidence of graft rejection and other serious complications associated with bone marrow transplantation. However, in most cases a suitable donor cannot be found in the family, and due to a small number of children per family, only one third of patients are able to find an HLA-identical sibling (Costeas, 2004). The probability of having an unaffected child who may also be an HLA match for an affected sibling is only one in five; these families often went through multiple cycles of pregnancy before conceiving an unaffected HLA match. In the remaining patients the only resort is the identification of a matched unrelated donor. However, the probability of finding an HLA matched unrelated donor cord blood from the cord blood units is extremely low. Therefore PGD is a much more attractive option, with this technique, sufficient number of embryos may be tested at one time, increasing the chances of identifying an appropriate match.

More than 2000 healthy children have already been born after PGD and the expanding indications include chromosomal abnormalities, single gene disorders, HLA tissue typing of the embryos, predisposition of adult onset disorders, translocations and cancer predispositions (Simpson 2001; Kuliev et al., 2004; Fiorentino et al., 2004; 2006; Kahraman et al., 2005; 2007; Van de Velde et al., 2004; Kokkali et al., 2007). In fact PGD can be carried out

for any disorder in which molecular testing can be performed. A partial list of disorders in which Preimplantation Genetic Diagnosis/HLA typing can be applied is shown in Table 1. Although the majority of these disorders are due to rare genetic defects, the incidence of some, such as β thalassemia, sickle cell anemia and cystic fibrosis are very common in certain parts of the world, such as Mediterranean region which include Turkey, Italy, Greece and Cyprus. Turkey is one of the Mediterranean countries in which thalassemia mutations are commonly seen, with a carrier rate of 2.1% in the population (Aksoy, et al., 1985).

Achondroplasia (FGFR3)	Hyper IgM
Acute Lymphocytic Leukemia (ALL)	Krabbe (GALC)
Acute Myelogenous Leukemia (AML)	Li-Fraumeni Syndrome (TP53)
Alpha-Thalassemia (HBA)	Marfan Syndrome (MFN1)
Alzheimer Early Onset (PSEN1)	Metachromatic Leukodystrophy (ARSA)
Beta-Thalassemia (HBB)	Mucolipidosis 2 (I-Cell)
Charcot-Marie-Tooth	Myotonic Dystrophy
Chronic Granulamatous Disease (CYBB)	Neurofibromatosis (NF1 &NF2)
Chronic Myelogenous Leukemia (CML)	Neiman Pick Type C
Crigler Najjar (UGTIA1)	Phenylketanuria (PKU)
Cystic Fibrosis (CFTR)	Polycystic Kidney Disease (AR-PKD1)
Diamond Blackfan Anemia(DBA-RSP19)	Retinoblastoma
Duchenne Muscular Distrophy (DMD)	Sanflippo A (MPSIIIA)
Fanconi Anemia A,C,F,G	Severe combined immunodeficiency (SCID-XI)
Fragile X (FMR1)	Sickle Cell (HBB)
Gaucher Disease (GBA)	Spinal Muscular Atrophy (SMN1)
Glycogen Storage Disease,type IA	Spinocerebellar Ataxia (SCA-2,SCA-3)
Hemophilia A,B	Tay Sacs (HEXA)
Huntington Disease (HD)	Tuberosclerosis (TSC1)
Hurler Syndrome (MPSI-IDUA)	Wiscott-Aldrich Syndome

Table 1. Some of the current indications of PGD/HLA Typing

According to data collected by the Turkish Association of Thalassemia, the heterozygosity rate may be higher than 10%, particularly in the southern regions of Turkey (Basak et al., 2007). A higher rate of consanguineous marriages in those regions is a factor which further increases the incidence of thalassemia. In addition, thalassemia has a great heterogeneity in Turkey, the total frequency of the 6 most commonly seen mutations is only 69% of the whole mutations. The selection of embryos for HLA typing necessitates the application of ART even though the vast majority of the couples are fertile. The successful outcome of ART

cycles is highly dependent on female age and ovarian reserve. This technique is made crucially important by the fact that, the theoretical probability of finding an HLA identical embryo in cases of acquired diseases is 25% (1/4) and the probability of finding both HLA identical and mutation free embryo in cases of single gene disorders no more than 18% (3/16). Using a standard IVF procedure, oocytes or embryos are tested for causative gene mutations simultaneously with HLA alleles, selecting and transferring only those unaffected embryos, which are HLA matched to the affected sibling.

The HLA Complex (Human Leukocyte Antigen) is located on chromosome 6 and represents one of the most polymorphic regions of human genome. Comparative DNA sequence analysis of HLA complex has shown the presence of a high number of alleles in this region. Linked short tandem repeat (STR) markers scattered through the HLA complex were studied to increase the accuracy of the analysis and to detect potential contaminations and crossing over occurrence between HLA genes.

Single cell PCR technique has several pitfalls, such as contamination by extraneous DNA, amplification failure, preferential amplification, and allele drop out (ADO) which is the failure of PCR to amplify one of the two alleles. If ADO occurs, only a single allele is amplified and detected after PCR, giving a heterozygous cell the appearance of homozygosity. This may lead to harmful consequences such as in the case for a dominant disease; failure to amplify the mutant allele may lead to the transfer of affected embryos. The ADO rate and the efficiency of amplification of targeted regions depend on efficient lysis methods (Shirazi et al., 2009) and also the type of cell analyzed. With simultaneous usage of linked STR markers the accuracy of single cell PCR is approximately 98% (Rechitsky et al., 2001). ADO rates in single cells can be decreased by analyzing more than one cell which is possible with blastocyst-stage biopsy. Trophectoderm biopsy is a good alternative to cleavage stage biopsy as it enables the evaluation of approximately 2-5 cells, thus decreasing both the rate of amplification failures and ADO associated with single cell PCR (McArthur et al., 2008; Pangalos et al., 2008). There are many advantages of blastocyst stage biopsy such that; since trophectoderm cells are extra-embryonic tissue, the removal of these cells avoids the risk of affecting the development of the fetus. Also the proportion of the cells that are removed is much lower compared to cleavage stage biopsy. Furthermore, blastocyst stage embryos have a higher implantation potential compared to day-3 or day-4 embryos, so a higher rate of implantation could be achieved by trophectoderm analysis (Kokkali et al., 2007; McArthur et al., 2008).

2. Materials and methods

2.1 Study group

The study group consisted of a total of 188 couples with a total of 362 cycles. Between 2003 and the mid of 2011 at Istanbul Memorial Hospital, ART and Reproductive Genetics Center, 149 couples were referred for both mutation analysis for a specific genetic disorder and HLA typing, while 39 couples were referred for the sole purpose of HLA typing for acquired disorders. The detailed list of diseases can be found in Table 2.

2.2 Pre-clinical work up

First, a haplotype analysis of mother, father and child, and when available of other family members, was performed for each family prior to preimplantation HLA typing. For this, genomic DNA is isolated from peripheral blood samples of father, mother and the affected

child. To rule out a possible recombination in the affected child, other family members such as unaffected child, or grandparents' DNA have been added to set up procedure. Figure 1 shows the polymorphic STR markers scattered through HLA region which were used to detect any possible ADO in relation to HLA typing.

	TOTAL	188 couples	362 cycles
HLA + Mutation testing	β-thalassemia	131	258
	Wiscott Aldrich	3	4
	X-Adrenoleukodystrophy	3	3
	Fanconi Anemia	3	4
	Alpha-Mannosidosis	1	4
	Gaucher Syndrome	1	4
	Hurler Syndrome	2	3
	Hyper IgD	1	1
	Glanzmann Trombasthenia	1	2
	Sickle Cell Anemia	1	1
	Diamond Blackfan Anemia	1	1
	Cd3 Deficiency	1	1
HLA only	Acute Lymphoblastic Leukemia	17	30
	Acute Myeloid Leukemia	11	20
	Diamond Blackfan Anemia	3	11
	Histiocytosis	1	3
	Chronic Myeloid Leukemia	1	2
	Burkitt's Lymfoma	1	2
	Aplastic Anemia	2	2
	Anaplastic Anemia	1	3
	Myelodysplastic Syndrome	1	2
	Non-hodgin Lymfoma	1	1

Table 2. Cycle participations of patients and indications for HLA Typing.

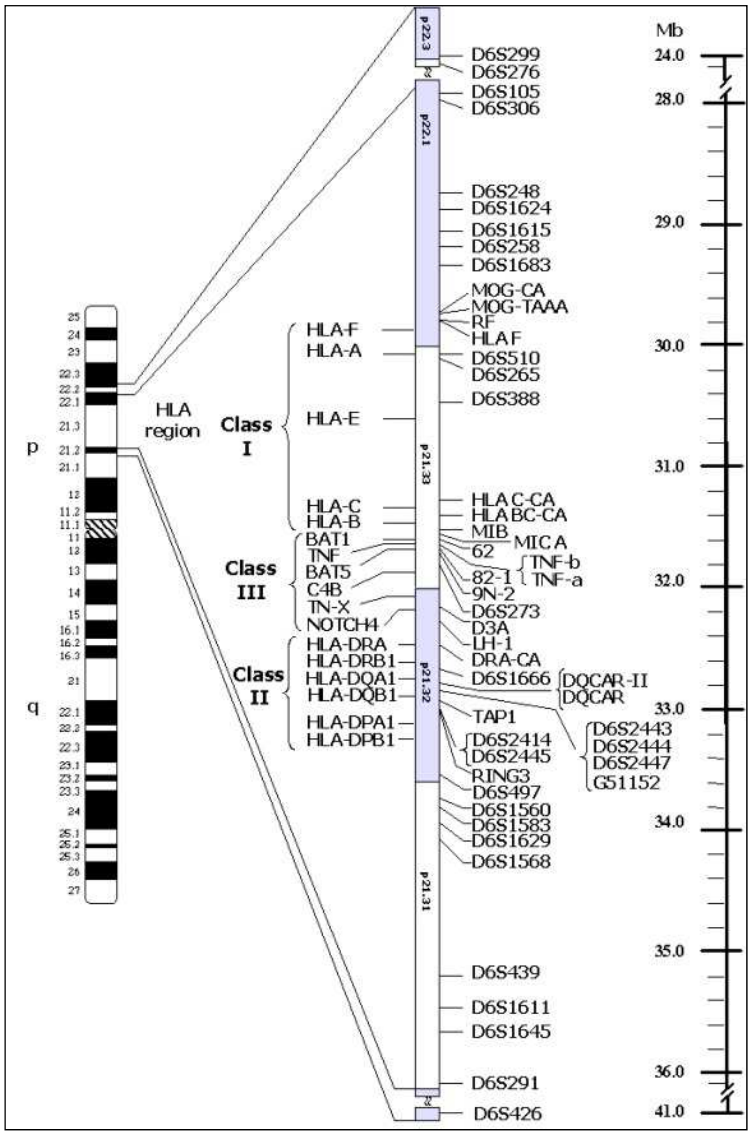


Fig. 1. Polymorphic STR markers used in HLA typing of the embryos.

A panel of 50 different short tandem repeat (STR) markers (figure 1) were tested on genomic DNAs to ensure the presence of enough informative markers (figure 2) to aid the identification of monosomy, trisomy, recombination, allele-drop out (ADO) and uniparental disomy (UPD) of the analyzed chromosomes and regions. For each family at least 12 heterozygous markers spanning the HLA-A, HLA-B, HLA-C, HLA-DR,HLA-DQ regions (HLA Classes I, II, and III) were selected for PGD Study.

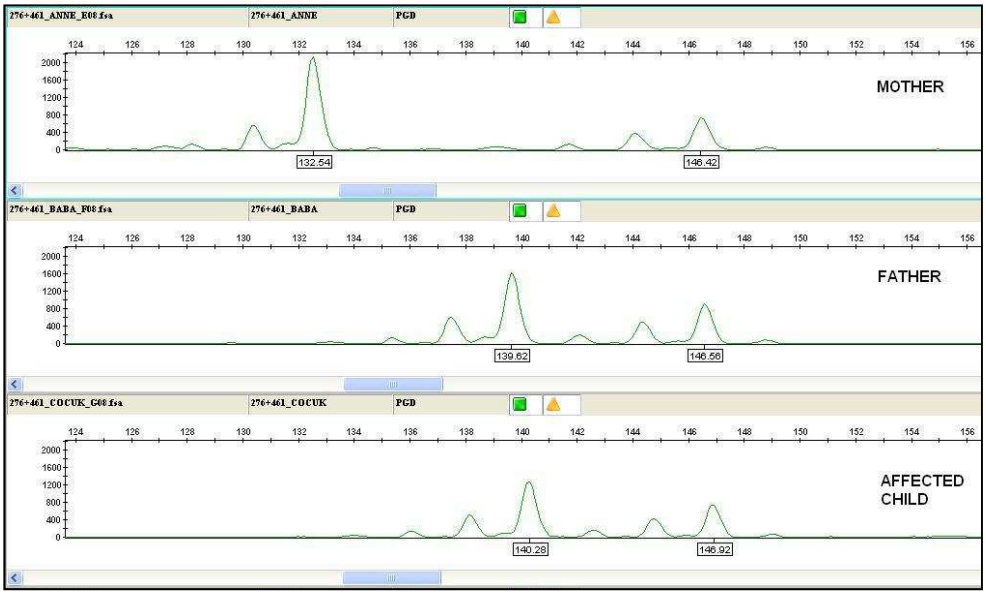


Fig. 2. Identification of informative markers during HLA set up study

The study period was divided into two according to the methods used which included lysis of single cells, mutation testing, polymerase chain reaction (PCR) conditions and primers used in the PGD study. Oocyte collections, inseminations, culture, biopsy and transfer of embryos were performed in Istanbul Memorial Hospital ART unit and all PGD studies and evaluations were performed in Istanbul Memorial Hospital Reproductive Genetics Unit.

2.3 PGD study

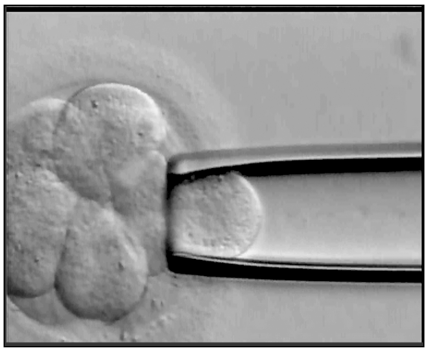
The methods can be found elsewhere (Kahraman et al., 2011). In the first period, the alkaline lysis method was used as described previously (Fiorentino et al., 2005). Cells were lysed by incubation at 65C° for 10 minutes in a sterile PCR tube containing 5 µl of lysis buffer (200nmol/1 KOH, 50nmol/1 DDT). The lysis buffer was then neutralized prior to adding the first-round PCR mix which contained all external primers for co-amplification of all selected HLA markers and mutation linked markers. Second-round PCR reaction for each locus was then performed using 2 µl of the first round product.

In the second period, the Proteinase K method was used for lysis of the cells as described previously (Verlinsky et al., 2001). The biopsied single cells were placed into a lysis solution containing 0,5 µl of 10xPCR buffer, 0,5 µl of 1% tween-20, 0,5 µl of 1% triton X-100, 3,5 µl of water, and 0,05 µl of proteinase K. The lysis reaction was as follows: 45 C° for 15 minutes for the lysis of the cells and 96 C° for 20 minutes for inactivation of proteinase K. Although the reaction conditions were different in the two periods, both can be briefly summarized as follows; DNA testing was performed by two rounds of PCR reactions: in the first round, using multiplex PCR which allows simultaneous amplification of HLA regions and mutation-linked markers and in the second round, using singleplex PCR which is a fluorescent PCR with semi or heminested primers. Primer sequences and polymerase chain

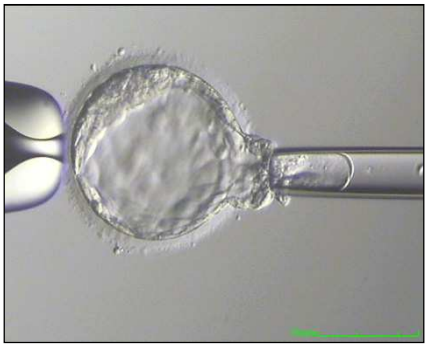
reaction conditions used in this study have been reported previously (Verlinsky et al., 2001; Fiorentino et al., 2004; 2005; Rechitsky et al., 2004; Verlinsky et al., 2004).
Between 2003 and 2008, mutation analysis was performed using the minisequencing technique, as described elsewhere (Fiorentino et al., 2003). After middle of 2008 restriction enzyme digestion reactions and subsequently polyacrylamide gel electrophoresis analysis were used (Rechitsky et al., 2004). Since the middle of 2009s, both methods are being used according to preference.

2.4 IVF and embryo biopsy procedure

The stimulation protocols were as outlined previously (Kahraman et al., 2004). Oocyte retrievals were performed 36 h after the injection of rhCG (ovitrel) by transvaginal-ultrasound-guidance. Approximately 2-3 h after oocyte retrieval, cumulus cells were enzymatically removed. Intracytoplasmic sperm injection (ICSI) was applied to metaphase II oocytes. One blastomere was removed from cleavage stage embryos (figure 3a) from an opening made using laser (IodoLaser, Research Instruments). Subsequently, embryo transfer



a) Clevage Stage Biopsy



b) Blastocyst Stage Biopsy

Fig. 3. Biopsy Techniques

was performed usually on day-4 but rarely on day-5. Recently, since 2009, trophectoderm tissue biopsies have also been performed. Blastocyst-stage biopsy was performed by making a hole in the zona pellucida on day-3 of embryonic development which allowed the developing trophectoderm cells to protrude after blastulation, facilitating the biopsy. On day-5 post-fertilization, approximately 4-5 cells were excised using laser energy, without loss of inner cell mass (figure 3b). After diagnosis, the embryos was replaced during the same cycle, on day-5 or 6. Pregnancy was first evaluated by serum hCG concentrations assay, 12 days after embryo transfer and clinical pregnancy was diagnosed by ultrasonographic visualization of one or more gestational sacs.

3. Results

In HLA+mutation testing group (Group I), and HLA-only group (Group II), 62.2% and 72.4% of the initiated cycles reached the stage of embryo transfer, respectively. The detailed distribution of indications and overall results for each group was shown in Table 2 and 3.
A full diagnosis was achieved in 91.0% of the biopsied samples. In Group I, 17.8 % of the analyzed embryos were found to be HLA compatible. HLA compatible and disease free embryos were 12.9 % of all diagnosed embryos. In group II, 17.2% of embryos were found to be HLA matched and 71.4% HLA non-matched.

	HLA+mutation testing (Group I)	HLA Only (Group II)	TOTAL
No of patients/cycles	149/286	39/76	188/362
Maternal age, mean	32.0±4.83	33.9±5.65	
Cycles with transfer, %	62.2	72.4	
No of embryos transfered, mean	1.55±0.71	1.56±0.72	
Clinical pregnancy rate per transfer, %	37.6	32.7	
Implantation rate,%	28.9	24.4	
Clinical miscarriages, n	14	3	
No of babies born, n	57	13	
No of succsessful transplantations, n	23	2	25*

*21 children are awaiting an appropriate time for HSC transplantation.
Table 3. Overall clinical results of HLA typing.

The majority of our HLA typing combined with PGD cases were β-Thalassemia carriers (87.9%). The mutations analyzed have high heterogeneity, the most frequent mutation was IVS-I-110 G-A and comprised 46.2% of all mutations. The total frequency of the most frequent 6 mutations were 74.0% (Table 4).
A total of 85 clinical pregnancies (36.5%) were achieved from 233 ET cycles. 5 pregnancies are ongoing. To date, 70 healthy and HLA compatible children have been born. 25 sick children have already been cured with cord blood cell and/or bone marrow transplantation.

21 children are waiting for their newborn siblings to gain sufficient weight and maturity for the donation of stem cells (Table 3). The successful transplantations have been performed for the following indications: β-Thalassemia (n=19), Wiskott Aldrich syndrome (n=2), Glanzmann Disease (n=1), X-Adrenoleukodystrophy (n=1) and acute myeloid leukemia (n=1) and Diamond Blackfan anemia (n=1) (Table 5).

Mutation	Frequency , %
IVS-I-110 G-A	46.2
Cod8 delAA	7.3
Cod39 C-T	6.5
IVS-II-745	5.7
IVS-II-1	4.6
IVS-I-1 G-A	3.8
TOTAL	**74.0**

Table 4. The most frequent Beta-Thalassemia mutations in our sample population

4. Conclusion

This data presents one of the world's largest experiences on preimplantation HLA typing, and the outcome of stem cell transplantation is the largest number available from one center. To date 25 children have been cured with this approach and 21 children are awaiting appropriate time for transplantation. Our results indicate HLA typing with or without mutation analysis is a promising and effective therapeutic tool for curation of an affected sibling.

Indication	Patients, n
Beta-Thalassemia	19
Wiscott-Aldrich	2
Glanzmann disease	1
X-Adrenoleukodystrophy	1
Acute Myeloid Leukemia	1
Diamond Blackfan Anemia	1
TOTAL	**25**

Table 5. The list of diseases and the number of patients who have complete cure after HSCT.

5. Acknowledgements

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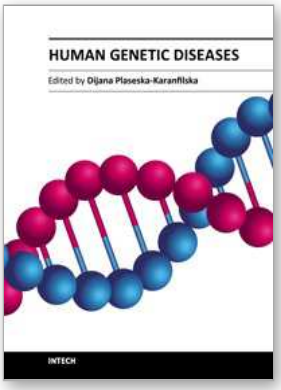

Human Genetic Diseases

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The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the â€œgenetic approachâ€ to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.

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