



PECULIARITIES OF HLA ANTIGENS INHERITANCE OF THE MAIN HISTOCOMPATIBILITY COMPLEX IN WOMEN AND MEN

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Abstract

The leukocyte antigens HLA of the major histocompatibility complex MHC play a key role in the histocompatibility of human organs and tissues. In connection with fact that the best results are obtained for transplants of organs and tissues from close relatives, the study of the peculiarities of inheritance of allelic variants of parents' leukocyte antigens to their children can be considered as one of the important problems of modern transplantology. Haplotypes of mother and father contain different parental *HLA-DRw* antigens that are linked to allelic variants of antigens of classes I and II of loci A, C, B, D. Leukocyte antigens are linked with *HLA-DRw1* and *HLA-DRw2* antigens in maternal haplotypes, and with *HLA-DRw1* and *HLA-DRw3* antigens - in paternal haplotypes. Sisters and brothers differ in the inheritance of paternal antigens. *HLA-DRw1* antigen, which is linked with antigens of other loci from the father, is inherited to sisters exclusively; a special paternal haplotype with *HLA-DRw3* antigen is inherited from the father, do not pass to sisters, it is inherited to brothers exclusively, it is limited to the male sex and transmitted from father to son. In the well-known common scheme of inheritance of HLA antigens, the mother's haplotypes can be differentiated as *ab*. The father's haplotypes can be differentiated as *cd* and sisters can inherit the haplotypes *ac* and *bc* from parents, and brothers – *ad* and *bd*; haplotype *d* is linked with *HLA-DRw3* antigen can be considered as the special paternal haplotype. Special paternal haplotype linked with *HLA-DRw3* antigen presented by glycoproteins in cell membranes of men. It is inherited as well as the uniparental haplotype of the noncombining NRY region of chromosome Y and is passed in generations from father to son through the male line. The HLA/MHC leukocyte antigens of the special paternal haplotype *d* with *HLA-DRw3* antigen are foreign to the body of women and can cause an incompatibility through leukocyte antigens and rejection during a graft of male organs and tissues in women. At the same time, it can be the reason for post-transfusion complications in women through transfusions of the blood from male donors. Also, it can happen through repeated transfusions or give blood transfusions of large blood volume to them especially.

Keywords: *leukocyte antigens, major histocompatibility complex, haplotype, incompatibility, codominant inheritance, siblings.*

Introduction

The HLA (Human Leukocyte Antigens) system of the Major Histocompatibility Complex (MHC) has a number some the important physiological functions, including the development of the immune response and the recognition of "foreign", and initiates the rejection of antigen-incompatible human's organs and tissues [2, 4, 5, 11, 12, 16, 19]. The leukocyte genes of the major histocompatibility complex MHC have a high degree of polymorphism and control the synthesis of glycoprotein molecules that are localized in cell membranes. Each person's cell membrane contains an individual set of HLA antigens [13, 15, 17, 18].

The study of the peculiarities of the content of individual HLA antigens in maternal and paternal haplotypes, ways of inheritance and, their distribution in the haplotypes of offspring remains a relevant problem of modern medicine. As leukocyte antigens, along with erythrocytes, play a key role in ensuring histocompatibility of human organs and tissues and get the best results when transplanting close relatives.

Based on the literature review on the inheritance of HLA\MHC haplotypes of mother and father antigens by their children, we are planning to differentiate how parental haplotypes of HLA\MHC antigens are inherited by siblings of different sexes (sisters and brothers).

Methods

To discover the inheritance pathways of individual antigens of parental haplotypes and to differentiate their distribution in the haplotypes of sisters and brothers, we used the materials of the reference manual on the inheritance of mother and father haplotypes by children [8]. In analyzing the inheritance of antigens by siblings of different sexes, first of all, the difference in their inheritance of HLA-DR antigens found on spermatozoa, which play a key role in their differentiated distribution among siblings, was taken into account, as in embryogenesis (respectively) with different leukocyte antigens. HLA-DR antigens are present on the surface of the human cell in large numbers They are linked to allelic variants of other antigens in haplotypes and are the most immunogenically

active. HLA-DR antigens are referred to as the most important typing leukocyte antigens [6].

Results

The human major histocompatibility complex MHC turned out to be the first large genomic region in which the complete sequence of about 260 gene loci encoded by the 6p21.3 loci of the 6th pair of autosomes was established, which occupies about 1.6 centimorgans on the short arm of the chromosome and contains about 4x10⁶ nucleotides. The HLA-DP, HLA-DQ, HLA-DR loci are more centromeric, and the HLA-A, HLA-C, and HLA-B loci are closer to the telomeres. Polymorphism of leukocyte HLA antigens of the MHC complex, as the most polymorphic system in the human genome, is due to the large number (polygenicity) and many allelic variants of HLA genes that produce alternative forms of proteins. Fragments of infectious agents of viruses and bacteria, by attaching to MHC antigens, thereby increase its polymorphism and stimulate the immune response. With the use of PCR, the number of identified alleles increases: 124 specificities were found in the HLA-A locus, HLA-B - 253, HLA-C - 174, HLA-E - 5, HLA-G - 14 specificities [6].

Each person's cell wall contains an individual set of HLA antigens. An exception is identical twins with the same MHC HLA antigens.

In the HLA\MHC system, there are 3 classes of histocompatibility antigens. Class I includes classic antigens HLA-A, HLA-B, HLA-C, HLA-D, and non-classical HLA-E, HLA-F, HLA-G. Nonclassical HLA genes include the TAP-A and TAP-B genes, as well as MIC-A and MIC-B, localized on chromosome 6 close to HLA-B [19].

Class II includes genes HLA-DPA1, HLA-DPA2 (encode α and β chains), genes HLA-Q1, HLA-Q2 (encode α and β chains), and HLA-DR genes: *DRA1*, *DRB1*, *DRB3*, -4 or -5. Class I and II molecules play an important role in processing and presentation [13, 14].

Ist Class molecules can be found on almost all nucleated cells (except for erythrocytes and trophoblast cells). Class II antigens are located only on cells of the immune system and can be expressed on B-lymphocytes, activated T-lymphocytes, macrophages, dendritic cells, as well as in vascular

endothelium and epithelial cells. I and II classes of histocompatibility antigens are localized in the lymphocytes' membranes, polymorphonuclear leukocytes, monocytes, platelets, liver, kidney, lungs, bone marrow cells, in blood plasma, placenta, as well as in other organs and tissues. *HLA-DR* antigens are found on monocytes, epithelial cells, and sperm.

There is an assumption that the conflict between the donor and the recipient may lead to a deterioration of transplantation results [9]. It has been shown that gender mismatch between donor and recipient may increase the risk of transplant rejection in kidney transplantation.

As a result of codominance, children inherit from each parent different alleles of leukocyte antigens of I and II classes, linked together in the form of haplotypes. The 1st human autosome controls the inheritance of 10 antigens *HLA-A*, *HLA-B*, *HLA-C*, *HLA-Dw*, and *HLA-DR* in 4 possible variants.

As is known due to codominant inheritance, haplotypes of parents *a*, *b*, *c*, *d* can be passed on to their children as haplotypes *ac*, *bd*, *ad*, *bc* [7]. In this case, the children receive from the father and mother one haplotype of maternal and paternal *HLA* antigens, which are distributed regardless of the sex of the child between siblings (sisters and brothers): one parental haplotype is inherited by each child.

Based on the study of the antigens' inheritance pathways of the parental (mother and father) haplotype and their distribution between sisters and brothers, we have drawn up the patterns of inheritance of *HLA*/MHC antigens in females (Fig. 1) and in males (Fig. 2).

Figures 1 and 2 demonstrate the inheritance pathways of maternal antigens *HLA-DRw1*, *HLA-DRw2* together with *HLA-DRw1 A3* father's antigens in sisters, as well as *HLA-DRw3* father's antigen along with *HLA-DRw1* and *HLA-DRw2* mother's antigens in brothers.

As shown in the 1st and 2nd figures maternal and paternal haplotypes with the same *DRw1* antigens differ in a different design: maternal *HLA-DRw1* is linked in the mother with *HLA-A1* antigens, while the paternal *HLA-DRw1* in the father - with *HLA-A3*.

Maternal and paternal haplotypes are inherited by siblings in different ratios: maternal haplotypes correlate with paternal ones like 2 is to 1 in siblings. This is because maternal haplotypes linked to *HLA-1* and *HLA-2* inherited in siblings are combined with only one paternal haplotype - with *HLA-DR1* (in two variants of sisters) and with *HLA-DR3* (in two variants of brothers). At the same time, paternal haplotypes are transmitted to both sisters and brothers in a ratio of 1 is to 2 (the ratio of paternal to maternal haplotypes) since one haplotype of the father with *HLA-DR1* antigen is inherited by two variants of sisters and one haplotype of the father with *HLA-DR3* - two variants of brothers.

Sisters (both variants), like brothers (both variants), inherit different paternal haplotypes: sisters - paternal *HLA-DRw1 A3 Cw1 B27 Dw1*, and brothers - paternal *HLA-DRw3 A9 Cw2 Dw3*.

Both maternal haplotypes *HLA - DRw1 A1* and *HLA - DRw2 A2* are contained in the genotypes of daughters and sons, however, paternal haplotypes are inherited by sisters and brothers in different ways: haplotype *DRw1 A3* is transmitted exclusively to sisters, and haplotype *HLA-DRw3 A9* - exclusively to brothers.

Discussion

Therefore, maternal and paternal haplotypes that differ in the content of *HLA* antigens are unequally distributed between siblings. Sisters and brothers inherit maternal haplotype, while only one of the paternal haplotypes with *HLA-DR3* antigen is transmitted to sisters (both sisters' genotypes). This paternal haplotype can be transmitted again to the male (mother to brothers) and female (mother to sisters) in subsequent generations. The special second paternal haplotype linked to the *HLA-DR3* antigen is inherited exclusively by the male sex - brothers and cannot be inherited by any of the two variants of the sisters' genotypes including subsequent generations.

In the familiar general pattern of inheritance of *HLA* antigens [7] maternal haplotypes with leukocyte antigens *HLA-DRw1* and *HLA-DRw2* can be represented as *ab*, and father's haplotypes with *HLA-DRw1* and *HLA-DRw3* antigens like *cd* following the above features of inheritance of specific allelic variants of leukocyte antigens by siblings. Sisters

can inherit haplotypes *ac* and *bc* from their parents, and brothers - *ad* and *bd*; haplotype *d* can be considered as a specific paternal haplotype linked to the *HLA-DRw3* antigen. Sisters inherit haplotype *c* from their father, the antigens of which are linked to the *HLA-DRw1* antigen, and brothers inherit from their father haplotype *d* with antigens linked to *HLA-DRw3*.

Therefore, women and men differ in the inheritance of parental *HLA|MHC* haplotypes. In women, sisters inherit *a* and *b* haplotypes from their mother and haplotype *c* from their father. In men, brothers inherit haplotypes *a* and *b* from the mother, and a special haplotype *d* is inherited from the father, which, when passed from father to son, is limited to the male sex and remains alien to the woman's immune system. This haplotype is linked to the father's *DRw3* antigen.

Mothers and daughters, fathers and sons have the same haplotypes of leukocyte antigens due to codominant inheritance. Sisters, as well as brothers, coincide in one paternal haplotype. Maternal haplotypes in siblings inherited from the mother may happen at the same time. There is a chance of coincidence in large families siblings is possible for two haplotypes simultaneously.

Daughters do not inherit the special paternal haplotype *HLA-DR3 A9 Cw2 B5 Dw3* inherited by brothers from the father. However, exclusively sons (both possible variants of sons' genotypes) inherit it at the same time. Passing from father to son, a special haplotype is represented by *HLA* antigens of glycoproteins in the cell walls of all men and is limited to the male sex. As a result, such a special haplotype remains "alien" for the woman's immune system.

Immunological incompatibility is observed in inbred mice during transplantation of male skin flaps to females and is explained by the ability of the immune system to recognize the products of the Y chromosome [3]. The ability of females to reject syngeneic skin grafts from males was observed by Eichwald and Silmsler in 1955; at the same time, no rejection was observed during skin transplantation from females to males, as well as in transplants between individuals of the same sex [10]. The incompatibility of transplants in inbred mice may be

due to the paternal haplotype of the *HLA H-2* system, which is contained in the genotype of all males and is absent in females.

Cytogenetic maps of X and Y chromosomes have *p21.3* loci located on the short arm of X chromosomes and *q21.31* loci. *q21.33* localized on the long arm of chromosomes X and Y which apparently can determine the inheritance of *HLA|MHC* antigens in generations of females and males. In males, the NRY region of the Y chromosome contains a homogeneous haplotype inherited by the male line [1]. The special paternal haplotype *d* linked to the *HLA-DR3* antigen, like the haplotype of the non-recombining NRY region, is probably also inherited in the male chain of generations, passing from father to son.

Therefore, maternal and paternal leukocyte antigens in the haplotypes of sisters and brothers are linked to various *HLA-DR* antigens. A special paternal haplotype *d* linked to the *HLA-DR3* antigen is foreign to the woman's body, both daughter and mother, and can cause incompatibility and rejection during transplantation of male organs and tissues to women. In addition, it can cause post-transfusion reactions in women when transfusing the blood of male donors, especially in cases where large volumes of blood are transfused during transfusion or the woman is injected repeatedly.

Thus, there is a different inheritance of the *HLA|MHC* haplotypes of the mother and father antigens by children of different sexes - sisters and brothers in females and males. In women, sisters inherit parental haplotypes *a* and *b* from the mother, and haplotype *c* from the father. In men, brothers inherit haplotypes *a* and *b* from mothers. And a special haplotype *d* linked to the *DRw3* antigen is inherited from the father. This haplotype which is passed from father to son is limited to the male sex and remains alien to the woman's immune system.

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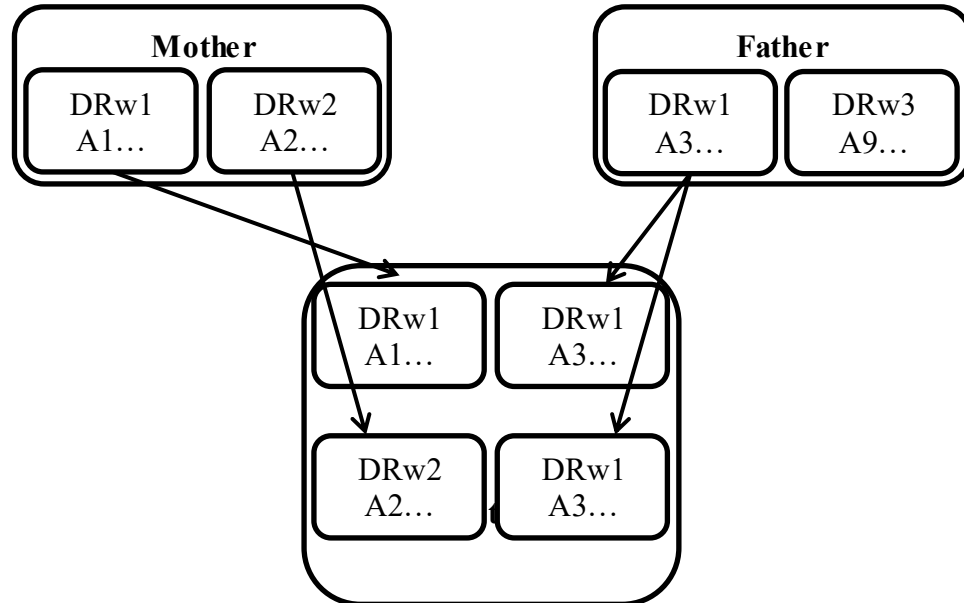


Figure 1. Inheritance pathways of HLA/MHC antigens in females.
 Symbols: A1... – A1 B8 Cw1 Dw3; A2... – A2 B7 Cw3 Dw2; A3... – A3 B27 Cw1 Dw1;
 A9... – A9 B5 Cw2 Dw3; « → » - the direction of antigens' inheritance.

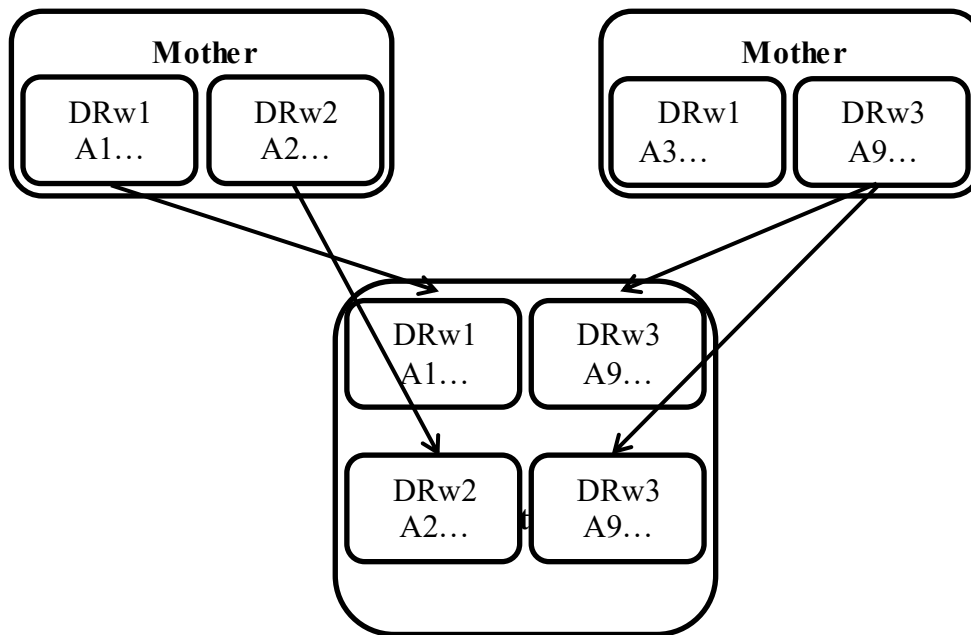


Figure 2. Inheritance pathways of HLA/MHC antigens in males.
 Symbols: A1... – A1 B8 Cw1 Dw3; A2... – A2 B7 Cw3 Dw2; A3... – A3 B27 Cw1 Dw1;
 A9... – A9 B5 Cw2 Dw3; « → » - the direction of antigens' inheritance