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HLA and keratoconus - A family study

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HLA AND KERATOCONUS - A FAMILY STUDY

By

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In partial fulfillment of the requirements for the Doctor of Optometry Degree, Pacific University, College of Optometry, Forest Grove, OR

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ABSTRACT

Linkage of a possible disease susceptibility gene for keratoconus with the HLA system was studied in 2 families where more than one member of each family had the disease. HLA haplotypes were obtained from all family members, both with and without keratoconus, and compared among family members and between families. Preliminary data indicates that a genetic linkage of a disease susceptibility gene to the HLA system is not present in the disease keratoconus.
INTRODUCTION

It is thought that genes of the HLA system have an effect on the immune response, and on susceptibility to a wide variety of diseases; that there is a disease susceptibility locus within the HLA region. It has been established that in over 100 diseases, many of them ocular or with ocular manifestations, an association exists between HLA antigens and the presence of a particular disease (Scharf, et al; Ladas).

HLA antigens are comprised of glycosolated polypeptide chains. The development of HLA antigens is controlled by a group of 5 genes located within a cluster on chromosome number 6. Within the HLA region, there are 5 loci, designated HLA-A, HLA-B, HLA-C, HLA-D and HLA-DR. HLA-A,B and C are on all nucleated cells and platelets, while HLA-D and DR are found primarily on B lymphocytes and monocytes. HLA-A,B and C are detected serologically, that is, aliquots of lymphocytes are individually mixed with antibodies specific to each of the known HLA antigens. HLA-D and DR antigens are detected using mixed lymphocyte cultures which are homozygous for a D specificity (for review, see Emery et al).

An HLA relationship to a disease can be studied by either population studies or family studies. Population studies are carried out by tissue typing unrelated patients with a particular disease, and comparing the frequencies of the various HLA antigens of this population with those observed in a random sample of non related, healthy controls.
Family studies are carried out as genetic linkage studies, linkage being when genes are closely located at loci on the same chromosome pair. By looking at inheritance patterns within families, it is thought that a disease susceptibility gene will be inherited with a particular HLA haplotype. The basis of family studies is to use the HLA haplotype as markers to trace the inheritance pattern of disease susceptibility genes. If, as it is thought, genes concerned with the immune response are located in the HLA region and therefore are in close genetic linkage with HLA loci, the etiology or susceptibility to a chronic disease may be due at least in part to an altered or abnormal immune response. Lastly, if disease susceptibility is shown to be linked to HLA antigens, a person with a susceptible haplotype who does not exhibit the disease may illustrate the environmental or non genetic factors that may play a role in the development of a disease.

HLA antigens then, are used as markers for a disease because of their genetic linkage with the immune response genes.

The diseases which show an HLA association to date have an unknown or uncertain etiology. All show some familial inheritance patterns, suggesting a genetic component to the disease susceptibility, and are thought to be related to an altered immune response.

Keratoconus is a disease for which an association with the HLA system has been sought because it is a disease that has an unknown etiology and has shown a clustering of some families (Duke-Elder). In addition, keratoconus has been associated with various immune system alterations.
such as atopic dermatitis (Spencer; Longmore), excema (Copeman; Galin) and increased levels of immunoglobulin E (Kemp). HLA associations with keratoconus to date have been inconclusive. Some investigators have found an association with keratoconus and HLA. Damgaard - Jensen et al found a suggestive but not significant decrease in the frequency of HLA-B7 and an increase in the frequency of HLA-B15 among 42 Danish patients with keratoconus. Karantinos et al found an increase of HLA-BW21 in 20 Greek patients and Blagojevic et al reported an increase of HLA-A9 and HLA-B12 among their 27 Belgrade patients. Klouda et al found a significant increase of HLA-B5 among 64 English keratoconic patients. Other studies have not found an HLA association with keratoconus. Vannas et al did not find any deviations of HLA frequencies in 51 keratoconic patients from Finland. McKinney and Yolton HLA typed 39 patients and also reported no significant alterations in HLA patterns from normal HLA population frequencies. The above studies were carried out as population studies.

Gasset et al performed a family study and showed a possible HLA linkage between keratoconus and HLA-B27 by HLA typing four family members and finding HLA-B27 present in three members of the family who had keratoconus, and absent in the one family member without keratoconus.

This study, then, is a pilot study to add to the data reported by Gasset. The questions asked are 1) is there an HLA association with HLA-B27 and keratoconus and 2) is there a suggestion of genetic linkage with the HLA system as a marker, and the disease keratoconus within families.
METHODS

Two families were selected for study. Each family had to have all parents and sibs available for HLA tissue typing. At least 2 members of each family have been diagnosed as having keratoconus by an eye care practitioner by standard criteria.

The HLA tissue type of each member of the family was determined by the American Red Cross Tissue Typing Laboratory, Portland, Oregon using the two stage lymphocytotoxicity technique of Terasaki (Terasaki). Typing was performed using 120 antisera specific for 63 HLA antigens; 18 A, 38 B and 6 C antigens. Certain splits, which are closely related subgroups of the HLA-A and B antigens were also tested for.

HLA haplotypes were obtained, and then compared amongst family members and between families, to see if an HLA haplotype existed in the keratoconic patients that would show if a disease susceptibility gene is linked with that particular haplotype.
RESULTS AND DISCUSSION

The HLA haplotypes and their pattern are seen in Figure 1. There appears to be no genetic linkage between HLA haplotypes and the susceptibility to or development of keratoconus. Evidence for this is individuals with haplotypes that are identical to keratoconic patients do not exhibit the disease. In family II, HN has an HLA haplotype of HLA-A2, B7, B14 and has keratoconus, while JN has the same haplotype and does not have keratoconus. In family II, the same thing appears with family members LM and RM. Both are HLA-A3, 30, B13, 51, yet only LM has keratoconus.

In addition, in both of the families, each of the individuals that have keratoconus have different HLA haplotypes, illustrating that a single HLA marker does not confer disease susceptibility in the case of keratoconus.

Data presented by Gasset showed a possible linkage of HLA-B27 to keratoconus in a family with multiple cases of keratoconus. My data indicates this is not the case. No family member, either with or without keratoconus had HLA-B27, and as this study shows, no linkage of the disease with HLA has been illustrated.

It is apparent that the eye disease keratoconus is probably not associated (population studies) nor linked (family study) to the HLA system as it is known today.
Research is on going in the genetics of the HLA system, new antigens are being discovered, and new functions are being ascribed to some of the antigens. Current research is shedding new light on the function of HLA-D and DR and their role in the immune response. As more knowledge is gained about HLA function, its role in keratoconus should be studied further.
Figure 1. HLA pedigree for two families, with multiple sibs effected with keratoconus. Arrows indicate individuals with keratoconus.


