Prevalence of HLA Alleles in Egyptian Population

Thesis

Submitted for Partial Fulfillment of Master Degree in Internal medicine

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List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
MHC	**Major histocompitability complex**
SNP	**Single nucleotide polymorphism**
LD	**Linkage disequilibrium**
HWP	**Hardy-Weinberg proportions**
HLA	**Human Leukocyte Antigen**
SLE	**Systemic lupus erythromatosis**
RA	**Rheumatoid arthritis**
EMA	**Expectation maximization algorithm**
DNA	**Deoxyribonucleic acid**
APC	**Antigen presenting cell**
CREG	**Cross reactive antigens groups**
NK	**Natural killer cell**
DTH	**Delayed type hypersensitivity**
HPC	**Hematopoietic progenitor cell**

INTRODUCTION

HLA (Human leukocyte antigen) typing is defined as identifying antigens on the white blood cells (WBCs) that determine tissue compatibility for organ transplantation, also known as histocompatibility testing. There are six loci on short arm of chromosome 6, where the genes that produce HLA antigens are inherited: HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP **(Berger, 2001)**

HLA system is the most polymorphic genetic human system. Human leukocyte antigen typing is performed for kidney, bone marrow, liver, pancreas, and heart transplants. The probability that a transplant will be successful increases with the number of identical HLA antigens**.** Human leukocyte antigen testing is performed to reduce the probability of both rejection and GVHD.

Typing is also used along with blood typing and DNA tests in paternity testing. The third use of HLA typing is to determine the likelihood of inheriting certain alleles as part of major histocompitability (MHC) genes that include both HLA alleles and alleles determining immunological processes and susceptibility to infections **(Bakker et al., 2006).** For example 2% of people who have the HLAB27 allele develop ankylosing spondylitis of the vertebrae **(Simon et al., 1977).** Recent studies

also show linkage between some adverse reactions to some drugs and patient's HLA type.

Internationally there is a tidal wave of immune-genetic mapping of different ethnicities and races, especially in communities with different races and ethnic groups. This move is encouraged by bone marrow donors worldwide (BMDW), the first international registry for stem cells and cord blood donors. They are now engaging 28 million donors. To have access to BMBW you have to have an active national registry in the first place.

HLA typing has so far proven important in the Egyptian scientific community in relation to HCV, HCC, tuberculosis, and pediatric celiac disease studies **(Beatty et al., 1995).**

Having a better idea on the prevalence of HLA alleles will encourage more research on diseases that affect the Egyptian people and its relation to HLA type. And to make it more challenging Egyptians are racially mixed. They are not only Arabs nor are they only Africans. They have both their ancestor's haplotypes and those of all their invaders.

This study aims to collect HLA typing data from donors and recipients' medical records in bone marrow transplant centers, Nasser institute's and Ain Shams University's, and from the medical records of Al-Salam International hospital's kidney transplant center, and statistically determine in numbers HLA

alleles' prevalence in the Egyptian population, which is of mixed ethnicity **(El-chennawi et al., 2008).**

It's in the hopes of the investigator that someday this study data will be used by a health politician to influence resources allocation for prevention and early intervention of autoimmune diseases and other diseases inherited along with HLA alleles **(Hafez et al., 1985).**

This study is also, hopefully, the first step upon which an organ donation registry can be built plus an institution for early detection of inheritable diseases can be established **(Abu-Zekry et al., 2008).**

AIM OF THE WORK

The aim of this study is to evaluate the prevalence of HLA alleles in the Egyptian population through gathering of HLA alleles data for recipients and donors in transplant of bone marrow and kidney. This study hopes to lay the ground work for a national data base of HLA alleles of Egyptians that may someday serve as a registry for organ donation from unrelated person.

HUMAN LEUKOCYTE ANTIGEN

MHC Genes

Major histo-compatibility genes are found on the short arm of chromosome 6 (6p21.31). In humans, they comprise 0.1% of the genome. MHC region is the densest with genes in the human genome. It contains 220 genes with an average of 1 gene in every 16 kilo bases. Only 50% of MHC genes are expressed. The remainders are pseudo-genes, unexpressed and believed to have a role in creating new alleles by gene conversion. About 40% of the products of expressed genes have a role in the body's immunity. The products for these genes' expression in humans are called human leukocyte antigens/ molecules, or MHC molecules ***(Mungall et al., 2003)***

Human leukocyte antigens are cell surface proteins that essentially bind peptides, forming MHC/peptide complex. This complex then activates T-cell lymphocytes. The HLA complex is essential for T-cell activation, therefore essential for immunity against a great number of foreign organisms. HLA are also responsible for the body's recognition of non-self, mismatched, allogenic grafts. They recognize them as foreign and lead to eventual graft rejection/ failure ***(Marrack et al., 2001)***.

Human leukocyte antigens are two classes: class I and class II. Class I molecules include: HLA-A, HLA-B, HLA-C. Class II molecules are: HLA-DP, HLA-DQ, and HLA-DR.

MHC Antigens: Structure and How They Work

Human MHC genes are divided in to 3 regions ***(Allcock, 2012)****:*

1) **Class I cluster** (telomeric), which comprises:

   a) Classic class I genes. (HLA-A, HLA-B, HLA-C)

      - Expressed by all nucleated cells.
      - Control function and activation of cytotoxic T-cells.

   b) Non-classic class I genes. (HLA-E, HLA-F, HLA-G)

      - Expressed in specific tissues.

   c) Class I- like genes. (MICA, MICB)

      - Expressed under stressful physiological conditions.
      - Products of both non-classic genes and class I- like genes serve as ligands to receptors which control function of natural killer cells (NK).

   d) Pseudo-genes.

2) **Class II cluster** (centromeric), which comprises:

   a) Classic class II genes. (HLA-DR, HLA-DP, HLA-DQ)

      - Expressed by antigen presenting cells (denderitic cells, macrophages, monocytes) and by B cells.

- Expression can be induced in endothelial cells and T-cell lymphocytes.

b) Non-classic class II genes. (HLA-DM, HLA-DO)

- Express heterotetrametric complexes involved in peptide exchange and loading on to classic class II molecules.

c) Pseudo-genes.

3) **Class III** (central region): Encodes critical immune system substances as; tumor necrosis factors complement proteins and heat shock proteins.

Class I and class II molecules have similar crystallographic three dimensional structures, but they differ in subunits structure ***(Brown et al., 1993).***

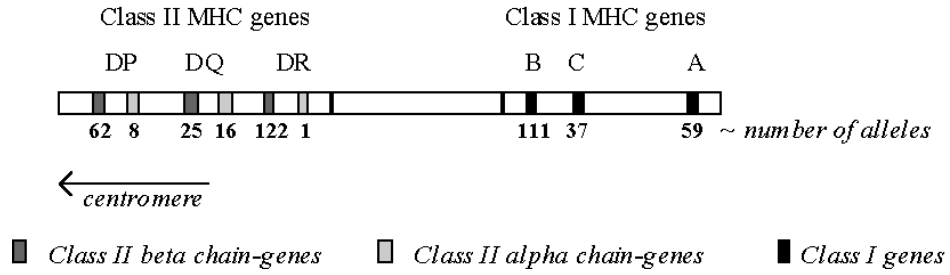

Figure (1): The distribution of the main genes that encode MHC class I and MHC class II molecules on the short arm of chromosome 6; the figure also shows the large number of allelic forms of most of these genes.

Class I molecules are structurally composed of *(Mungall, 2003)*:

(1) A polymorphic alpha chain (also called: heavy chain) (45kDa), formed of 3 globular extracellular domains (alpha 1,2,3), trans-membrane and an intracellular domain, stabilized and bound to:

(2) A non-polymorphic, non-MHC B2 micro-globulin (light chain) (12kDa).

Class II molecules are composed of: polymorphic alpha and beta chains, (35kDa, 31kDa), bound non-covalently. They are both trans-membranes with no extracellular globular domains ***(Mungall, 2003).***