Major Histocompatibility Complex, Class I, A

Alternative Names
HLA-A
HLA-A Histocompatibility Type
Major Histocompatibility Complex, Class I, H Pseudogene
HLA-H
Major Histocompatibility Complex, Class I, J Pseudogene
HLA-J
Skin Hypersensitivity, Carbamazepine-Induced, Susceptibility to

Record Category
Gene locus

WHO-ICD
N.B.: Classification not applicable to gene loci.

Incidence per 100,000 Live Births
N/A to gene loci

OMIM Number
142800

Mode of Inheritance
Autosomal dominant (6p23-p21, probably 6p21.3)

Gene Map Locus
6p21.3

Description
The genes of the Human Leukocyte Antigen (HLA) system reside on chromosome 6 and code for cell-surface proteins that play a crucial role in the presentation of endogenic peptides to effector cells of the immune system. The HLA Class I protein molecule is a heterodimer, made up of two chains; a heavy one, and a light one (beta 2 microglobulin). The HLA Class I protein presents peptides from the lumen of the endoplasmic reticulum to T-cells, thereby effecting a cascade of immunologic reactions. The HLA-A gene is one of the three HLA Class I heavy chain paralogues.

Hundreds of HLA-A alleles have been described, and typing and matching of these polymorphisms between the donor and the receiver is a pre-requisite for organ transplantation. Certain polymorphisms in the HLA-A locus have been linked to certain disease conditions, like Insulin Dependent Diabetes Mellitus, Rheumatoid Arthritis, Ankylosing Spondylitis, Nasopharyngeal Carcinomas, tumors of the head and neck, Myasthenia Gravis, Buerger's Disease, and Multiple Sclerosis.

Molecular Genetics
The HLA-A gene is expressed in almost all the tissues of the body. The gene spans a length of about 2.7 Kb and the encoded protein weighs about 41 KDa (365 amino acids). The HLA-A gene is made up of 8 exons that are translated into a single-pass membrane protein. The protein itself, is made up of a leader peptide (exon 1), the alpha1 and alpha 2 domains (exons 2 and 3), an alpha 3 domain (exon 4), a transmembrane region (exon 5), and a cytoplasmic tail (exons 6 and 7). The protein is polyubiquinated in a post endoplasmic reticulum compartment; a modification that renders it susceptible to rapid degradation via the ubiquitin pathway. The HLA-A chain forms a binding cleft, whose sides are composed of alpha helices, while the base is made up of a beta sheet. The peptide to be presented is bound by the alpha 1 and alpha 2 domains. It comes as no surprise, therefore, that polymorphisms within exon 2 and 3 are responsible for determining the specificity of the peptide binding interaction.

Epidemiology in the Arab World
Egypt
Using a probe containing Alu repeat sequences, Paabo (1985) isolated a 3.4-kb DNA fragment from a 2,400-year-old Egyptian mummy, which was subsequently shown to contain an intron of the nuclear gene HLA-DQA (Del Pozzo and Guardiola, 1989).

Jordan
Sánchez-Velasco et al. (2001) studied major histocompatibility complex (MHC) class I and class II alleles in 100 unrelated adult Jordanians of both

sexes from the capital Amman and in 46 individuals from the Jordan valley. Sánchez-Velasco et al. (2001) detected 20 alleles for the HLA-A locus in the Jordanian population, indicating the existence of high polymorphisms in this area. As expected, the HLA-A*0201 allele was found to be the most frequent in Jordaniana (0.1344) followed by A*3001 (0.0931), A*0101 (0.0793), and A*1101 (0.0793) alleles. In addition, 220 different five-loci haplotypes with several unusual allelic combinations were observed, although many of them are pan-European haplotypes. The most frequent five-loci haplotype was found to be the A30-B7-DRB1*03-DQA1*0501-DQB1*0201 (0.0138). Since several Jordanian haplotypes were not found in the literature at the time, Sánchez-Velasco et al. (2001) suggested that the specific Jordanian haplotypes are the following: the A31-B7-DRB1*04/07-DQA1*0301/0201-DQB1*0302/0202 haplotypes (0.0103) and the A1-B7-DRB1*07-DQA1*0201-DQB1*0202, A2-B7-DRB1*04-DQA1*0301-DQB1*0302, and A11-B7-DRB1*07-DQA1*0201-DQB1*0201 haplotypes but at lower frequencies (0.007). Sánchez-Velasco et al. (2001) made a tree analysis of HLA class I and class II alleles for several Caucasian populations and calculated individual genetic distances. Haplotype frequencies, genetic distances, and dendrograms did not reveal great differences as compared with those in other Mediterranean countries and Western Europeans populations. These results led Sánchez-Velasco et al. (2001) to suggest that both HLA class I and class II polymorphisms (but especially the former) of the Jordanian population demonstrate considerable heterogeneity, which reflects ancient and recent admixture with neighboring populations, and important human migratory trends throughout the history.

Oman

Agarwal et al. (1996) compared the frequencies of HLA-A antigens in 50 Omani patients diagnosed with Idiopathic Dilated Cardiomyopathy, with those of 247 healthy Omani control subjects. Data obtained was statistically analyzed by chi square test or the Fisher exact test (where appropriate) with the Bonferroni correction obtained by multiplying the P value by the numbers of antigens tested to correct the P value for any chance associations (PC). The antigens tested for included HLA1, 2, 3, 9, 10, 11, 19, 23, 24, 25, 26, 28, 29, 30, 31, 32, and 33. None of these antigens showed a significant difference in frequency between the patient and control group. The most common antigens in both groups were HLA-A2 (44% in patient, and 38% in control group) and HLA-A19 (42% in patient, and 38% in control group).

White et al. (1999) determined the frequencies of histocompatibility antigens (HLA A and B) in 321 healthy Omani blood, kidney and bone marrow non-related donors by HLA serology, and compared those results with those recorded from Saudi Arabia and Kuwait. In locus A, 19 serological specificities were determined. It was found that HLA-A11 (20%) and A32 (21%) were significantly more frequent in Oman than in Saudi Arabia and Kuwait, while HLA-A9 (14%) was significantly lower in Oman than in the other two countries. White et al. (1999) postulated different migration patterns in Oman as the frequencies of HLA antigens differed significantly between the population of Oman and those of Saudi Arabia and Kuwait.

Middleton et al. (2000) used a two-stage sequence specific oligonucleotide probe (SSOP) typing method to determine the HLA-A allele frequencies in seven populations of different ethnic and geographical locations which included 118 unrelated healthy Omani representatives of the normal population of Oman. PCR amplification was followed by medium resolution HLA-A SSOP analysis, which in turn was followed by typing the samples to allele level using secondary SSOP systems depending on the initial results obtained from the first stage system. The PCR products were dot blotted, hybridized with digoxigenin probes and detected with chemiluminescence procedures. Individuals who were HLA-A*2402101 were further analyzed for other non-expressed alleles of HLA-A*24 (HLA-A*2409N and HLA-A*2411N). The HLA-A allele genotype frequencies were determined by direct counting. In all the populations studied, 48 alleles were identified with three alleles common in all groups studied (HLA-A*0201, -A*2402101, and –A*31012 with the former two predominating in frequency among all populations studied). In this study, HLA-A allele families could be categorized according to their allelic variation in the different populations. In the Omani population, alleles from 16 HLA-A families were identified with four families (HLA-A*02, HLA-A*11, HLA-A*26, and HLA-A*32) having the highest frequencies of 21.6%, 11.4%, 10.2% and 11.4%, respectively. On the other hand, HLA-A*0202, -A*0208, -A*0214, -A*2402102L, -A*2901, -A*3601, and HLA-A*74 showed the least frequency of 0.4%. Within the allele families, one or more variants were detected with one variant being the more frequent one, as in HLA-A*02 in which five variants were detected but only –A*0201 had a frequency of 21.6% while the rest varied between 0.4 to 7.2%. None of the individuals who were HLA-A*2402101 positive had expression of the other variants, -A*2409N and –A*2411N. Three alleles were found to be unique

to the Omani population - HLA-A*0208 with a frequency of 0.4%, -A*0214(0.4%) and -A*2402102L (0.4%). Middleton et al. (2000) explained the HLA polymorphism as due to the need for development of novel patterns for antigen presentation for protection against infectious diseases. They also highlighted the possibility of using the DNA typing method used in this study in different populations and explained the importance of determining HLA-A allele frequencies in populations as it would give a probability of finding a matched HLA-A allele donor for a patient who needed bone marrow transplant, and would determine the composition and size of a donor registry to reduce the mismatches between donors and recipients.

Saudi Arabia

In a study of the HLA gene and antigen frequency among Saudi Arabian subjects, Sheth et al. (1985) discovered that the Aw19 antigen showed the highest frequency (20.2%) among all Middle Eastern populations. The various different HLA-A antigens showed the following gene frequencies: A1 (10.5%), A2 (24.9%), A3 (8.9%), A9 (16.7%), and A28 (7.9%). These frequencies were similar to those observed in the Turkish population, prompting the Sheth and colleagues (1985) to suggest an influence of such other populations on the Arab population.

Abanmi et al. (2006) investigated the HLA loci antigens and alleles in a group of 40 unrelated Saudi patients with vitiligo (18 males, 22 females) and compared the results to that in a group of 40 matched controls. The most frequent HLA-A antigens among the patient group were A19, A28, A2, and A10. The only statistically significant difference between HLA-A antigens among the disease and control groups was HLA-A9, which was found to be decreased in vitiligo patients.

References

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Related CTGA Records

Major Histocompatibility Complex, Class I, B
Major Histocompatibility Complex, Class I, C
Major Histocompatibility Complex, Class II, DR Alpha
Vitiligo

External Links

http://www.genecards.org/cgi-bin/carddisp.pl?gene=HLA-A
http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=3105

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