DR AND MT PHENOTYPE IN THE EGYPTIAN RHEUMATOID ARTHRITIS PATIENTS

Thesis

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BY

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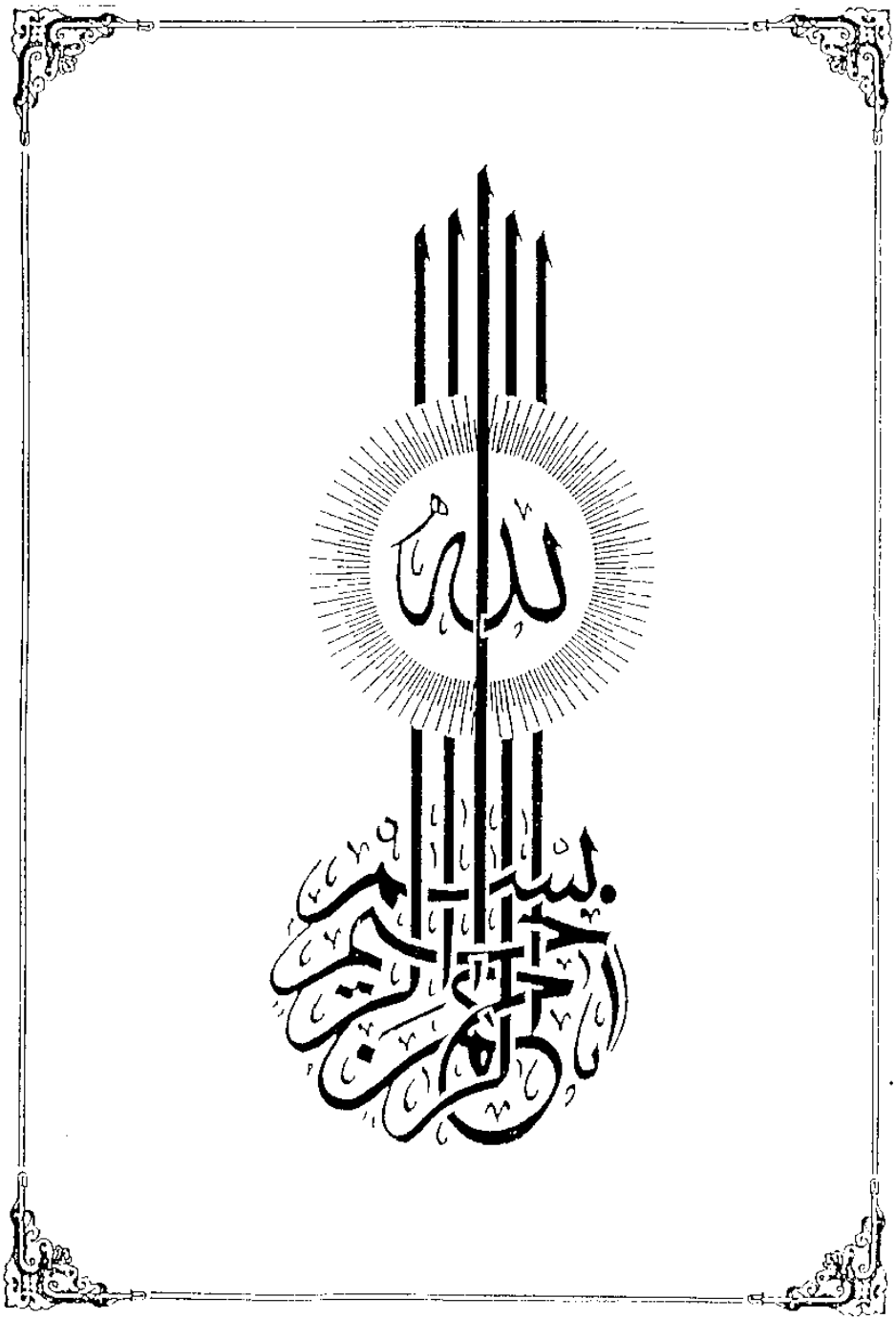
TO MY PARENTS,
MY WIFE AND MY
SON AMIR



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AIM OF THE WORK

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The possibility of finding an association between specific HLA antigens and a disease process was appreciated since the discovery of the strong association between HLA-B27 and ankylosing spondylitis. It represents one of the most important advances in clinical medicine and provides a firm foundation for understanding the etiology and the pathogenesis of a wide range of diseases. The HLA antigens may act as genetic markers which can indicate a predisposition to disease.

The pathogenesis of rheumatic diseases continues to be an area that is challenging to the researcher who deals with these problems. One of the major break-throughs in the recent years is the discovery that HLA system is involved with both the genetics and the immunology of rheumatic diseases.

Rheumatoid arthritis is a disease with abundant evidence for immunological abnormalities, and it is therefore of interest to look for its associations with the major histocompatibility complex. Testing for the HLA-A, -B and -C did not yield any significant

association with rheumatoid arthritis(Brewerton and Albert 1977), but when HLA-DR antigens were described and tested for, it was possible to establish significant associations between rheumatoid arthritis and certain DR antigens. Most of these studies were made on Caucasian and Japanese patients with rheumatoid arthritis, other population groups were not investigated. The present study is the first one to deal with the relation between DR and MT antigens in Egyptian rheumatoid arthritis patients.

The aim of the present work is to study the frequencies of DR and MT alloantigens in a group of Egyptian rheumatoid arthritis patients to be compared with those found in the normal Egyptian controls to find out any significant difference in the antigens frequencies between patients and controls.

REVIEW OF THE HISTOCOMPATIBILITY SYSTEM

HISTORICAL NOTE

The histocompatibility system has been recognized since 1900. At that time certain mouse tissues and tumours could be transplanted to animals of the same inbred strain without rejection and rejected if transplanted to other strains, being recognized by the host animal as foreign. Based on these experiments the discovery of the mouse major histocompatibility system which was called "H-2" system was followed. Snell in 1948 called the antigens involved in the transplantation matching "histocompatibility antigens". The "H-2" system was the model for the study of the HLA system in man. Dausset in 1954 found antibodies which he called "leukoagglutinins" in the sera of polytransfused patients. Dausset in 1958 discovered the first HLA antigen and named it mac (now HLA-A2), (Klein 1975).

Van Rood in 1962, discovered a two allele system 4a-4b (now Bw4 and Bw6) which he called "group 4" system. Payne in 1964 found independent allelic system of antigens which he called "LA" (L for leucocyte and A for the first locus). As further antigens associated with "LA" and "4" groups were defined it became clear that these antigens belonged

to two series each of which behave as if controlled by a set of alleles at two closely linked loci, the "LA" and "four" loci (now known as HLA-A and HLA-B loci). This simplified model of HLA system was presented by Kissmeyer-Nielsen in 1968 (Bach and Van Rood 1976)

Sandberg et al (1970), suggested the existence of a third segregant series (AJ, now C) strongly associated with B series. AJ are the initials of the swedish woman whose serum first allowed detection of C antigens.

Yunis et al (1971), suggested the presence of the D locus which controls the mixed lymphocyte culture test (MLC).

The coordination and standardization of techniques.the comparison and consolidation of antigens are being achieved by means of a series of collaborative work-shops; the international histocompatibility work-shops, the first of which was held in 1964 and the last one was in 1984 (Albert 1985).

NOMENCLATURE

The name "HLA" includes two parts ; "HL" meaning human leucocyte, the cell type first studied, and "A" for the first system (not for antigen as it is often assumed). This nomenclature was achieved by international committee sponsored by the World Health Organisation (WHO). The main function of the WHO nomenclature committee which generally meets after each International Histocompatibility Workshop is to review nomenclature of the antigens.

The prefix "HLA" is used to describe the whole system, each antigen of the HLA system is identified by a letter for the locus which controls it, followed by a number defining the particular specificity of the locus, e.g.; HLA-B27, HLA-DR3.

The letter "w" following the locus symbol and preceding the number indicates that specifity is still provisionally indentified e.g.; HLA-Cw1, this letter is removed when there is no further doubt about the specificity of an antigen, and the appropriate antisera are generally available for its definition.

A complete list of officially recognised HLA specifities is given in table (1), (Albert 1985).

Table (1)

HLA-A	HLA-B		HLA-C	HLA-D	HLA-DR
HLA-A1	HLA-B5	HLA-Bw45(12)	HLA-Cw1	HLA-Dw1	HLA-DR1
HLA-A2	HLA-B7	HLA-Bw46	HLA-Cw2	HLA-Dw2	HLA-Dr2
HLA-A3	HLA-B8	HLA-Bw47	HLA-Cw3	HLA-Dw3	HLA-DR3
HLA-A9	HLA-B12	HLA-Bw48	HLA-Cw4	HLA-Dw4	HLA-DR4
HLA-A10	HLA-B13	HLA-Bw49(w21)	HLA-Cw5	HLA-Dw5	HLA-DR5
HLA-A11	HLA-B14	HLA-Bw50(w21)	HLA-Cw6	HLA-Dw6	HLA-DRw6
HLA-Aw19	HLA-B15	HLA-Bw51(5)	HLA-Cw7	HLA-Dw7	HLA-DR7
HLA-Aw23(9)	HLA-Bw16	HLA-Bw52(5)	HLA-Cw8	HLA-Dw8	HLA-DRw8
HLA-Aw24(9)	HLA-B17	HLA-Bw53		HLA-Dw9	HLA-DRw9
HLA-A25(10)	HLA-B18	HLA-Bw54(w22)		HLA-Dw10	HLA- D R w10
HLA-A26(10)	HLA-Bw21	HLA-Bw55(w22)		HLA-Dw11	
HLA-A28	HLA-Bw22	HLA-Bw56(w22)		HLA-Dw12	
HLA-A29	HLA-B27	HLA-Bw57(17)			
HLA-Aw30	HLA-Bw35	HLA-Bw58(17)			
HLA-Aw31	HLA-B37	HLA-Bw59			
HLA-Aw32	HLA-Bw38(w16)	HLA-Bw60(40)			
HLA-Aw33	HLA-Bw39(w16)	HLA-Bw61(40)			
HLA-Aw34	HLA-B40	HLA-Bw62(15)			
HLA-Aw36	HLA-Bw41	HLA-Bw63(15)			
HLA-Aw43	HLA-Bw42	HLA-Bw4[b)]			
	HLA-Bw44(12)	HLA-Bw6			

HLA-A, -B, -C ANTIGENS

They include three segregent series; A (LA or first), B (four or second), and C (AJ or third). These are determined by genes of the three A, B, and C loci.

The HLA-A, B and C antigens are present on the surface of all cells except erythrocytes, sperms and placental trophoblast. These antigens exist in the cell membrane as separate molecules (Bach and Van Rood 1976).

The HLA-A, B and C antigens are highly polymorphic, where each molecule carries both "private" antigenic determinant (unique for a given ABC allele) as well as "public" determinants shared between different allelic products. Most antisera available have dominant specifity but also react to a lesser degree with other cross-reacting specifities. This may reflect complexity of the antigens and the presence of number of antigenic determinants, some of which are shared by more than one specifity. The antigens within each allelic series show a large amount of cross-reaction, but there is no cross-reaction between series. The HLA-B7 can cross-react with HLA-B27,