II. LITERATURE REVIEW

A. Human Leukocyte Antigen

1. Molecular structure

The human leukocyte antigens (HLA, or major histocompatibility complex antigen (MHC) of human) are an important group of cell surface glycoproteins which are required for the communication between T lymphocyte and other cells of the human (Sachs, 1984). The HLA system is devided by structural and functional characteristics into two different sets of very polymorphic genes, namely class I and class II gene. The class I molecule is a non-covalently heterodimeric cell surface molecule with a polymorphic glycoprotein heavy chain of 42 kD and linked protein of 12 kD beta-2-microglobulin (β_2m) (Robinson and Kindt, 1989). β_2 microglobulin is not encoded within the HLA gene system (Goding and Walker, 1980) and is well conserved. The HLA class II molecules are expressed in nearly all types of nucleated cells (Harris and Gill, 1986). Function of class I molecules is in the presentation foreign antigens to $CD8^+$ T lymphocytes that mainly act as cytotoxic cells. Class I-restricted T cells recognize cell-associated antigen such as virus infected cell or cell expressing foreign alloantigens. Peptides associated with the class I molecules are derived from endogenously synthesized proteins (Paul, 1984).

The HLA class II molecule is also a non-covalently linked heterodimer cell surface molecule with a polymorphic glycoprotein acidic alpha chain of 35 kD and basic beta chain of 25 kD. Each HLA class II molecule has two extracellular domains: α1, α2, and β1, β2. The α1 domain is about 90 amino acids in length and contains a disulfide loop, whereas the β1 domain is shorter and has no disulfide loop. The interaction between α1 and β1 domains at the outer most part of the molecule results in peptide binding region, which consists of a long groove formed by floor of beta-pleated segments and surrounding of alpha helical segment (Brown et al, 1988). The peptide binding regions from different individuals exhibit structural polymorphism that enables them to bind to structurally distinct selective peptides. The membrane proximal α2 and β2 domains are highly conserved,

contain a disulfide loop, and have sequence similar to immunoglobulin constant region domains, so, HLA class I and class II molecules are in immunoglobulin superfamily. Both α and β chains contain a highly hydrophilic connecting peptide that links the membrane proximal domain to the hydrophobic transmembrane domain. Their constitutively expression on the surface of a limit number of cell types such as B lymphocytes, macrophages, dendritic cells, thymic epithelium and a few other cell types (Abbas, 1991) confer to these cells the ability to present peptide antigen to T cells via T cell receptors. Function of class II molecule is presentation processed antigen to $CD4^+$ T lymphocyte which most function as helper T cells. Thus, HLA class II molecules are involved in the activation of T lymphocyte both in thymus and peripheral blood that are necessary for clonal proliferation, differentiation of B lymphocyte and cytotoxic T lymphocyte, also activation of phagocytic cells, such as macrophages and neutrophils and also control of immune response. Class II-restricted T cells recognize antigens that enter the system as soluble components. Peptides associated class II molecule drives from protein that are taken up by antigen presenting cells from the extracellular part (Long, 1989).

2. Structure of Gene and Localization

The HLA class I and II molecules are separately encoded by a member of a group of similar and closely linked genes on short arm of the sixth chromosome. These gene regions span approximately 3300 kb. The orders of these genes from telomere are HLA-A, -C, -B, -DR, -DQ, -DO, -DN, and -DP (Trowsdale, J. et al., 1991). Between HLA class I and class II, the cluster of HLA class III genes and tumor necrosis factor (TNF) α and β genes that encode the cluster of complement component C2, Bf and C4 and 21-hydroxylase genes and TNFα and TNFβ protein, respectively as shown in Figure 1. The HLA-DR and HLA-DQ genes are so close (recombination frequency < 2%) that they are usually inherited together as haplotypes (Hansen and Sachs, 1989). The genomic arrangement of HLA gene reflects the domain structure of protein. The α and β chain genes of each HLA class II locus consist of 5 exons. The first exon encodes the 5' untranslated region, the signal sequence and the first two to four amino acids of the extracellular domain. The α1, β1 and α2, β2 domains are encoded by the second

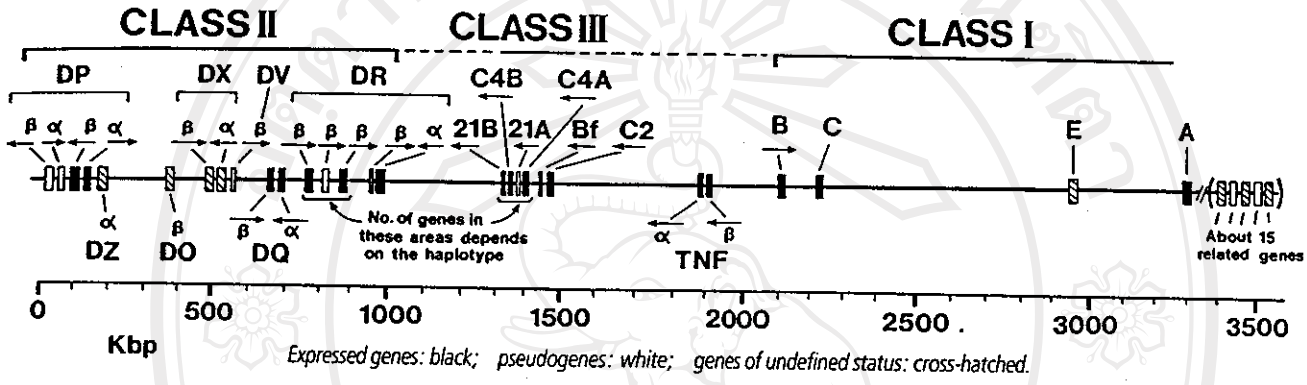


Figure 1. Physical map of the human HLA region (Trowsdale and Campbell, 1988)

and third exons, respectively. The connecting peptide, transmembrane region, cytoplasmic region and the 3' untranslated region are encoded in the remainder exon (Robinson and Kindt, 1989)

The HLA-DQ subregion contains the α1, α2, and β1, β2 genes. Only transcripts and products of the DQα1 (DQA1) and DQβ1 (DQB1) genes have been detected (Auffray et al., 1987). It has been difficult to identify products of the DQ α2 (DQA2) and DQβ2 (DQB2) genes and it has been suggested that they are not expressed (Auffray et al., 1984). The DQA1 and DQB1 genes are transcribed from different strands as they are oriented in tail to tail fashion (Jonsson et al., 1987)

3. HLA typing

HLA-DQ molecules were initially differentiated by serological methods into three serotypes (DQw1, DQw2 and DQw3) (WHO, 1991). The serological classification of the HLA-DQ molecules primarily reflects difference of the beta subunit of the DQ molecules, only the information derived from HLA-DQB1 typing were used for the designation of corresponding HLA-DQ molecules (Nepom and Erlich, 1991). But the data from sequence analysis have shown that the numbers of HLA-DQ alleles are greater than those detected by serological methods. It is known that both HLA-DQ alpha and beta chain are polymorphic, especially in the alpha 1 and beta 1 domains. In the most recent compilations, 14 HLA-DQA1 and 19 HLA-DQB1 alleles have been identified (WHO, 1992). The diversity of the cell surface HLA-DQ molecules is generated not only by cis-association but also by trans-association of the DQ alpha and beta chains encoded on the paternal and maternal chromosomes. So, the heterozygous individuals can express four different HLA-DQ molecules on their cell surface because of the trans- and cis- association of their alpha and beta chains (Hansen et al., 1992).

3.1. Serological HLA typing method

HLA antigen typing was initially tested by leukoagglutination by clinician who were interested in blood typing in the late 1950s (Amos and Ward, 1975). They analyzed the leukoagglutination patterns of a panel of antisera derived from

multiparous females with leukocytes from unrelated donors. Most different donors gave different agglutination patterns.

In the early 1960s, the cytotoxicity assay replaced the leukoagglutination assay because it was found to be more reproducible and generally applicable (Paul, 1989). The cytotoxicity assay is now a widely used method for HLA typing in transplantation. The outline of this method is as follows. Lymphocytes of donor are added to each of histocompatibility antisera. Serum complement is added. After incubation, dead cells are stained with trypan blue. This method can determine the certain antiserum-complement combination that are cytotoxic for the lymphocyte, in that case, the antigen corresponding to that antiserum is present on the lymphocyte surface (James, 1988). The serologic method can classify HLA-DQ antigen into three forms: DQw1, DQw2, and DQw3.

The alternative method that widely used for studying HLA class II was mix lymphocyte reaction (MLR). Lymphocyte from two individuals who has different HLA class II antigen will proliferate when mixed *in vitro*. Proliferation can be quantified by measuring the uptake of radiolabeled thymidine (van Rood et al., 1981).

3.2. Restriction fragment length polymorphism (RFLP)

Restriction fragment length polymorphism (RFLP) is the technique that has been used for differentiation in variation of nucleotide sequence by using the specific locus probes that can detect a specific pattern of mobility of restriction endonuclease enzymes-digested genomic DNA. Initially, human genomic DNA is digested with appropriate restriction enzyme, and the digested DNA fragments are resolved by electrophoresis. Then the DNA is transferred onto nitrocellulose and is hybridized with labelled specific locus oligonucleotide probes. The allelic difference can be identified by autoradiography based on length of digested DNA. At most, the RFLP technique can identify five and seven allelic forms of the HLA-DQA1 and DQB1 genes, respectively. In one of the most informative assays, TaqI-digested genomic DNA can be separated into distinct allele specific patterns, for example, the HLA-DQα1a, 1b, 1c, 2, and 3 patterns of HLA-DQA1 locus and the DQB1a, 1b, x, 2a, 2b, 3a, and 3b patterns of the HLA-DQB locus (Hui and Bidwell, 1993). The DQα and DQβ RFLP hybridization patterns highly correlate with the HLA-DQ serologic specificities (Bidwell, 1987). An analysis of a large

number of Caucasian haplotypes confirmed that DQβ RFLP identified an allelic series correlate with the DQ serologic specificities. They found that DQβ1a, DQβ1 b, DQβx bands corresponded to DQw1 serotype; DQβ2a, DQβ2b bands corresponded to DQw2 serotype; and DQβ3a, DQβ3b bands corresponded to DQw3 serotype. (Bidwell et al., 1994). This technique can identify HLA-DQ allelic forms more finely than the serologic methods; moreover, this technique is quit simple and does not require complicated equipments, and need only few probes for typing of each locus. The RFLP method can detect differences in the distribution of restriction enzyme sites, but is limited when the enzyme recognition sites are altered (Mach and Tiecy, 1991).

3.3. Polymerase chain reaction and Sequence-specific oligonucleotide (PCR-SSO) hybridization

The recent advances in molecular genetic have elucidated the molecular basis of polymorphism of class II alleles and identified HLA alleles finely at the DNA level. Most recently, the polymerase chain reaction and sequence specific oligonucleotide hybridization (PCR-SSO hybridization) has been employed. Initially, the polymorphic second exon of HLA-DQA1 and DQB1 genes are amplified from genomic DNA by the polymerase chain reaction (PCR). The amplified DNA products are then reacted under stringent hybridization conditions with multiple oligonucleotide probes that correspond to known variant sequences of these two genes. The SSO hybridization requires the knowledge of the DNA sequence of all recognized alleles. The SSO probes hybridize best to absolutely matched target sequences, and thus can discriminate down to a single base pair difference. Thus the SSO probe can be designed to be specific for one or particular alleles at certain specific nucleotide positions. Then the HLA-DQ allelic forms at each locus can be assigned according to the identified hybridization pattern with HLA-DQA1 and HLA-DQB1 probes, respectively. This method is rapid, efficient and appropriate for distinguishing multiple DNA sequence variation (Mach and Tiercy, 1991). This method allows the fine identification of upto nine and nineteen distinct allelic forms of the HLA-DQA1 and DQB1, respectively. Sequence and amino acid position of HLA-DQA1 and DQB1 alleles are shown in Figures 2 and 3.

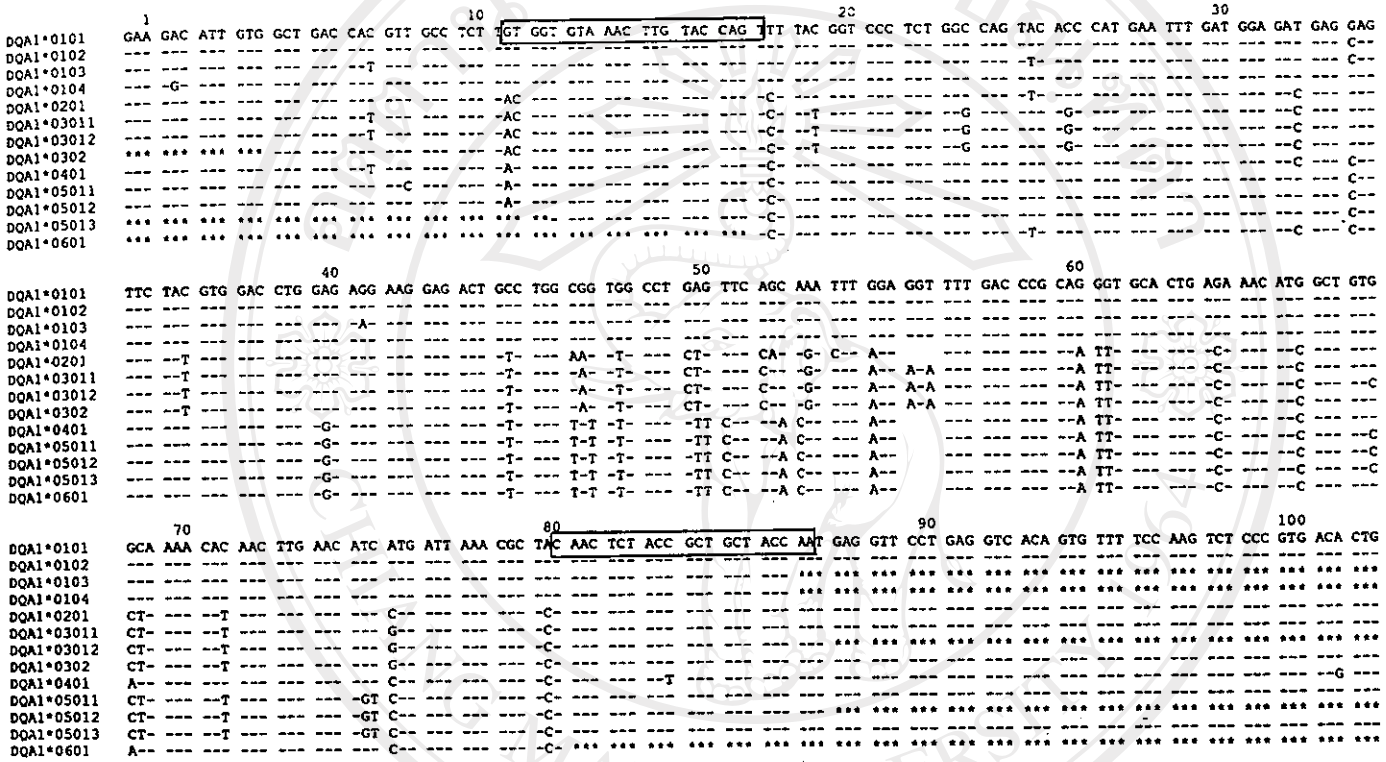
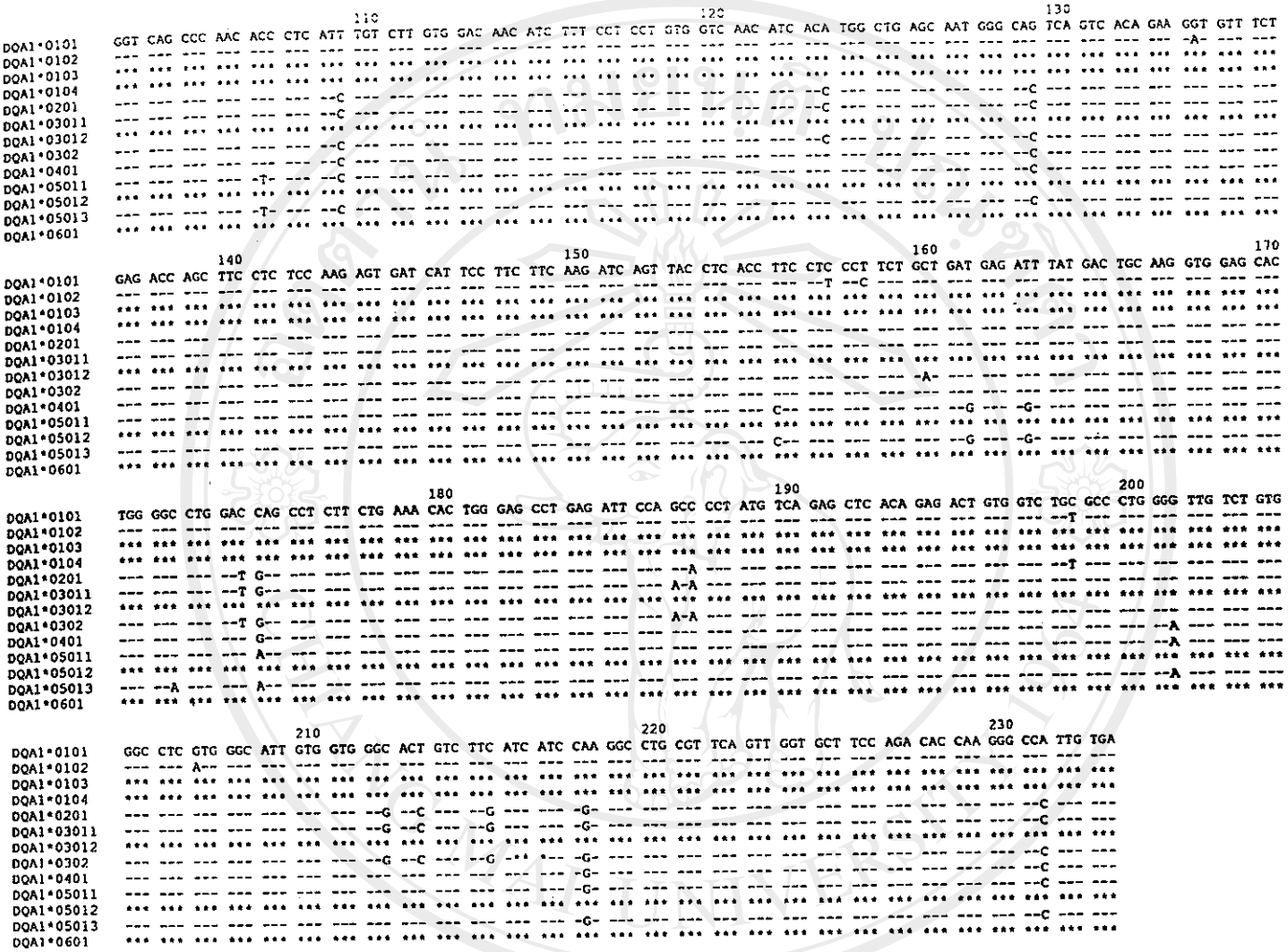


Figure 2. Nucleotide sequence of the second exon the HLA-DQA1 alleles and positions of DQA1 primer binding regions.



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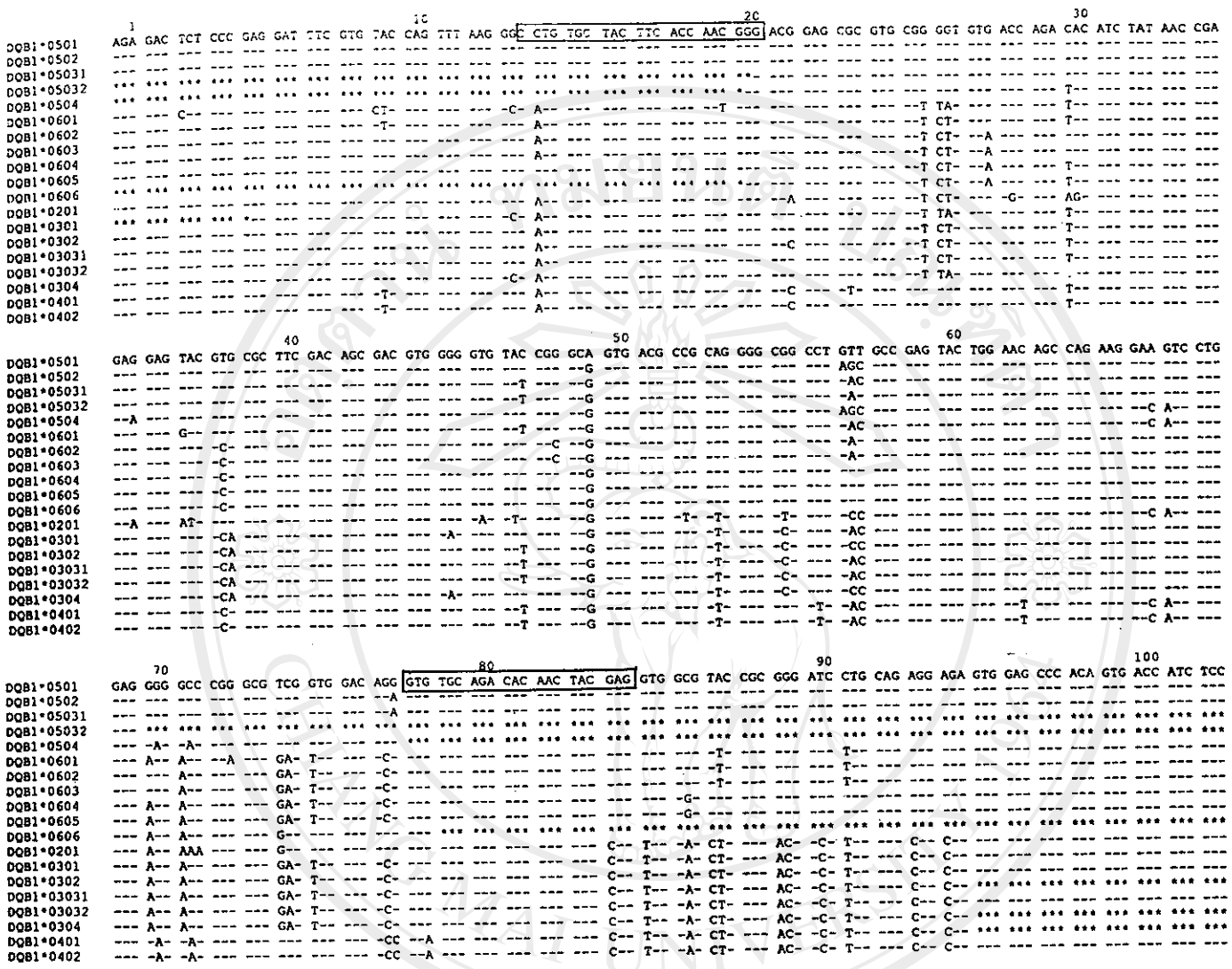

Figure 3. Nucleotide sequence of the second exon of the HLA-DQB1 alleles and positions of DQB1 primer binding regions.

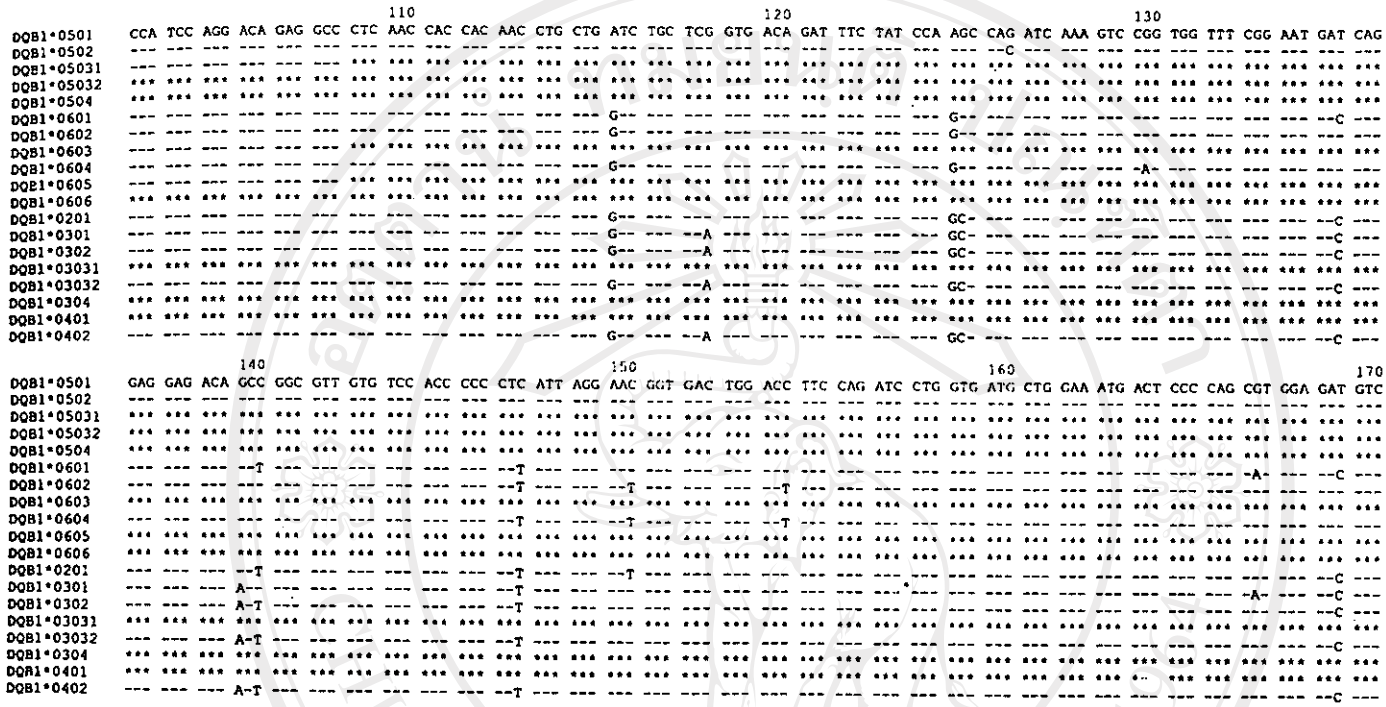

Figure 3. (continued).

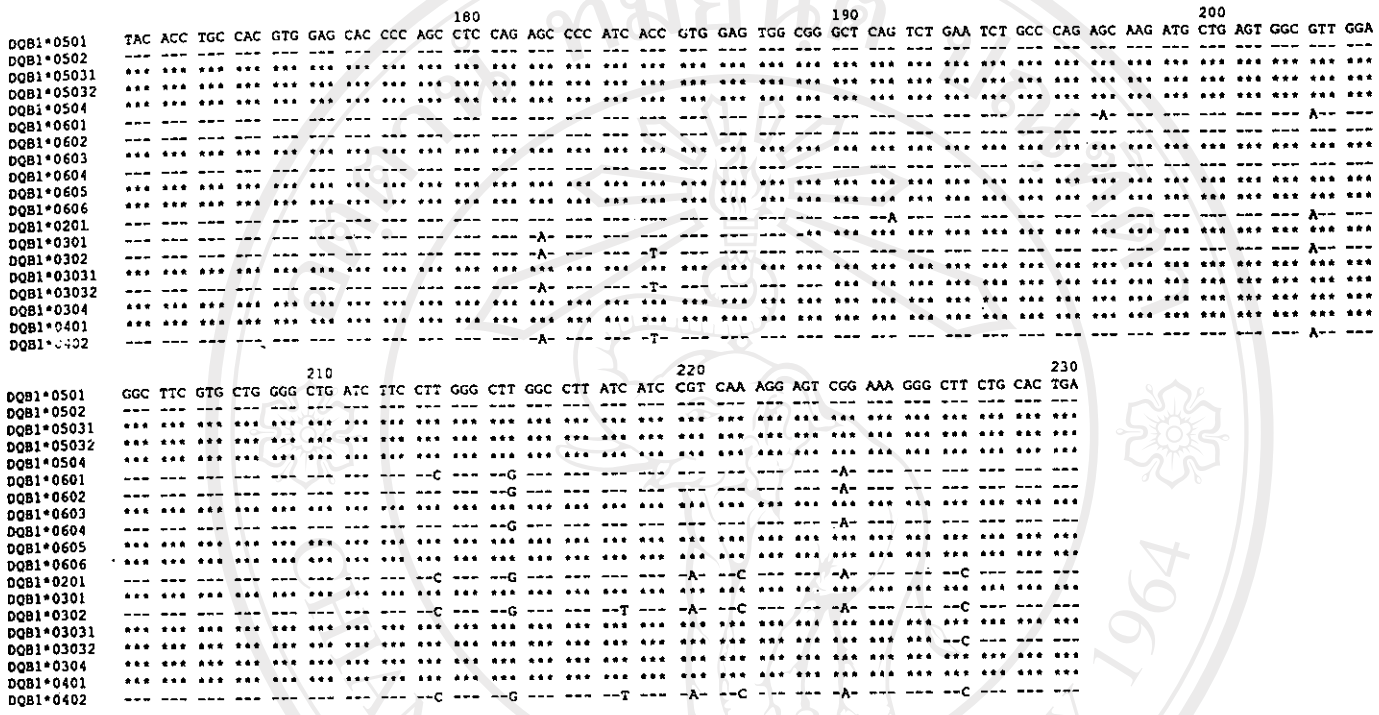

Figure 3. (continued).

The serological classification of the HLA-DQ molecules primarily reflects difference of the beta subunit of the DQ molecules (Nepom and Erlich, 1991). So only the information derived from HLA-DQB1 typing can be used for the designation of corresponding HLA-DQ molecules. According to previous findings from homozygous cell lines derived largely from Caucasian population, HLA-DQB1*0501, DQB1*0502, DQB1*05031, DQB1*05032, DQB1*0504, DQB1*0601, DQB1*0602, DQB1*0603 and DQB1*0604 alleles correspond to HLA-DQw1 antigen; HLA-DQB1*0201 allele to HLA-DQw2 antigen; and HLA-DQB1*0301, DQB1*0302, DQB1*03031, DQB1*03032 allele to HLA-DQw3 antigen, respectively (Nepom and Erlich, 1991).

B. Leprosy

1. Historical background of discovery

Leprosy is a chronic infectious disease of human caused by *Mycobacterium leprae* that damage peripheral nerve and skin (Hasting, 1985). Leprosy bacillus was first discovered in small rod-shaped body by Hansen in 1873 in Fresh human tissue fluid in Bergen, Norway. The discovery led to the knowledge that this microorganism was the causative agent leprosy (Hansen, 1874). Leprosy is transmited only between human. It existed in China (Skinness and Chang, 1985) and India in about 600 BC or earlier and from there it slowly spreaded westward to Europe, Africa and America. Now, leprosy patients are concentrated mainly in low socioeconomic standard zone in developing countries in the tropical and subtropical area (Ridley, 1988). It affected approximately 13 million people in the world (Binford et al., 1982). The most occurence of leprosy is found in South East Asia (74.6%) when compared with the other regions of the world (WHO, 1988).

2. Causative agent and classification of clinical manifestation

Leprosy is caused by *Mycobacterium leprae*. The outcomes of leprosy were the impairments of: (i) the face, giving rise to facial disfigurement and deformities; (ii) the nerve, damaging their structure and function; (iii) the eyes, causing defective vision; and (iv) the minds of patients, giving rise to personality disorder.

It may lead to injuries of insensitive hands and feet and further complication that result from unprotected use of insensitive hand and feet, e.g. ulcers, stiff joints or contractors of fingers, shortening of fingers and toes and disintegration of bones of the foot (Srinivasan, 1993). The modes of transmission from lesions are still unknown. There were some evidences for respiratory transmission from lesion to the upper respiratory tract, however, how this leads to invasion of peripheral nerve is not understood. Most individuals infected with *M. leprae* do not develop any clinical signs of disease, whereas a few of infected people develop various forms of disease. A number of different forms of leprosy can be distinguished into two poles by clinical, histological and immune responses of the patients (Ridley and Jopling, 1966). The first pole of leprosy is tuberculoid form (TT). This form is identified by few and hypopigmented skin lesions with various degrees of anaesthesia. In the skin lesions, a few *M. leprae* can be detected. Tuberculoid leprosy patients have a low humoral immune response but strong specific cell-mediated immune response as manifested in granulomatous histopathology, positive lymphocyte transformation assay and delayed type hypersensitivity to certain skin tests employing antigens of the leprosy bacilli (Ridley and Jopling, 1966). The second pole is lepromatous leprosy (LL), characterized by the opposite features of many diffuse lesions with extensive anaesthesia in late stage. Numerous of *M. leprae* bacilli can be found in this skin lesion. LL patients do not exhibit specific cell-mediated immune response, but display good humoral response that is not protective (Bryceson and Pfaltzgraff, 1979). Between these two poles, borderline leprosy (BB) shows variable degree between TT and LL forms of leprosy. Ridley and Jopling (1966) further classified the clinical manifestations of leprosy into five groups (TT, BT, BB, BL, and LL) according to clinical and histologic criteria shown in Table 1.

3. General properties of *M. leprae*

M. leprae is a member of the Genus Mycobacterium that causes disease in human, consists of two species; *M. leprae* and *M. tuberculosis*. *M. leprae* is non spore-producing, gram positive bacillus, can grow in a temperature range of 28°C to 45°C. The bacillus cannot be cultured on artificial medium but can grow in mouse foot-pad and in nine-banded armadillo (Kirchheimer and stone, 1971). It has special staining properties in resisting the decolouration by weak mineral acid after

Table 1. Cardinal signs and classification of leprosy according to Ridley and Jopling (1966), modified

Classification	Skin lesions	Sensation of skin lesions	Nerve Involvement	Immunity CMI	HMI
TT	One or few macules, hypopigmented, not symmetrical, raised and well definded edges	-	+ +	+ + +	-
BT	Variation in number, shape, and limitation of edges	+/-	+	+ +	+
BB	Variation in number, shape, and limitation of edges	+/-	+	+	+ +
BL	Variation in number, shape, and limitation of edges	+/-	+	-	+ + +
LL	Hypopigmented macules or erythematous papules or nodules, bilaterally symmetrical, vague edges	+	+ (late)	-	+ + +

staining with one of the arylmethane dyes. This property depends on a capacity to form acid resistant complexes with cationic arylmethane dyes, which mycobacteria share with ceroid and keratin. *Mycobacterium leprae* contains many antigenic polypeptides, polysaccharides and glycolipids that act as immunogen. The phenolic glycolipid consists of two types: phenolic glycolipid PGL-1 which contains a unique trisaccharide and a mycoside of the phenol-glycol type, phthiocerol dimycocerosate (PDIM), which contains no polysaccharides (Ridley, 1988). PGL-1 and PDIM are important immunogens. Antibodies to PGL-1 have been found in both TT and LL patients (Ridley, 1988). In molecular studies, the dominant T-cell antigens of *M. leprae* are mycobacterial heat-shock proteins (hsp) (Young et al., 1988; Ottenhof et al., 1988). The important immune target of *M. leprae* is hsp65 protein (Thole and Van der Zee, 1990).

4. Pathogenesis

Leprosy is cause by an infective agent, *M. leprae*. The important clinical manifestations of leprosy reflect the destruction of affected skin and peripheral nerves. The difference in clinical manifestations of patients was considered to be influenced by environmental and genetic factors.

The genetic factor(s) may be involved in the pathogenesis of leprosy is known from many studies and observations. The earliest observation was the increased incidence of leprosy in certain ethnic groups and its occurrence in some particular clustering families (Hopkin et al., 1929). A twin study reveals that the concordance rate for leprosy in monozygous twin reaches 60-85%, while dizygous twin concordance rate was low at 15-20% (Mohamed Ali and Ramanujam, 1964). Studies of twin in India found that the concordance rate for clinical leprosy was significantly higher among monozygotic (59%) than dizygotic (20%) pairs (Chakravartti and Vogel, 1973). These twin studies suggested that genetic factors are more important than the environmental factors.

By using segregation analysis, the statistical method for determining the mode of inheritance of a given trait, and influence of genetic factor, Abel et al (1988) performed complex segregation analysis to analyze five genetic markers Rh, Km, HLA, ABO and Gm for linkage with susceptibility with leprosy in 27 large pedigrees from a Caribbean island in order to determine the mode to of inheritance

of the trait from family data. They found the presence of recessive major gene(s) controlling the development of leprosy per se and non-lepromatous leprosy (Abel et al, 1988).

In early studies of the association between leprosy and the HLA-class I (A, B and C) antigens, it is found that there were different HLA class I antigen associated with leprosy or types of leprosy in various populations (Table 2). These associations are weak and inconsistent. For example, the HLA-A9 antigen was increased in the tuberculoid leprosy group in Thailand (Greiner et al., 1978 and Youngchaiyud et al., 1977), chinese from Singapore (Chan et al, 1979) and in non lepromatous leprosy group in India (Dasgupta et al., 1975). The HLA-A9 antigen was also increased in lepromatous leprosy group in Japan (Takata et al., 1978). Other HLA-class I antigen, such as HLA-B7, was increased in tuberculoid leprosy in Chinese from Singapore (Chan et al, 1979). In Thailand, Youngchaiyud et al. (1977) found significant increased frequency of HLA-A9 and HLA-Bw40 antigens in tuberculoid and lepromatous leprosy patients when compared to controls whereas Greiner et al. (1978) found that HLA-B7 was significantly increased in lepromatous leprosy patients. It is suggested that the association between leprosy and these HLA class I antigens itself is caused by the closely linked HLA-class II genes. When HLA class II typing was studied in various populations (Table 3), stronger and more consistent association were found. Tuberculoid leprosy was associated with HLA-DR2 or -DR3 antigens and lepromatous leprosy was associated with the DQw1 antigen (De Vries et al., 1988). However, the association of HLA-DR2 and DR3 antigens with leprosy appeared to be inconsistent in different population studies. In several Asian populations such as India (De Vries, 1980), Japan (Miyanaka et al.,1981) and Thailand (Schauf et al.,1985) HLA-DR2 was associated with tuberculoid leprosy whereas in Surinam (Ottenhoff and De Vries, 1987) and Mexico (Clara Gorodezky, et al., 1987) HLA-DR3 was associated with tuberculoid leprosy. The population studies in Venezuelan (Ottenhoff, et al., 1984) and Thailand (Schauf, et al., 1985) indicated that the HLA-DQw1 antigen was associated with tuberculoid leprosy.

A recent study of the association between HLA class II alleles and leprosy from North India employing polymerase chain reaction and hybridization found that the allele frequency of HLA-DRB1*15 was significantly higher in LL and BL patients (relative risk 16.3), in TT patients (relative risk 5.7) than in normal

Table 2. Significant association between HLA class I antigen and leprosy or types of leprosy in different populations (modified from Greiner et al., 1978)

HLA class I antigen	Mode of association	Types of leprosy	Population	Reference
no differences			Japanese	Miyanaka et al. (1981)
no differences			Brazilian	Reis et al. (1974)
A2	-	total	Mexican	Escobar-Gutierrez et al. (1973)
	+	tuberculoid	Thais	Greiner et al. (1978)
A3	-	total	Mexican	Escobar-Gutierrez, et al. (1973)
A9	-	not lepromatous	Indian	Dasgupta et al. (1975)
A10	+	lepromatous	Filipino	Smith et al. (1975)
A11	+	leprosy	Korean	Kim et al. (1987)
Aw24	-	lepromatous	Japanese	Takata et al. (1978)
	-	tuberculoid		
Aw33	+	leprosy	Korean	Kim et al. (1987)
B5	-	total	Indian	Mehra et al. (1976)
	-	tuberculoid	Japanese	Takata et al. (1978)
B7	+	lepromatous	Thais	Greiner et al. (1978)
B8	+	tuberculoid	Japanese	Takata et al. (1978)
B13	+	total	Mexican	Rea et al. (1976)
	+	lepromatous		
B14	+	total	Spanish	Kreisler et al. (1974)
	+	lepromatous	Spanish	Kreisler et al. (1974)
	+	tuberculoid	Japanese	Takata et al. (1977)
Bw17	+	tuberculoid	Thais	Greiner et al. (1978)
Bw21	+	total	Ethiopian	Thorsby et al. (1973)
	-	total	Mexican	Rea et al. (1976)
Bw22	-	total	Thais	Youngchaiyud et al. (1977)
	-	lepromatous		
	+	total		
Bw40	+	lepromatous	Thais	Youngchaiyud et al. (1977)
	+	tuberculoid		
Bw52	+	BL	Indian	Rani et al. (1992)
Bw60	+	lepromatous	Indian	Rani et al. (1992)

+ = positive association

- = negative association

Table 3. Significant association between HLA class II antigen and leprosy or types of leprosy in different populations (modified from Fine, 1988)

HLA class II antigen	Mode of association	Types of leprosy	Population	Reference
DR1	+	leprosy	Koreans	Kim et al. (1987)
	+	leprosy	Japanese	Miyanaka et al. (1981)
DR2	+	tuberculoid	Thais	Schauf et al. (1985)
	+	leprosy	Koreans	Kim et al (1987)
	+	lepromatous	Japanese	Kikuchi et al. (1986)
	+	leprosy	Japanese	Miyanaka et al. (1981)
	+	tuberculoid	Indian	De Vries (1980)
	+	lepromatous	Japanese	Izumi et al. (1982)
	+	lepromatous	Indian	Rani et al. (1992)
	+	leprosy	Turkish	Mat et al. (1988)
	+	tuberculoid	Mexican	Rea et al. (1980)
DR3	+	tuberculoid	Mexican	Gorodezky et al. (1987)
	+	TT	Surinam	Ottenhoff (1987)
	+	lepromatous	Surinam	Ottenhoff (1987)
	+	tuberculoid	Indian	Van Eden et al. (1981)
	+	tuberculoid	Mexican	Rea et al. (1980)
DR4	-	leprosy	Koreans	Kim et al (1987)
	-	leprosy	Japanese	Miyanaka et al. (1981)
DRw8	+	leprosy	Japanese	Miyanaka et al. (1981)
	+	lepromatous	Indian	Rani et al. (1992)
DRw9	+	leprosy	Koreans	Kim et al (1987)
	+	BL	Indian	Rani et al. (1992)
DRw53	-	leprosy	Koreans	Kim et al (1987)
DQw1	+	tuberculoid	Thais	Schauf et al. (1985)
	+	leprosy	Koreans	Kim et al (1987)
	+	leprosy	Japanese	Miyanaka et al. (1981)
	+	lepromatous	Japanese	Izumi et al. (1982)
	+	lepromatous	Venezuelans	Ottenhoff et al. (1984)
	+	lepromatous	Indian	Rani et al. (1992)
DQw3	-	leprosy	Koreans	Kim et al (1987)
DQw7	+	BL	Indian	Rani et al. (1992)

+ = positive association
- = negative association

controls (Rani et al., 1993). The HLA-DQB1*0601 allele was significantly increased in leprosy per se and HLA-DQA1*0103 was increased in the LL group and the DQA1*0102 allele was increased in the BL group (Rani et al., 1993). However, when the DRB1*15 antigen was excluded, the significant association of the DQA1*0102 or DQA1*0103 or DQB1*0601 alleles was at a loss. On the contrary, the significant association of DRB1*15 with types of leprosy still remained after exclusion of the three HLA-DQ alleles (Rani et al., 1993). In a previous study, these investigations found that the HLA-B60, DR2, DR8 and DQw1 antigens were significantly increased in LL patients (Rani et al.,1992).

De Vries et al. (1988) proposed the immune response gene hypothesis that different antigenic epitopes of *M. leprae* are presented by the products of different HLA class II alleles to functionally different T cell subsets, causing either protective immunity or immunopathology. Li et al. (1989) found that peripheral blood mononuclear cells' specific proliferative response to M. leprae of the non-responder lepromatuos leprosy patients can proliferate after adding anti-DQ mAb. From these evidences, Li and De Vries (1989) suggest that HLA-DQ molecule may be products of the immunosuppressive genes that caused non-responsiveness to *M. leprae*.