HLA TYPING IN SELECTED PEDIATRIC DISORDERS OF MULTIFACTORIAL ETIOLOGY

THESIS

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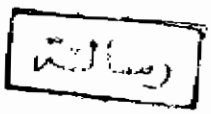

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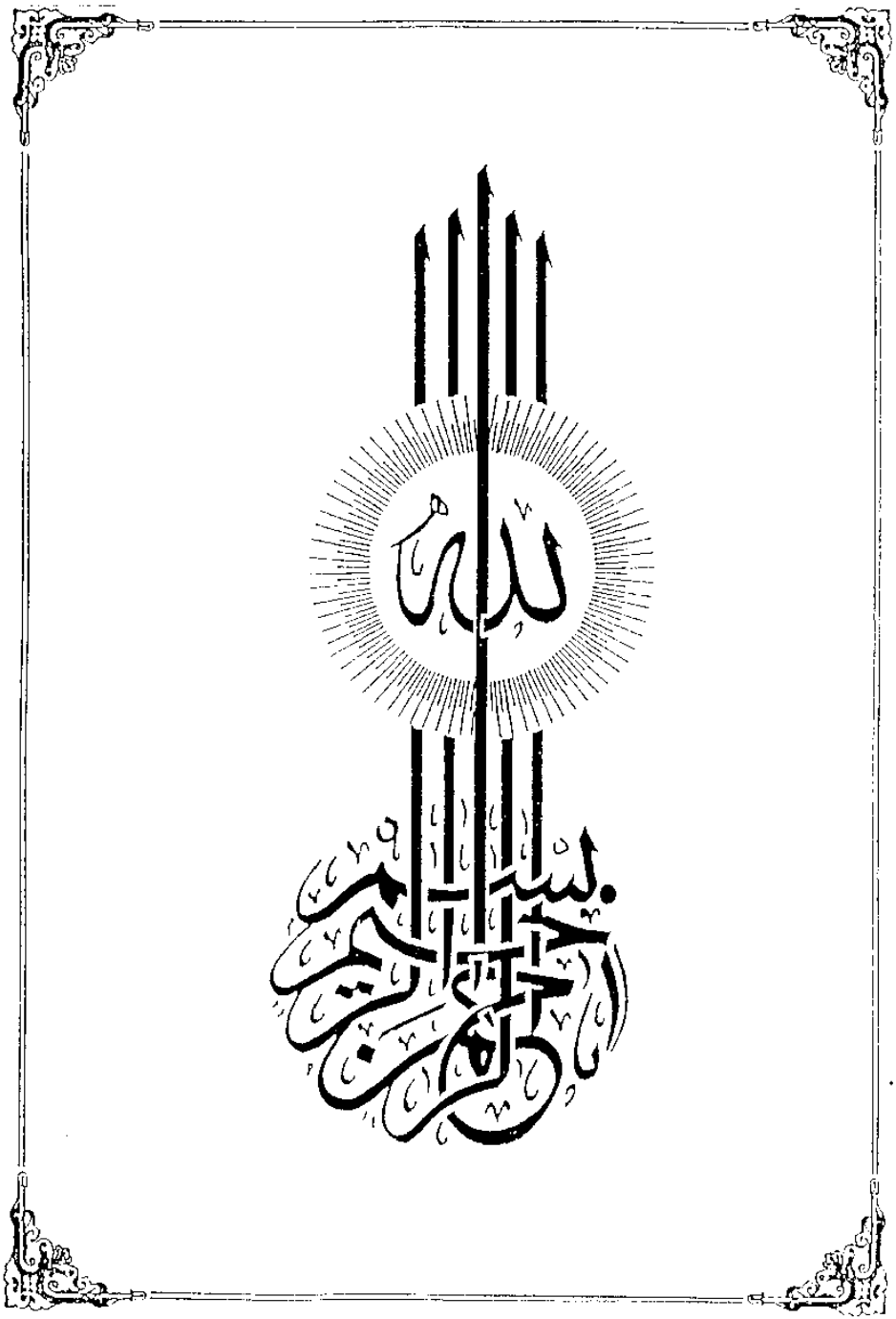

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AIM OF WORK

The discovery of associations between certain diseases and HLA system represents one of the most important advances in clinical medicine of the last decade and provides for the first time a firm foundation for understanding the genetics and pathogenesis of many diseases.

This work comprises the study of three different disease categories: Xeroderma Pigmentosum, Retinoblastoma and Medulloblastom , with their linkage to the HLA system.
As for xeroderma pigmentosum, although the disease seems clinically uniform, various biochemical defects could possibly be involved in the disease, various inherited forms and wide spectrum of symptoms and signs suggest the possibility of a hetero-geneous group of disease that may have quite different predisposing and precipitating factors.
Also a proof for the penetrance of retinoblastoma allele or increased susceptibility to the disease through a defect in the immune response is still lacking and under medical researches.
Also, there is a lack of clearcut epidemiologic studies, indicating any particular factors (viral, chemical or traumatic) that cause brain tumors including medulloblastoma, and also there is no available proof of genetic predisposition for most central nervous system tumors.

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So, aim of this study is to examine the frequencies of HLA-A,B and C antigens in a group of Egyptian children with those three diseases, in order to know if there is a significant difference in antigen frequency between the patients and controls. This significant difference - when it is prooved - helps to clarify any epidemiologic, aetiologic, immunologic or genetic factor, concerned in the three disease categories studied.

This study is the first one to deal with the relation between HLA system and Xeroderna Pigmentosum, Retinoblastoma and Medulloblastoma in Egyptian patients.

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REVIEW OF

LITERATURE

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THE HLA - SYSTEM

Introduction:

The HLA system has developed out of a search for blood groups of leucocytes that could form the basis for matching donors and recipients for transplantation. Early work with transplantable tumors in the mouse had established that genetic difference, between recipient and donor tissue, determines the outcome of a graft.

It was on this basis that Gorer started the work that led to his discovery of the mouse major histocompatibility system H_2. The subsequent development of the H_2 system by Gorer, Snell and others depended very much on the use of inbred strains of mice, many of them developed especially for this purpose. The antigens relevant for transplantation matching called histocompatibility antigens by Snell (1948) and so, as it comes to be realized that the H_2 antigens were the most important to match for, this becomes the major histocompatibility system of the mouse. The H_2 system has in many respects been an important model for studies of the HLA system in man (Munroe & Waldman, 1978).

There are no human inbred lines and so the development of the HLA system has depended on approaches different

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from those used in the work on the mouse, namely on population and family studies, and on appropriate statistical methodology using the development of the human red cell blood groups as a model.

The first evidence in favour of the existence of human leukocyte blood groups was put forward by Dausset (1954), who observed that patients, whose sera contained leukoagglutinins, had received a larger number of blood transfusion than patients lacking such antibodies. This observation indicated that these antibodies were not auto-antibodies, as was previously thought, but rather isoantibodies (alloantibodies) induced by the infusion of cells, carrying isoantigens not present in the recipient.

Dausset (1958) provided strong support for this assumption, when he observed that sera from seven poly-transfused patients agglutinated leukocytes from about 60% of the French population, but not the leukocytes of the seven patients. Dausset termed the leukocyte isoantigen MAC (now HLA-A_2 A_{28}) and this was the first discovery of an HLA antigen.

Dausset and Brecy (1957) also provide evidence from twin studies that leukocyte isoantigens are genetically

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determined and family studies by Payne and Roles (1958) substantiated this interpretation.

These authors also showed thatpregnancies may induce the formation of leukocyte isoantibodies as did Van Rood et al., (1958); independently Van Rood (1962) fought the imperfect serology of this early stage by computer analysis and discovered the diallelic leukocyte antigen system, 4 a, 4 b (now W 4 and W 6).

By means of absorption studies, Van Rood (1962) also found that these antigens are present on most human tissues. Simultaneously, Shulman et al., (1962, 1964) showed that typing for leukocyte antigens can also be done by means of a reliable complement-fixation test with blood platelets as antigen source. However, sera reacting sufficiently strong in this test are unfortunately rare, and it was therefore of great importance, when Terasaki and McClelland (1964) introduced the more sensitive microlymphocytotoxicity test, which in various modifications has maintained its major role in serological HLA typing untill the present time.

Following the discovery of the first leucocyte antigens the number increased rapidly, and Dausset et al. (1965) and Van Rood et al. (1965) suggested on the basis

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of population studies that most of these antigens belong to one and the same genetic system.

The development of the HLA system has been greatly stimulated by a series of international collaborative workshops started by Amos in 1964. These workshops, the international histocompatibility workshops, which have involved the exchange of reagents amongst a large number of participating laboratories and the combined analysis of the resulting data, have each major turning points in the development of knowledge of all aspects of the HLA-system.

The second and third workshops, organised by Van Rood in 1965 and Ceppellini in 1967, placed the definition of the first described antigen on a firm footing and established that antigens belonged to a single system of closely linked genes (Ceppellini et al., 1967).

The close genetic relationship of the determinants of these leukocyte antigens was so convincing that the term HLA the first (A). Human leukocyte antigen system discovered was approved by WHO (Nomenclature Committee, 1968) for this genetic system. The fourth and fifth workshops organised by Terasaki (1970) and Dausset (1972) established the control by two linked loci of the main serological

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specifities and, through a worldwide series of population studied, the universality of this genetic model and the general distribution of the antigens amongst the major human population groups was established. (Joint report, 4th, 5th, 1970, 1972).

The sixth workshop was organised by Kismmeyer - Neilsen (Joint report 1975), clarified the definition of the third, or, HLA-C serological locus and established the HLA-D, locus identified by the mixed lymphocyte culture reaction.

The seventh of these workshops was organised by Bodmer and led to the serological definition of the HLA-DR types, establishing their relationship to the HLA-D type and clarifying their role in disease association (Bodmer, 1978).

The WHO nomenclature committee meets after each international histocompatibility workshop to review the nomenclature of the antigen, in particular with reference to the information gained during the workshop.

Originally the antigens were simply assigned numbers preceeded by HLA, but as the complexity of the system increased, it was agreed to use letters for the loci with the prefix HLA reserved to describe the whole system.

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Thus now each antigen is identified by a letter for the locus which control it, followed by a number defining the particular specifity of that locus. The letter W following a locus symbol and preceeding the number, indicates that a specifity is still provisionally identified. This designation is removed when there is no further doubt about the clarity and reproducibility of definition of an antigen, and when the appropriate antisera are generally available for its definition (Bodmer, 1978).

The term haplotype (derived from haploid genotype) was introduced by Ceppellini in the context of the HLA system to describe the combination of genetic determinants that lead to a set of antigenic specifities (or other gene products) which is controlled by one chromosome and so inherited together from one or other parents (Ceppellini et al., 1967).

The complete current list of officially recognized HLA specifities together with some of the previous names, that have been used for these, is given in table 1, page 10.

The two best studied major histocompatibilities are those of the mouse designated H_2 complex and the human designated the HLA complex. Table 2 gives designation of

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