REVIEW OF LITERATURE

3.1. DELUSIONAL DISORDER: Characteristic features

3.1.1. Historical overview of delusional disorder

3.1.2. Comparative account of the Diagnostic Features of delusional disorder

Diagnostic and Statistical Manual of mental disorders, 4th edition

International Classification of Diseases, 10th edition

Summary of the diagnostic features of DSM-IV and ICD-10

3.1.3. Classifications of delusional disorder

3.1.4. Epidemiology of delusional disorder

3.1.5. Familial pattern of delusional disorder

3.1.6. Clinical Heterogeneity, Paranoid spectrum & Differential Diagnosis

3.1.7. Etiological Models of Delusional Disorder

Organic Brain Factors

Risk factors of delusional disorder

Genetical Basis of delusional disorder

Autoimmune basis of Paranoid disorder

3.1.8. Pathogenesis of delusional disorder

Psychodynamic mechanism

Disordered Reasoning

Psychobiological mechanism

3.2 MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

3.2.1. Historical Perspective

3.2.2. Molecular Genetics, DNA Sequence and Gene Content of human MHC Comple:

HLA Class-I Region

HLA Class- II Region

HLA Class-III Region

3.2.3. Polymorphism and linkage disequilibrium

3.2.4. Biologic functions of MHC

3.2.5. HLA and disease associations

3.3. MHC AND SUSCEPTIBILITY TO PSYCHIATRIC DISORDERS

3.4. CHROMOSOMAL ABERRATIONS AND PSYCHIATRIC DISORDERS

3.1. DELUSIONAL DISORDER: Characteristic features

3.1.1. Historical overview of delusional disorder

Historically, the concept of delusional disorder is derived from the classic Greek concept of *paranoia*. The term paranoia, from which the modern adjective paranoid is derived, has a long and chequered history. It has probably given rise to more controversy and confusion of thought than any other term used in psychiatry. The word paranoia was derived from the Greek *Para* (beside) and *nous* (mind). It was used in ancient Greek literature to mean "out of mind', i.e. of unsound mind or insane. Paranoia was historically used to describe a variety of mental states, including dementia and delirium.

The disease entity, delusional disorder, was first delineated by Karl Ludwig Kahlbaum (1863). He used the name paranoia and first applied the term to a chronic delusional disorder. Karl Kahlbaum classified paranoia as a separate mental illness and referred to the condition as a partial insanity, which throughout the course of disease, principally affected the sphere of the intellect but not other areas of mental functioning. His work also led to recognition that paranoid features are nonspecific characteristics of many medical diseases.

Emil Kraepelin (1856-1926) also recognized a condition that he called *paranoia,* characterized by a persistent delusional system in the absence of hallucinations and personality deterioration. He recognized subtypes with delusional contents of grandiosity, persecution, erotomania and jealousy, and also allowed for the possibility of a hypochondriacal content. He clearly differentiated paranoia from *dementia precox* (later renamed schizophrenia by Bleuler).

Subsequently, Kraepelin introduced the concept of paraphrenia, an illness similar to paranoid schizophrenia but with significantly better preservation of affect and of personality. He regarded paranoia, paraphrenia, and paranoid schizophrenia as a relatively discrete group of illnesses, later referred to as the paranoid spectrum.

Kraepelin, like Kahlbaum, was concerned with the longitudinal course and gradually altered his formulation of paranoia. By the eighth revision of his *Lehrbuch der Psychiatrie,* he had restricted the term to describe persons with systematized delusions, an absence of hallucinations, and a prolonged course without recovery but not leading to mental deterioration (Kendler 1988).

Eugen Bleuler (1906) broadened the definition of paranoia to include cases with hallucinations - a paranoid form of dementia precox for which he coined the term schizophrenia and an intermediate group. Bleuler's contributions reinforced a trend toward the diagnosis of paranoid illness as a form of schizophrenia.

Despite this, various workers continued to contribute to speculation on the nature of delusions and paranoia. Karl Jaspers (1883-1969) wrote outstandingly on the phenomenology and psychopathology of delusions (Jaspers, 1963). Kretschmer (1988-1964) proposed that paranoid symptoms tended to occur in abnormally sensitive individuals who suffered from lifelong conflict between feelings of inadequacy and of unrequited self -importance and who, after undergoing some 'key experience', were precipitated in to a delusional psychosis. Kretschmer's observations tended to emphasize the importance of pre-existing personality disorder in paranoid illness. Sigmund Freud (1856-1939) wrote extensively on paranoia (Freud, 1958), proposing 'latent homosexuality as the underlying psychopathology', a view no longer widely accepted.

Although these and many other speculations have contributed much to the descriptive phenomenology of delusions, little or nothing about the mechanisms underlying delusions and their associated illnesses have been explored (Maher, 1992).

From the 1970s onwards, interest in paranoia began to reappear (Winokur, 1977) and a more optimistic view of treatment emerged (Munro, 1982). In 1987, DSM-IIIR returned to a description of the illness which was essentially that of Kraepelin, except that non-prominent hallucinations were allowable, and renamed

it delusional (paranoid) disorder, now simplified to delusional disorder in DSM-IV and ICD-10. The definition of delusion by Mullen (1979) is widely quoted and its implications are largely accepted by DSM-IV and ICD-10. He characterizes delusion as follows: i) they are held with absolute conviction, ii) the individual experiences the delusional belief as self-evident and regards it as of great personal significance, iii) the delusion can not be changed by an appeal to reason or by contrary experience, iv) the content of delusions is unlikely and often fantastic, and v) the false belief is not shared by others from a similar socio-economic group.

3.1.2. Comparative account of the diagnostic features of delusional disorder

Delusion, as "the basic characteristic of madness" (Jasper, 1963), has appropriately attracted an enormous amount of theoretical interest but remarkably little is known with any certainty. Arthur (1964) in his classic review concluded: "delusion can still claim to be the most outstanding and baffling behavior symptom of mental illness." The problem of delusion is one of the basic problems of psychopathology and has impaired an impressive diversity of theoretical speculation. The last few decades have seen a renewed interest in studying the psychological phenomena of psychoses. Considerable effort has been devoted to establish reliable diagnoses through operational definitions and multiaxial classifications. However, these have failed to shed any further light on the symptoms used to construct them because their origins are unclear and the literature consists largely of unsupported speculations, a small number of experimental studies and some associations with demonstrable pathology. The current concept of delusion is increasingly being challenged. It seems unlikely that delusion is a single entity, and attempts to dissect out its component parts have demonstrated that they vary with considerable independence from each other over time and during the progression of a delusional disorder (Brett-Jones *et al*, 1987).

Presently, there are two classificatory systems for all the mental illnesses managed by two different organizations. The International Classification of Diseases (ICD) is a disease classification system developed by World Health Organization (WHO) to promote international comparability of health care

statistics. Diagnostic and Statistical Manual of Mental Disorders (DSM) is another such system which is managed by American Psychiatric Association. The long developmental history of psychiatric classification along with the subsequent improvement of different diagnostic schemes have been observed in different editions of ICD and DSM. However, a comparative account of the diagnostic features emphasized by the 10th edition of ICD (ICD-10) and 4th edition of DSM (DSM-IV) are represented below.

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was published in 1994 and it defines the core psychopathological features of delusional disorder as persistent, nonbizarre delusions not explained by other psychotic disorders.

The delusions are unusual yet they refer to aspects of life that might occur, such as being conspired against, cheated on, physically ill, in love, jealous and so forth. Delusions are categorized according to their content. The delusions are fixed (persistent) and unarguable.

The person's emotional contact and behavior are generally intact. The emotional response is usually consistent with the delusional concern, and the mood is often appropriately depressed, frustrated, or even intensely angry or elated. Social and marital functioning is more likely to be compromised than intellectual and occupational functioning.

Associated features in delusional disorder include those of the paranoid syndrome. The degree of hostility and suspiciousness may be such that violent or aggressive behavior results. Litigious behavior is common among such patients. However, some patients, notably those with somatic delusions, may not display hostility, anger, or even suspiciousness to any considerable degree. DSM-IV diagnostic features are represented in **Table-1.**

Table-1: DSM-IV diagnostic criteria and subtypes of delusional disorder (297.1)

Principal features

a) Non-bizarre delusions of at least 1 month's duration.
b) Criterion A for schizophrenia has never been met, although tactile and olfactory hallucinations may be acceptable if they are related to the delusional theme.
c) Apart from the impact of the delusion(s) or its consequences, functioning is not markedly impaired and behavior is not obviously odd or bizarre.
d) Concurrent mood episodes, if present, are belief relative to the duration of the delusional disorder
e) The disturbances are not the direct outcome of a drug or medication or of a medical disorder.

Subtypes

Erotomanic
Grandiose
Jealous
Persecutory
Somatic
Mixed
Unspecified or other

International Classification of Diseases (Tenth Edition) was published in 1992. Delusional disorders are characterized by the development either of a single or of set of related delusions, which are usually persistent and sometimes lifelong. Onset is commonly in middle age but sometimes, particularly in the case of beliefs about having a misshapen body, in early adult life. Apart from actions and altitudes directly related to the delusion or delusional system, affect, speech, and behavior are normal. **Table-2** depicts the ICD-10 diagnostic features as well as subtypes of delusional disorder.

Table-2: ICD -10 diagnostic criteria for persistent delusional disorders

Delusional disorder (F22.0)
Principal features

a) A delusion or set of related delusions, other than those described as typically schizophrenic, must be present; the most common are persecutory, grandiose, hypochondriacal, jealous, or erotic
b) The delusion(s) must be present for at least 3 months
c) The general criteria for schizophrenia are not fulfilled
d) There are no persistent hallucinations, but there may be transitory or occasional auditory hallucinations that are not speaking in the third person or making a running commentary
e) Depressive symptoms or episodes may be intermittently present, but the delusional symptoms must persist at times when there is no disturbance of mood.
f) There must be no evidence of primary or secondary organic mental disorder or of a psychotic disorder due to psychoactive substance use.

Subtypes

Persecutory

Litigious

Self-referential

Grandiose

Hypochondriacal

Jealous

Erotomanic

Other persistent delusional disorders (F22.8)

This is a category for persistent disorders with delusions that do not fully meet the criteria for delusional disorder or schizophrenia. Illnesses with prominent delusions accompanied by persistent hallucinatory voices or by psychotic symptoms insufficient to satisfy the criteria for schizophrenia are included here. A delusional disorder of less than 3 months' duration is coded under Acute and Transient Psychotic Disorders (F23) until proven otherwise.

Summary of the diagnostic features of DSM-IV and ICD-10

DSM-IV and ICD-10 descriptions are very similar in overall outline but with a number of rather striking minor differences. These are noted below:

1. DSM-IV uses the term 'non-bizarre' delusion; this criterion has been shown to have little or no validity (Flaum *et al*, 1991).
2. DSM-IV allows the presence of tactile and olfactory hallucinations, while ICD-10 mentions only auditory hallucinations; in practice most modalities may be represented but the important point is that they are relatively non-prominent and usually parallel the content of the delusion(s).
3. DSM-IV says that delusions should have been present for 1 month and ICD-10 insists on 3 months.
4. Both classifications exclude delusional illnesses due to organic brain disorder, medical illnesses, medication effects, or psychoactive substance abuse. In essence this is correct, especially in an illness of acute onset.
5. DSM-IV and ICD-10 agree emphatically that delusional disorder is not schizophrenia and DSM-IV notes that general functioning is not impaired. Both

say that mood disturbance may accompany the delusional illness but is not a cause of it.

6. The list of subtypes according to delusional content is similar in both classifications, although ICD-10 adds self referential and litigious theme.
7. Neither classification specifies that the essence of delusional disorder is a highly organized delusional system, largely encapsulated from normal aspects of the personality, although DSM-IV hints at this when it comments that functioning is not markedly impaired and behavior is not obviously odd or bizarre.
8. The ICD-10 category of 'other persistent delusional disorder' is vaguely described and is largely a catch-all heading.
9. Over all, DSM-IV and ICD-10 give rather laconic descriptions of delusional disorder and it will be necessary to flesh them out with relevant clinical details.

The essence of the modern concept of delusional disorder is that of a permanent and unshakable delusional system developing insidiously in a person in middle or late life. Recent study has found that the diagnosis of delusional disorder was temporally consistent in only about 50% of the patients (Fennig *et al*, 1996). This suggests that an initial diagnosis of delusional disorder should be considered as provisional, and that patients need to be reassessed longitudinally.

3.1.3. Classifications of delusional disorder

Delusions are sufficiently idiosyncratic that sharp distinctions and inclusive classifications have remained elusive. Nash (1983) listed 44 varieties of delusions and admitted that the list is not yet complete. Vast differences can be seen in the content of any single variety of delusions. The current classificatory systems bypass the etiological discussion by implementing pure symptomatological criteria closely to the Kraepelinian category of paranoia (Gabriel, 1999). A general scheme of descriptions of delusions has been suggested by many as given in **Table -3** (Gelder *et al*, 1996).

Table - 3: Descriptions of delusions

1. According to fixity	
	Complete
	Partial
2. According to onset	
	Primary
	Secondary
3. Other delusional experiences	
	Delusional
	Delusional perception
	Delusional memory
4. According to theme	
	Persecutory (Paranoid)
	Delusions of reference
	Grandiose (expansive)
	Delusions of guilt and worthlessness
	Nihilistic
	Hypochondriacal
	Jealous
	Sexual or amorous
	Delusions of control
	Delusions concerning possession of thought
	Thought insertion
	Thought withdrawal
	Thought broadcasting
5. According to other features	
	Shared delusions

While no single classification of the varieties of delusion is satisfactory, most emphasize on alterations of thought content. Nine of the most common and dramatically distinct types of delusion are presented in **Table-4.**

Table- 4: Showing nine of the most common and dramatically distinct types of delusion

1. Delusion of Persecution	
	Delusion of Reference
	Delusions of Loss of Property
	Delusions of Poison or infection
	Delusions of influence
	Delusions of innocence
2. Nihilistic Delusions	
3. Delusions of ill health	
	Hypochondriasis
	Monosymptomatic hypochondriasis
	Somatic Delusions
4. Delusions of Grandeur	
5. Delusions of Poverty	
6. Delusions of Love	
7. Delusions of Jealousy	
8. Delusions of Possession	
9. Delusions of Reduplication	

3.1.4. Epidemiology of delusional disorder

Overall, delusional disorders are rare; the prevalence in the population is estimated at 0.03%. The epidemiological information is meager, however, it is now increasingly being realized that although the prevalence is low, delusional disorder is not rare (Manschreck, 1996). Most studies suggest that the disorder account for 1-4% of psychiatric admissions and from 2% - 7% of admissions for functional psychosis. The prevalence of these disorders is probably much higher than commonly recognized, since the delusions often remain concealed for years and may be manifested only in nonmedical situations, where they can go unrecognized as a medical condition (Dyke, 2000). The demographic evidence covering a period from 1912 to the 1970s has been represented in **Table-5,** which provides an estimate of incidence, prevalence and related statistics (Kendler, 1982).

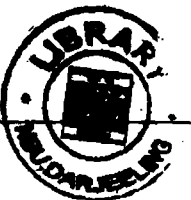


Table-5: Epidemiological features of delusional disorder:

[illegible]	[illegible]
Prevalence	24 - 30
[illegible]	[illegible]
Type of Onset	Acute or gradual
[illegible]	[illegible]
Prognosis	Best with early, acute onset
[illegible]	[illegible]

The age of onset of delusional disorder is generally middle or late adult life, with a peak frequency of first admissions between 35 and 55 years of age but can be at younger age with variable patterns of course. Delusions are exceptional until puberty (Werry, 1992). Recent studies have highlighted the relationship between age and delusional proneness, younger subjects scoring higher on most dimensions of delusional ideation, such as persecution, thought disturbances, grandiosity, and paranormal beliefs. However, 'religiosity' was the only dimension that was positively associated with age (Verdoux *et al*, 1998).

The age of onset may differ significantly according to the type of delusional disorder, the oldest age at onset was associated with the persecutory type whereas the youngest with the somatic type (Yamada *et al*, 1998).

More women than men develop the disorder as documented, and while 60-70% of patients are married, up to one-third are widowed, divorced, or separated. Few studies have reported that the female / male ratio is 2:1 (Jorgensen & Munk-Jorgensen, 1986). Recent study reveals that delusional persecution is predominant in female patients while males present significantly with delusions of jealousy and grandiosity (Gutierrez-bobos *et al*, 2001).

Persons with delusional disorder are economically and educationally disadvantaged, and immigrants seem especially prone to develop the disorder. Once established, delusional disorder is generally chronic and life long. However, it

appears to have a better long-term prognosis (Opjordsmoen, 1989). Remission is reported in one-third to one-half of cases (Jorgensen, 1994).

3.1.5. Familial pattern of delusional disorder

Family studies have been consistent in showing that most major disorders such as schizophrenia, bipolar disorder and depression are common in relatives of affected individuals than in the population at large (Tandon & McGuffin, 2002). Family studies that have begun to appear in the literature indicate the possible specific family transmission of delusional disorder. It has been reported that delusional disorder is more likely to be associated with a family history of such traits as suspiciousness, jealousy, secretiveness, and the presence of paranoid behavior or delusions (Winokur, 1986). Some studies have found that delusional disorder is more common among relatives of individuals with schizophrenia than would be expected by chance, whereas other studies have found that the families have no increase in schizophrenia or mood disorders (Watt, 1985; Winokur, 1985). There is limited evidence that avoidant and paranoid personality disorders may be especially common among first degree of biological relatives of individuals with delusional disorder.

3.1.6. Clinical heterogeneity, Paranoid spectrum and Differential diagnosis of delusional disorder

Delusional disorder is probably a heterogeneous group of illness and delusion occurs in a variety of psychiatric and medical conditions. Delusional symptomatology has been poorly investigated with factor analytic studies. Delusional symptomatology consisted of four independent factors like core depressive symptoms, hallucinations, delusions and irritability symptoms which indicate a substantial heterogeneity of this diagnostic category (Serretti *et al*, 1999). The clinical heterogeneity of delusional disorder has also been supported by other studies (Campana *et al*, 1998).

Paranoid symptoms are commonly seen in various psychiatric disorders, known as "Paranoid spectrum" (Fujinawa, 1981). Delusional disorder, a psychosis previously called "paraphrenia" (Roth, 1987), is characterised by monosymptomatic

paranoid symptoms. Delusional disorders possess features characteristic of the full range of paranoid illnesses. There are many conditions to consider (**Table- 6**), especially the more common disorders associated with paranoid (delusional) features are alcohol abuse, drug abuse (especially CNS stimulants), anticholinergic toxicity, sedative-hypnotic withdrawal, delirium, dementia, HIV infection, brain tumor, epileptic disorder, mood disorders and schizophrenia/schizoaffective disorders. Among these paranoid associated disorders, dementia of Alzheimer's type, mood disorders and schizophrenia are reviewed to understand the psychopathological basis of formation of delusion in these disorders. Delusions in depression, if present, are frequently related to mood, called mood congruent delusions and usually indicate severe depression (Coryell, 1996). Grandiose delusions are the most common symptoms (Dunayevich & Keck, 2000). Delusional thoughts are common in patients with Alzheimer's disease and contribute prominently to morbidity (Rao & Lyketsos, 1998). It has been reported that the prevalence of delusion ranged from 10% to 73% (median 33.5%) in the patients with Alzheimer's disease (Cooper *et al*, 1990; Gormley & Rizwan, 1998). The pathophysiologic underpinnings for delusions in Alzheimer's disease are not well understood. Delusional disorders are usually thought to overlap with schizophrenic disorders, and there may be a continuum with paranoid schizophrenia (Munro, 1988). Although paranoid schizophrenia is invariably grouped with other schizophrenia subtypes, there is still justification for Kraepelin's original concept of its belonging with the delusional disorders (Munro, 2003).

Table-6: Conditions and agents associated with Delusions and Other Paranoid Features

[redacted]	[redacted]	[redacted]
Adrenoleukodystrophy	Alcohol withdrawal	Acute intermittent pophyria
Arteriosclerotic psychoses	Amphetamine	Addison's disease
Blunt head trauma	Anesthetic nitrous oxide	Complication of surgical Portcaval anastomosis for cirrhosis
Brain tumors	Atropine toxicity	Cushing's syndrome
Cerebrovascular disease	Barbiturate	Folate deficiency
Cerebral anoxia	Chronic alcohol hallucinosis	Hemodialysis
Complex partial seizure disorder	Chronic bromide intoxication	Hypercalcemia
Delerium	Cocaine	Hypoglycemia
Dementia	Ephedrine	Hyponatremia
Fat embolism	Marijuana	Hypopituitarism
Hearing loss	Mescaline & other hallucinogens	Liver failure
Huntington's disease	Perbitine	Malnutrition
Hydrocephalus	Withdrawal from minor tranquilizers & hypnotic medications	Niacin deficiency
Hypertensive encephalopathy	[redacted]	Pancreatic encephalopathy
Idoppathic basal ganglia calcification	Adrenocorticotropic hormone	Parathyroid disorders
Idiopathic Parkinson's Disease	Amphetamine and related compounds	Pellagra
Intracranial hemorrhage	Antiparkinson agents	Pernicious anemia
Marchifava-Bignani disease	Anabolic steroids	Phenylketonuria
Menzel type ataxia	Antiarrhythmic drugs	Systemic lupus erythematosus
Metachromatic leukodystrophy	Hyponatremia	Thiamine deficiency
Migraine	Antibiotics (cephalosporin,penicillin)	Thyroid disorders
Motor-neuron disease	Anticholinergic drugs	Uremia
Multiple sclerosis	Antihypertensive agents	Vitamin B_{12} deficiency
Muscular dystrophy	Antimalarials	Wilson's disease
Narcolepsy	Antitubercular drugs	[redacted]
Postencephalitic parkinsonism	Bromocriptine	Brief psychotic disorder
Presenile dementia	Bupropion	Delusional disorder
Roussy-Levy syndrome	Chemotherapeutic agents (asparaginase)	Shared psychotic disorder
Senile psychoses	Cimetidine	Mood disorders
Spinocerebellar degeneration	Corticosteroids	Psychotic disorders not otherwise specified
Subarachnoid hemorrhage	Diphenylhydantoin	Schizoaffective disorders
Subdural hematoma	Disulfiram	Schizophrenia (all types)
Sydenham's chorea	Imipramine & other tricyclic drug	Schizophreniform disorder
Temporal arteritis	Levodopa	[redacted]
[redacted]	Mephentermine	47 XXY
AIDS	Methyldopa & imipramine	Klinefelter's syndrome
Encephalitis lethargia	Pentazocine	Turner's syndrome
Creutzfeldt-Jakob disease	Phenylpropanolamine and sympathomimetic agents	[redacted]
Malaria		
Syphilis		
Toxic shock syndrome		
Trypanosomiasis		
Typhus		
Viral encephalitides		

A careful assessment is necessary in order to rule out other functional or medical causes for the delusions. This work up should include a physical examination to rule out alcohol-, amphetamine-, cocaine-, and other drug induced conditions; dementia; and infectious, metabolic and endocrine disorders (Manschreck, 1996). The major diagnostic task remains in separating delusional

disorder from mood disorders, schizophrenia and paranoid personality. Associated features of delusional disorder include anger, social isolation and seclusiveness, eccentric behavior, suspiciousness, hostility and sometime violence prompted by the delusion (Kennedy *et al,* 1992). Winokur (1977) reported that patients with delusional disorders frequently develop sexual problems and depression and described many as over talkative and circumstantial. Clinical wisdom suggests that many patients become litigious and end up as lawyer's clients rather than as psychiatrists' patients.

3.1.7. Etiological Models of Delusional Disorder

The knowledge of etiology of delusional disorder is scanty and highly speculative, as little modern research has been conducted. A general outline of the etiological factors is described as below.

Organic Brain Factors

Recent evidence from the study of delusional misidentification syndrome indicates that delusions of very specific type may arise in association with certain well-defined brain insults. There are strong hints, but much less supportive evidence, to suggest that organic brain factors may also be important in cases of delusional disorder, for example, head injury may lead to the development of marked paranoid symptoms, and there is a long-established association between chronic alcoholism and pathological jealousy (Michael *et al,* 1995). Old age itself may be linked to the onset of symptoms typical of delusional disorder and early evidence of brain changes, especially in subcortical areas, is starting to appear in studies of various kinds of senile 'paranoid' illness (Feinstein & Ron, 1990). Amphetamine and cocaine abuse (Satel & Edell, 1991) can induce delusional illness. Delusional illness induced by the brain effects of AIDS infection has been documented in recent years (Reilly & Batchelor, 1991).

Gorman & Cummings (1990) have proposed that delusional illnesses of organic origin have underlying features in common, particularly temporal lobe or limbic involvement and an excess of dopamine activity in certain areas of the brain.

It is very possible that organic brain factors are much more common than we suspect in delusional disorder, especially in younger males who have previously abused alcohol or drugs or have suffered a head injury in the past, and in older patients (more commonly female) who suffer from effects of an aging brain (Munro, 1988).

Risk factors of delusional disorder

The cause of delusional disorder is unknown. The epidemiological and clinical literature suggests that certain risk factors may be relevant to etiology and deserve further research elaboration. Whether they are risk predictors or simply characteristics or markers of the disorder are unknown. Familial psychiatric disorder, including delusional disorder, is the best-documented risk factor at present. Advanced age, sensory impairment/isolation, family history, social isolation, personality features (e.g. unusual interpersonal sensitivity), and recent immigration may act as risk factors associated with delusional disorder (Manschreck, 2000).

Genetic Basis of delusional disorder

Disturbances of dopamine transmission have been implicated in the pathogenesis of many psychiatric disorders. Since delusional disorder is characterized by monosymptomatic paranoid symptoms, many investigators proposed that it could be a good clinical model for investigating the dopaminergic mechanisms responsible for paranoid symptoms. Several studies have implicated the involvement of gene polymorphisms of dopamine receptors, DRD2, DRD3 and its synthesizing enzyme (TH) as well as dopamine transporter (DAT) gene variants in the etiopathology of delusional disorder. Serretti *et al*, (2000) demonstrated a significant association between the Ser311Cys variant and delusional features in major psychoses (including delusional disorder and schizophrenia) in Italian patients. Multiple genetic polymorphisms of the human dopamine D4 receptor may also confer susceptibility to delusional disorder but in combination with other genetic or environmental factors (Zenner *et al*, 1998). In other studies, Serretti *et al.* (1999b) reported an association between DRD4* long variants and delusional

symptomatology in major psychosis. Persico & Catalano (1998) studied DAT gene VNTR polymorphisms in delusional disorder but did not support relevant contributions of DAT gene variants to the pathogenesis of delusional disorder. Morimoto *et al,* 2002 have tried to investigate biochemical and molecular etiology with respect to dopamine hypothesis of delusional disorder. To obtain direct evidence to confirm this hypothesis, they employed pHVA (plasma homovanillic acid) as a "state marker" of the disorder where as polymorphism of the DR gene as a "trait marker". They have shown that dopamine signal transmission may be increased in delusional patients with DRD2Ser311Cys mutation and DRD3 gene homozygous for Ser9Ser may be one of the etiological genes responsible for producing the high pHVA level which in turn causes paranoid symptoms. From this classic experiment they have proposed that polygenes of both the pre-and post-synaptic mechanisms of dopamine systems may be involved in the genetic etiology of delusional disorder, especially in the persecution type. The positive association of different receptor gene variants with delusional symptomatology were tested with a few isolated studies, however, majority of the studies shows that there is no overall genotypic association between DRD2 S311C polymorphism and bipolar, major depressives, schizophrenics and delusional disorders (Serretti *et al,* 1999) and the majority of linkage (Nanko *et al,* 1994; Shaikh *et al,* 1994; Sidenberg *et al,* 1994) and association studies (Hong *et al,* 1998; Serretti *et al,* 1999a; Frisch *et al,* 2000) have failed to reveal any major association of DRD4 with psychiatric disorders. These studies are not consistently uniform and need to be replicated on a large sample size.

In case of psychiatric disorders, the largest hurdle in the process of assigning the disease traits to specific genes is the rigorous clinical definition of psychiatric traits. The situation is further muddled by the lack of objective, quantifiable tests for delusional disorders. Moreover, because familial clustering of certain behavioral traits can be due to genetics (nature) or upbringing (nurture), the construction of accurate pedigrees strictly according to genetic criteria may be impossible.

Autoimmune Basis of Paranoid Disorder

A possible immunological etiology of schizophrenia has been discussed for over 60 years (Ganguli *et al*, 1994). In particular, the hypothesis of involvement of autoimmune processes has been challenging, since psychiatric complications such as psychosis, depression and anxiety have been described in autoimmune disorders (Denburg *et al*, 1997). Conversely, a higher frequency of autoimmune diseases have been reported in first degree relatives of schizophrenic patients (Wright *et al*, 1996b). These findings are further supported by detection of increased autoantibodies in schizophrenics i.e. antinuclear and antihippocampal antibodies (Knight *et al*, 1992; Ganguli *et al*, 1993). It has been suggested that viral infections and/ or autoimmune reactions against central nervous structures may play a vital role in the pathogenesis of schizophrenia (Kirch, 1993). So far there is no evidence of autoimmune processes involved in the pathogenesis of delusional disorder. However, strong evidence in favour of autoimmune etiology of paranoid psychosis came from the recent study by Wilke *et al*, (1996) where they have shown that a significantly decreased production of IFN-γ in acutely ill paranoid schizophrenics.

Now the broad agreement that there should have a substantial genetic predisposition to psychotic disorders, constituting a biological vulnerability and that the most common and successful 'antidelusional' treatment remains various medications. However, the successful neuroleptic treatment of delusions may be mediated through a cognitive reappraisal (Hole *et al*, 1979), and there appears to be complex and uncertain interrelationship between organic factors and delusional beliefs. The tension between genetic, psychodynamic and cognitive perspectives continue and seem to be best resolved by a model incorporating the insights of each and acknowledging the breadth and limitation of the data.

3.1.8. Pathogenesis of Delusional Disorder

There is no generally accepted model of delusional development and there remains a need to develop a complex integrated model, able to incorporate factors, at present subsumed under different disciplines, which may exert their effect at different stages. A review of literature essentially reveals that three interwinning

trends of theories - cognitive, psychodynamic and psychophysiological were proposed in varied forms regarding the development, maintenance and the content of delusional beliefs (Malancharuvil, 2004) Three approaches are suggested for the formation and development of delusion, these are psychodynamic mechanisms, disordered of reasoning and psychobiological mechanisms.

Psychodynamic Mechanism

Freud (1911) in his classic psychoanalytic view stated that all delusions are a protection against homosexual urges. Homosexual feelings unacceptable to the individual are transformed by projection into suspiciousness and rejection - in this theory, an understandable warding-off of supposed homosexual advances. This scenario involving repressed homosexuality is assumed with no convincing proof and there seems to be no established connection between homosexuality and delusional disorder, although cases of delusional disorder in homosexuals are recorded (Ovesey, 1954; Aronson, 1989).

Klein (1957) postulated a fixation at the paranoid-schizoid position, said to occur between the sixth and ninth months of life, inducing profound hatred by the infant of the mother, symbolically represented by the maternal breast, and envy of other women, ultimately leading to paranoia. Paranoid delusions have been described as an escape, via projective mechanisms, from shame, guilt and inadequacy, with persecutory and grandiose beliefs attempting to overcome a prevailing sense of inferiority. A recurring suggestion of weakness counteracted by paranoid aggressiveness which is projected on to the external object who can then be perceived and blamed as an aggressor (Hesselbach, 1962).

Disordered Reasoning

The definition of delusion emphasizes the operation of reasoning processes that have gone haywire, but it is not surprising that a number of attempts have been made to establish that disorder of reasoning is related to delusion formation and that such disorders can be observed among deluded patients. Related to psychodynamic formulation is the proposal that delusions arise on the basis of defects in formal logical reasoning. However, Kemp *et al,*

(1997) reported that differences in reasoning between deluded patients and controls were small.

Two other proposals involving disturbance in reasoning have been studied recently. The first portrays the difficulty underlying delusion formation as a failure in the application of Bayesian reasoning. According to this model of developing beliefs, making choices, and drawing conclusions, delusional patients accept conclusions at levels of probability too low for acceptance by nondelusional persons. The second proposal suggests that the reasoning processes of delusional patients are influenced by the subject's tendency to assign meaning in a biased manner. Application of this model reflecting motivational and reasoning difficulties (based on social attribution theory) has been tested, but the results do not provide sound support for the formulation. However, a recent study on the two components of social cognition (attentional and attributional biases) that contribute to the formation and maintenance of delusion has been supported by fMRI imaging approach (Blackwood *et al*, 2000).

Psychobiological Mechanisms

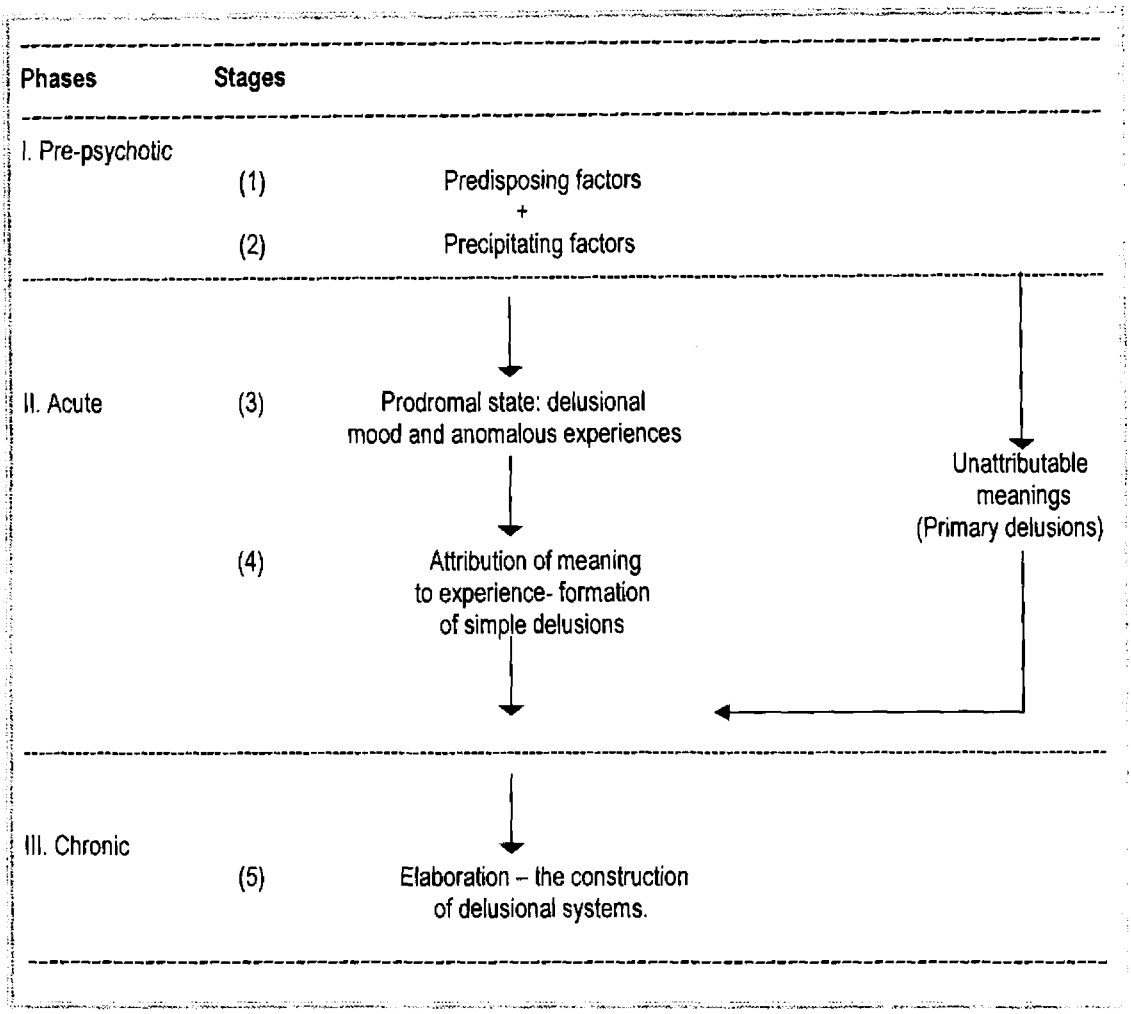
Delusional thinking may have proved difficult to explain by consistent psychological mechanisms but the nature of the disorder has led many to suggest psychological explanations (Strauss, 1988). Anomalous perceptual experiences that lead to thought disorder are often suggested (Maher & Ross, 1984) and the relationship between psychotic delusions and less deviant but still aberrant beliefs has been explored (Chapman *et al*, 1982). Disturbing social experiences establishing delusional defense mechanisms has been a suggested explanation (Higgins, 1987) and reasons for an individual's vulnerability to delusional belief have been explored (Neale *et al*, 1985). Personality disorder, situational stresses (particularly recurrent) and cultural background have been proposed as significant in the formation of delusional beliefs (Westermeyer, 1985). Despite the many psychological approaches proposed over the years, a consistent psychological explanation for delusional beliefs remains elusive

Psychological factors are, nonetheless, obviously significant in the content and quite possibly govern the formation and longitudinal consistency of a delusion. Psychological factors clearly affect both the genesis and course of delusional thinking.

There is broad acceptance among many psychological theorists that delusions are derived from some unknown constitutional predisposition and initiated by some unaccountable change, which is probably organic (Freeman, 1988). There is also agreement among organic theorists that where delusions are associated with known pathology the association is neither characteristic of any particular lesion nor any specific delusions are characteristically produced. Hence, the evolution, expression, and elaboration of delusions depend chiefly on psychological factors.

A general model of delusion formation has been proposed by different schools, which has been used as a means of ordering the wide range of disparate theories and data and are represented in **Fig.1**. It is intended as a general framework based on the assumption that the formation of normal belief, follows a temporal sequence and according to the complexity and persistence of the belief, may progress through a number of stages (Bleuler, 1951; Cameron, 1959; Arieti, 1964 and Cutting, 1989). It has been divided into pre-psychotic, acute and chronic phases representing the vulnerability, inception and increasing complexity of delusional development. It allows the multiplicity of proposed causal factors to be located where they are considered to exert their effect.

Fig.1: A general model of delusion formation after Bleuler, 1951; Cameron, 1959; Arieti, 1964; Cutting, 1989.



3.2. MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

3.2.1. Historical Perspective

Major histocompatibility complex (MHC) is a cluster of genes encoding for polymorphic human leucocyte antigens (HLA) in man involved in the presentation of antigens to T lymphocytes. The history of MHC dates back to early twentieth century when Karl Landsteiner in 1900 discovered the ABO blood group, laying the basis for blood transfusion. Matching of these antigens had a major effect on the survival of a transplanted tumor. Following this, an extensive search for antigens on white blood cells was undertaken. In 1937, Peter Gorer first introduced the term "tissue and transplantation antigens". He observed that a transplanted tumor

between two unrelated strains of mice was genetically controlled and dependent on the degree of histocompatibility.

George Snell in 1948 coined the term 'Major Histocompatibility Complex' because its products were strong transplantation antigens involved in graft rejection. Thus individuals who express the same MHC molecules accept tissue grafts from one another and those who differ at their MHC loci vigorously reject such grafts.

The first evidence for the existence of human leucocyte antigens (HLA) in man was obtained in 1954 by Jean Dausset in France who observed that patients whose sera contained 'leucoagglutinins' had received a large number of blood transfusions than those lacking such antibodies. He termed the leucoisoantigen thus identified as 'MAC' (now HLA-A2 + A28). Another important landmark in the history of HLA is 1958 when Rose Payne in the USA and Jon vanRood in Holland showed simultaneously in independent studies that pregnancy *per se* provided an effective stimulus for the induction of leucocyte isoantibodies since the mother raises antibodies to the antigens that the foetus has inherited from the father. Sera obtained from pregnant women therefore, provided most efficient source of HLA typing reagents. Based on computer methodologies, vanRood soon discovered the diallelic leucocyte antigen system 4a, 4b (now Bw4 and Bw6)(van Rood, 1962; van Rood & van Leeuwen, 1963). One year later, Payne and Bodmer defined a single leucocyte antigen locus with at least three alleles; LA1, LA2 and a blank (Payne *et al*, 1964). Subsequently, studies carried out worldwide have demonstrated marked polymorphism of the HLA system with several individual loci and an appreciable number of alleles (antigens) in each of them. Originally, leucoagglutination was the only technique used to detect the antigens but later other techniques were introduced, particularly the cytotoxicity and the complement fixation tests. Miniaturization of cytotoxicity test by Terasaki permitted the use of small volumes of antisera and cell suspensions (Terasaki & McClelland, 1964). This test is valid even today and the microtest typing trays are referred to as "Terasaki Trays".

Later, Kissmeyer-Nielson and co-workers in 1969 described crossing over between two loci thus establishing the existence of two independent loci, HLA-A and -B. The third locus, AJ (now HLA-C) was discovered in 1970 by Sondberg and co-workers. Antigens of all these loci were serologically defined. In 1975, Thorsby and Piazza described an alternative approach to study the HLA complex, the mixed lymphocyte culture (MLC). The locus coding for differences in surface antigens leading to strong mixed lymphocyte reaction was designated as HLA-D.

Although the role of MHC molecules as targets for immunologic rejection of transplants raised considerable interest, the importance of MHC in controlling immune responses was established much later after the discovery of the genetic loci. An important contribution was made by Benacerraf, McDevitt and many others whose pioneering efforts have led to the current understanding of the role of MHC gene products in immune regulation. The concept of the existence of Ir genes in the MHC was forwarded by these scientists in elegant experiments conducted in the 70's. Notably, it was demonstrated that antigen specific T lymphocytes recognize protein antigen only when it is non-covalently bound to MHC gene products. An important discovery was that MHC molecules bind peptides both from external sources as well as self-peptides. Thus MHC molecules are integral components of the MHC-peptide complex that T cells recognize.

One of the turning points in the history of the HLA system was in the beginning of 1964 when productive International Collaboration in the form of International Histocompability Workshops (IHWs) was started. Presently thirteen such workshops have already been completed. During 2nd IHW, the new nomenclature for HLA was applied when the complex was named as HL-A; HL for 'Human Leucocyte' and A for 'locus A'. 'A' was later changed to mean 'Antigen' and the locus designations were added after this HLA symbol (i.e. HLA-A, HLA-B, etc.). The 'WHO nomenclature committee for factors of the HLA system' meets from time to time to review and designate HLA loci and alleles according to their definition by serology or molecular methods. The new nomenclature has recently been published that takes into consideration all the molecular subtypes defined by

PCR-SSOP and other similar techniques (Bodmer *et al*, 1995). Accordingly, the locus name is followed by an asterisk (*) to separate the locus name from the allele name, followed by the allele designation by an Arabic number of exactly four digits. The first two digits indicate the classical serologic specificity associated with the expressed allelic product, if any. A leading zero is used if the serological specificity is only one digit. The second two digits are reserved for assignment of subtypes of that particular allele. For example, HLA-DR1 encoding DRB1 loci has four alleles, i.e., DRB1*0101, *0102*, 0103, *0104.

3.2.2. Molecular genetics, DNA sequence and Gene content of Human MHC genes

Historically, the MHC has been divided into three regions: class II (centromeric), class III and class I (telomeric) (Trowsdale & Campbell, 1997) **(Fig.2).** Human MHC gene cluster spans a region of about 4000 kb (4×10^6 nucleotides) on the short arm of chromosome 6 in the distal portion of the 6p21.3 band (Lamm and Olaisen, 1985; Hardy *et al*, 1986). Data of physical mapping, DNA cloning and sequencing of MHC region from a number of laboratories showed the presence of 224 gene loci, of which 128 are predicted to be expressed (Beck & Trowsdale, 2000). Analyses of the immediate flanking regions reveal that the 'classical' class I and class II regions extend much further than previously thought (Stephens *et al*,1999). These regions are referred to as 'extended' class I and class II regions. Loci in the extended class I region are not included in this count because their exact number still needs to be determined. Many of the 224 identified gene loci are still of unknown function and of the 224 MHC loci, 93 (42%) were discovered or located at the MHC solely as a result of genomic sequencing. Including pseudogenes, the average gene density is one gene per 16 kb. The class I and class II regions contain many pseudogenes. Up to half of the genes in the class I region are nonfunctional. Both regions appear to have duplicated multiple times, generating novel gene family members, which have then diverged (Dawkins *et al*, 1999; Shiina *et al*, 1999). The high numbers of pseudogenes may not be totally redundant because they could in theory play a role in generating new alleles by gene conversion. The gene density differs markedly in the three regions. The class III region contains an expressed gene for every ≤ 15kbp and is extremely gene dense. In some cases (e.g.

TNXB and P450-C21B), mRNA transcripts overlap (Bristow *et al*, 1993). This region is also unique in that, except in certain haplotypes in which the C4 regions have been duplicated, there are no pseudogenes for the entire region spanning 800kbp (The MHC Sequencing Consortium, 1999).

Considering expressed loci only, 40% of the total contingent of loci in the MHC have immune function (The MHC Sequencing Consortium, 1999). This figure includes at least 10 novel genes that were identified from the genomic sequence. The class II region contains several such novel genes, which are members of the immunoglobulin (Ig) or Ly6 superfamilies (C5b, C5c, G7f, G6b, G6c, G6d, G6e and

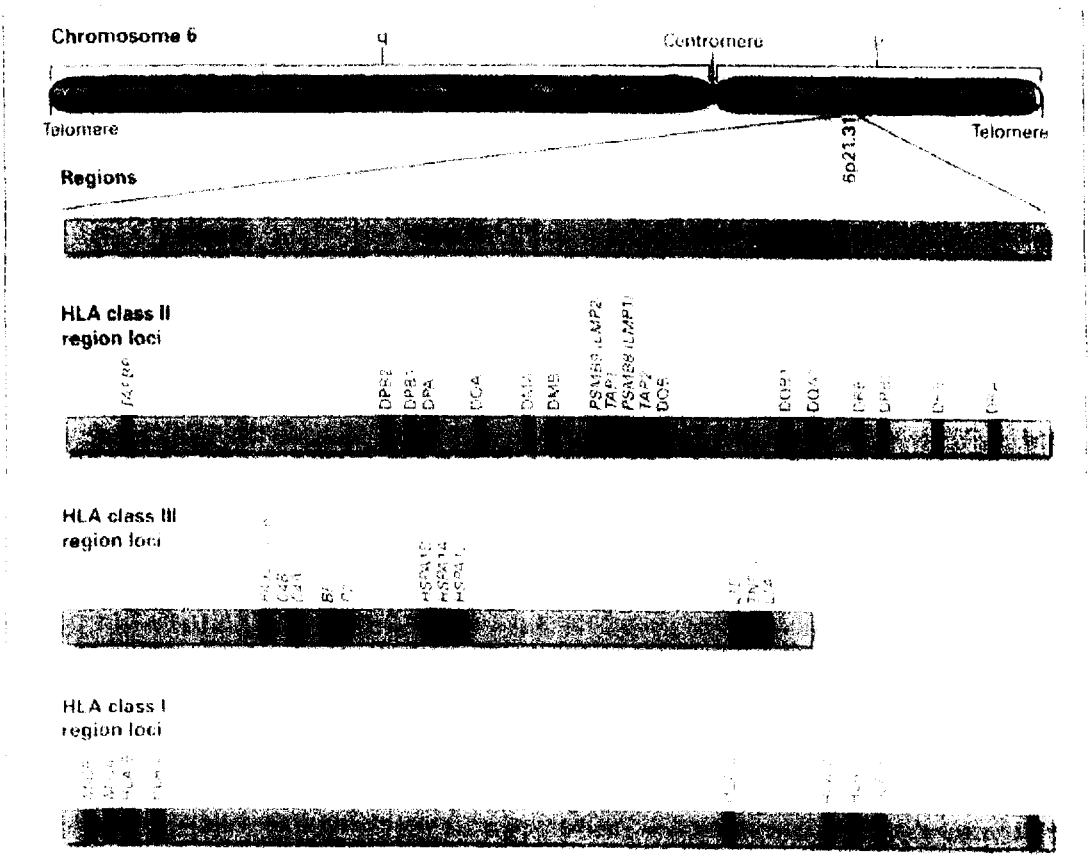


Fig. 2: Location and organization of the HLA complex on Chromosome 6.

1C7). In the extended class I region is set of butyrophilin-related loci (Tazi-Ahnini *et al*, 1997), another member of which is located between class II and class III regions (Stammers *et al*, 2000). All of the genes in the class II region, with one exception, have immunefunctions. This includes class II A and B genes, LMPs, TAPs and

TAPBP (Herberg *et al*, 1998; Herberg *et al*, 1998), which are in the extended class II region. A set of more than seven genes involved in inflammation, including three members of the tumor necrosis factor (TNF) super family, within the class III region is sometimes specified as the class IV region (Gruen & Weissman, 1997).

Apart from the immune system genes, the MHC contingent includes genes involved in a variety of processes. These include a large set of olfactory-receptor genes in the extended class I region, as well as some members of the ubiquitous zinc-finger, RING-finger and transcription factor gene families (Gruen & Weissman, 1997). In the class I region, there is a set of loci potentially involved with DNA repair or cell growth, including TFIIH (transcription factor), DDR (receptor tyrosine kinase), PRG1 (expressed in pancreatic carcinoma), DBP2 (RNA helicase) and TC4 (Ras-related) (Shiina *et al*, 1999). There is also a large representation of genes involved in other cellular control processes, including NOTCH4, RXRB, SC1, FB19 and HSR1. Complete sequence and gene map of a human MHC is shown in **Fig. 3.**

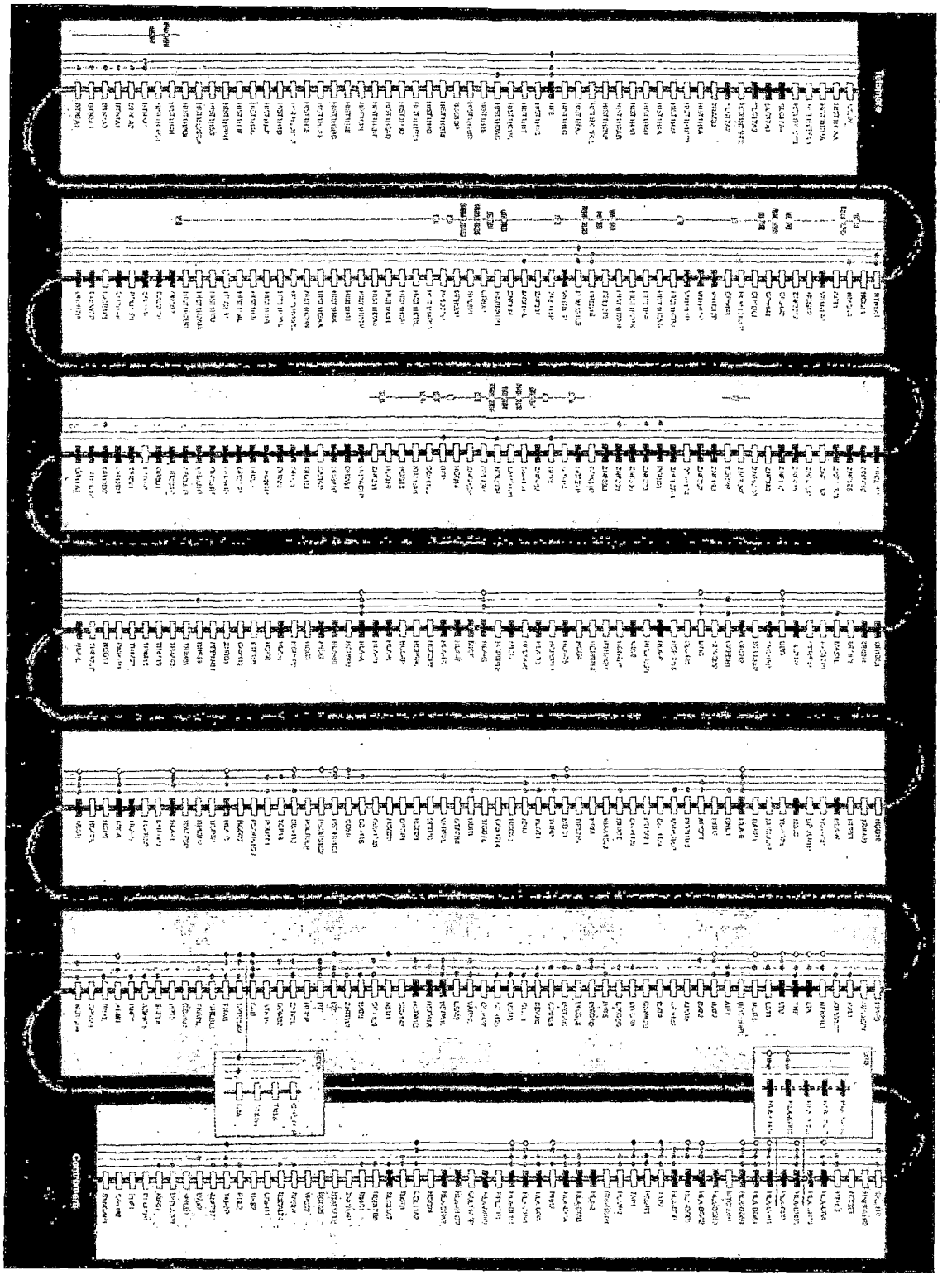


Fig. 3: Gene Map of the extended Major Histocompatibility Complex (Adapted from Horton *et al*, 2004)

HLA Class I Region

The class I region is the most telomeric part of the MHC complex. Although 36 genes have been identified so far in this region, HLA-A, -B and -C are the only products well defined as 'classical transplantation antigens'. Other human class I genes with less defined gene products have been identified like HLA-E, -F, -G, -H and-J, known as 'nonclassical class I genes'. A number of currently recognized HLA class I antigens are expressed on the surface of most nucleated cells of the body.

The HLA class I antigens comprise a 45 kilodalton (kDa) α chain associated noncovalently with a 12-kDa β2 microglobulin (β2m) molecule. The α chain is a transmembrane glycoprotein encoded by polymorphic genes within the A, B, and C regions of human HLA complex. β2m is a protein encoded by a highly conserved gene located on chromosome15 (Ploegh *et al*, 1981). Structural analysis have revealed that the α chain of class I HLA molecules is organized into three external domains (α1, α2 and α3), each containing approximately 90 amino acids (aa); a transmembrane domain of about 25 hydrophobic amino acids followed by a short by a short stretch of charged amino acids; and a cytoplasmic anchor segment of 30 amino acids. The β2 microglobulin is similar in size and organization to the α3 domain; it does not contain a transmembrane region and is noncovalently bound to the class I glycoprotein **(Fig. 4).**

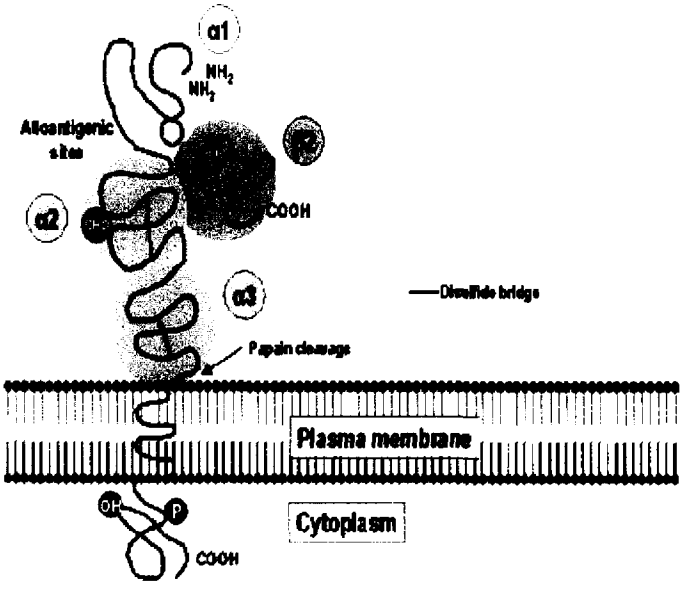


Fig 4: Schematic diagram of a class I MHC molecule showing the external domians, transmembrane segment, and cytoplasmic tail.

The full 3 dimensional structure of HLA class-I molecules has been determined from X-ray crystallography. The α1 and α2 domains interact to form a platform of eight antiparallel β strands spanned by two long α-helical regions. The structure forms a deep groove or cleft, called *peptide binding cleft* and it is large enough to bind a peptide of 8-10 amino acids. The amino acid differences that account for the rich polymorphisms of HLA class I molecules are located in the α1 and α2 domains, but occur in specific regions. About seven 'hypervarible' regions have been identified in class I molecules, corresponding to amino acid residues 9-12,40-45,62-83,94-97,105-116,137-163 and 174-194 (Lopez de Casro *et al*, 1985). The membrane proximal α3 domain and β2 microglobulin are organized into two β pleated sheets each formed by antiparallel β strands of amino acids and are invariant. **Table-7** shows complete list of recognized HLA class I specificities defined by serological procedures and their allelic variants of MHC genes, as defined by molecular methods.

Table-7: List of class I HLA alleles [The list summarizes the designations of the HLA class I gene products as they have been known based on serology, and they have been assigned by nucleotide sequences. Current serological designations are given in the "serology" columns, with older (broader) serological assignments listed in parentheses. The list is based on a listing of alleles maintained by Dr. Steve Marsh on behalf of the WHO Nomenclature Committee for Factors of the HLA system, as of July 2002. The IMGT/HLA Database was referred via the web at **http://www.ebi.ac.uk/imgt/hla**].

HLA-A		HLA-B		HLA-C	
SEROLOGY	ALLELES	SEROLOGY	ALLELES	SEROLOGY	ALLELES
A1	A*0101 – 0109	B7	B*07021 – 0731	Cw1	Cw*0102 – 0106
A2	A*0201 – 0258	B8	B*0801 – 0815	Cw2	Cw*02021 – 0205
A3	A*0301 – 0309	B13	B*1301 – 1310	Cw3	Cw*03021 – 0315
A11	A*1101 – 1110	B14	B*1401 – 14062	Cw4	Cw*0401101-0409
A23 (9)	A*2301 – 2308	B15	B*1501101 – 1573	Cw5	Cw*0501 –0505
A24 (9)	A*2402 – 2433	B18	B*1801 – 1818	Cw6	Cw*0602 – 0607
A25 (10)	A*2501 – 2504	B27	B*2701 – 2725	Cw7	Cw*07011 –0716
A26 (10)	A*2601 – 2618	B35	B*35011 – 3541	Cw8	Cw*08011-0809
A29 (19)	A*2901 – 2905	B37	B*3701 – 3705	-	Cw*12021 – 1208
A30 (19)	A*3001 – 3012	B38 (16)	B*3801 – 3808	-	Cw* 1301
A31 (19)	A*3101 – 3108	B39 (16)	B*39011 - 3926	-	Cw* 14021-1405
A32 (19)	A*3201 – 3207	B40	B*40011 – 4044	-	Cw*15021 – 1511
A33 (19)	A*3301 – 3306	B41	B*4101 – 4106	-	Cw*1601 – 16041
A34(10)	A*3401 – 3404	B42	B*4201 – 4204	-	Cw*1701 –1703
A36	A*3601 – 3603	B44 (12)	B*44021011 - 4432	-	Cw*1801 - 1802
A43	A*4301	B45 (12)	B*4501 – 4506		
A66	A*6601 – 6604	B46	B*4601 – 4602		
A68(28)	A*6801 – 6822	B47	B*4701101 – 4704		
A69(28)	A*6901	B48	B*4801 – 4807		
A74 (19)	A*7401 – 7408	B49 (21)	B*4901 – 4903		
-	A*8001	B50 (21)	B*5001 – 5004		
		B51 (5)	B*51011 – 5129		
		B52 (5)	B*52011 – 5203		
		B53	B*5301 – 5309		
		B54 (22)	B*5401 – 5402		
		B55 (22)	B*5501 – 5512		
		B56 (22)	B*5601 – 5608		
		B57 (17)	B*57011 – 5709		
		B58 (17)	B*5801 – 5806		
		B59	B*5901		
		B67	B*67011 – 6702		
		B73	B*7301		
		B78	B*7801 – 7805		
		-	B*7901		
		-	B*8101		
		-	B*8201 – 8202		
		-	B*8301		

Class II or HLA-D Region

The class II HLA region encodes three classical class II molecules designated as HLA-DR, DP and DQ. Genes encoding nonclassical class II HLA molecules have also been identified and are designated as DM and DO. They are expressed as heterodimers on cell surface of B lymphocytes, macrophages, endothelial cells and activated T lymphocytes.

Class II molecules are constitutively expressed as heterodimers primarily on cells such as macrophages, dendritic cells, Langerhans' cells, B cells, activated T cells and bone marrow derived precursor cells. Structurally HLA class II molecules are composed of two different polypeptide chains, a 33 kDa α (alpha) chain and a 28-kDa β (beta) chain (Kaufman *et al*,1984). Class II HLA molecules are membrane bound glycoproteins that contain external domains, a transmembrane segment and a cytoplasmic anchor segment.

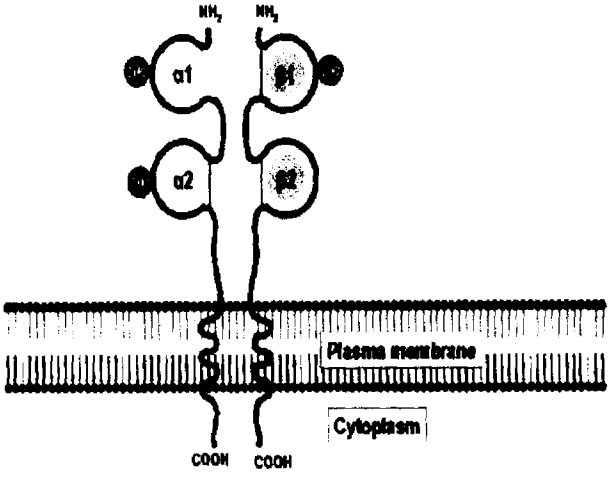


Fig. 5: Schematic diagram of a class II MHC molecule showing the external domains, transmembrane segment, and cytoplasmic tail.

Each chain in a class II molecule contains two external domains: α1 and α2 domains in one chain and β1 and β2 domains in the other **(Fig. 5)**. The membrane - distal portion of a class II molecule is composed of the α1 and β1 domains and forms the antigen binding cleft for processed antigen. The class II gene structure contains three hyper variable regions in the first domain which are functional sites for peptide binding. The exons coding for the transmembrane and cytoplasmic domains are invariant.

HLA-DR molecules are the predominant class II products on the cell surface, and the polymorphism is associated with B gene. The DR subregion contains multiple highly polymorphic B genes and only one invariant A gene. A total of nine DRB genes (DRB1-9) have been identified so far in the DR subregion. The conventional serologically defined DR molecules (DR1 - DR18) are coded for by DRB1 gene in association with invariant DRA gene, while DR52 and DR53 specificities are coded for by the DRB3 and DRB4 genes respectively (Gorski *et al*, 1987). DRB2, DRB6, DRB7, DRB8 and DRB9 are pseudogenes without a first domain exon.

Using the tools of molecular biology, it has become clear that there are at least six α and ten β genes known in HLA class-II, not all of which are expressed as functional molecules. Within the DR sub region, there are six genes: DRA, DRB1, DRB2, DRB3, DRB4 and DRB5. DRA gene is invariant while the DRB2 lacks the first domain exon and therefore is a pseudogene (Rollini *et al*, 1987)

DQ subregion contains five genes, DQA1, DQA2, DQB1, DQB2 and DQB3 of which DQA2, DQB2 and DQB3 are not known to be expressed because no protein or mRNA product has been defined in them. In contrast, both DQA1 and DQB1 are functional and polymorphic.

The DP subregion contains two A and two B genes with DPA2 and DPB2 being pseudogenes. DPB1 shows extensive polymorphism while DPA1 displays limited polymorphism.

Two new sub regions DO and DN were named recently lying between the DQ and DP loci. The extent of polymorphism in these loci is not well known yet.

The locus specific sequences that distinguish DR, DQ and DP are located in the α and β domains of class II molecules. The sequences that distinguish between allelic variants are localized within three to four hypervariable regions within the β1 domain of DRB1, DQA1 and DQB1 molecules (Marsh & Bodmer, 1995). PCR amplification of DNA using sequence specific primers and hybridization with allele specific oligonucleotide (ASO) probes have a wide range of allelic variation within these genes. Currently, 2 DRA, 124 DRB1, 4 DRB3, 5 DRB4, 5 DRB5, 3 DRB6, 2 DRB7, 16 DQA1, 24 DQB1, 8 DPA1 and 62 DPB1 specificities have been recognized. **Table-8** shows complete list of recognized HLA class II specificities defined by serological procedures and their allelic variants as defined by molecular methods.

Table 8: List of class II HLA alleles (The list is based on a listing of alleles maintained by Dr. Steve Marsh on behalf of the WHO Nomenclature Committee for Factors of the HLA system, as of July 2002. The IMGT/HLA Database was referred via the web at **http://www.ebl.ac.uk/imgt/hla**).

HLA-DR		HLA-DQ		HLA-DP		HLA-DM & HLA-DO	
SEROLOGY	ALLELES	SEROLOGY	ALLEELS	SEROLOGY	ALLELES	SEROLOGY	ALLELES
α Chain		α Chain		α Chain		α Chain	
DRA		DQA1	DQA1*01011-0106	DPA1		DMA	DMA*0101-0104
-	DRA*0101-01022	-	DQA1*0201	-	DPA1*01031-0108	DOA	DOA*01011-01015
		-	DQA1*03011-0303	-	DPA1*02011-0203		
β chain		-	DQA1*0401	-	DPA1*0301-0302	β chain	
DRB1		-	DQA1*05011-0505			DMB	DMB*0101-0106
DR1	DRB1*0101-0108	-	DQA1*06011-06012	β chain		DOB	DOB*0101101-0104102
DR15(2)	DRB1*15011-1513	β chain		DPB1			
DR16 (2)	DRB1*16011-08	DQB1		DPw1	DPB1*01011-01012		
DR3	DRB1*03011-0322	DQ5(1)	DQB1*05011-0504	DPw2	DPB1*02012-0202		
DR4	DRB1*04011-0444	DQ6(1)	DQB1*06011-0620	DPw3	DPB1*03011-03012		
DR11(5)	DRB1*11011-1143	DQ2	DQB1*0201-0203	DPw4	DPB1*0401-0402		
DR12(5)	DRB1*12011-1208	DQ3(7,8,9)	DQB1*03011-0313	DPw5	DPB1*0501		
DR13(6)	DRB1*13011-1351	DQ4	DQB1*0401-0402	DPw6	DPB1*0601		
DR14(6)	DRB1*14011-1433			-	DPB1*0801		
DR7	DRB1*07011-0706			-	DPB1* 0901		
DR8	DRB1*08011-0824			-	DPB1*1001		
DR9	DRB1*09012-0902			-	DPB1*11011-11012		
DR10	DRB1*10011-10012			-	DPB1*1301-4101		
				-	DPB1-4401-9201		
DRB3							
DR52	DRB3*01011-0110						
	DRB3*0201-0217						
	DRB3*03011-0303						
DRB4							
DRB53	DRB4*01011-0106						
-	DRB4*0201N						
-	DRB4*0301N						
DRB5							
DRB51	DRB5*01011-0110N						
-	DRB5*0202-0205						
DRB6	DRB6*0101						
	DRB6*0201-0202						
DRB7	DRB7*01011-01012						
DRB8	DRB8*0101						
DRB9	DRB9*0101						

HLA Class III Region or Central Genes

The class III region of the HLA contains a heterogeneous collection of genes located centrally in a 1000 kb stretch of DNA. These genes encode several proteins involved in the immune system i.e. the complement genes C4, C2 and Bf (Factor B), the TNF- α (tumor necrosis factor alpha), and TNF- β (lymphotoxin) gene and HSP 70 (heat shock protein) genes. The serum complement factors are genetically polymorphic and mapping of their structural loci within the HLA complex makes them useful as additional genetic markers of this region. Although complement alleles have an important role as additional disease susceptibility markers, their involvement in the transplantation context has never been suggested.

Apart from the complement components, this region also contains genes coding for the steroid hormone, 21-hydroxylase (21-OH) or CYP21 genes. The 21-OH genes associate very closely with the C4A and C4B genes.

Intermingled with the TNF genes, a series of nine new genes of unknown function have been described. These genes are called HLA-B associated transcripts or BAT genes (Spies *et al*, 1989). Klein (1987) argued that the central region of the MHC has no structural and functional correlation with the class I or class II regions and hence should be viewed as a part of the MHC. Interestingly, however, certain haplotypes containing fixed alleles of class-I and class-II region carry specific central region i.e. extended haplotypes or supratypes. Recently the concept of 'ancestral haplotypes' has been put forward highlighting the presentation and co-inheritance of certain MHC genes (Dawkins *et al*, 1989).

3.2.3. Polymorphism and linkage disequilibrium

The extreme polymorphism is one of the most prominent features of the MHC. Variation levels of 5-17% have been reported at some loci (HLA-DP, DQ, B and C), which are the highest levels found in the human genome so far. With the introduction of DNA based methods of HLA typing, extensive molecular polymorphism has been discovered in each of the relevant HLA class I and Class II loci, which is far in excess of polymorphism obtained by serological methods (**Table-9**). For example, currently, a total of 1496 alleles in the HLA region have been defined according to the ImMunoGeneTics (IMGT) / HLA database statistics (http://www.ebi.ac.uk/imgt/hla), updated by the European Bioinformatics Institute. Of these: in the MHC class I region, 237 alleles have been identified in HLA-A, 472 in HLA-B and 113 in HLA-C; in the MHC class II region, 304 alleles have been identified in HLA-DRB1, 49 in HLA-DQB1, 22 in DQA1 and 96 in DPB1. The high degree of polymorphism in HLA appears to have resulted from recombination and exchange of genetic material between alleles of the same locus and also from point mutations and other genetic events. Theoretically, several million genotypic combinations (approximately 150 billion or even more) are possible in the HLA system. According to Klein (1987), such a polymorphism is not only advantageous

for an individual, but even more for the survival of the species surrounded by many different and often changing pathogens. Thus the polymorphism is probably essential for efficient functioning of the system.

Despite the enormous number of alleles at each expressed loci, the genes of the MHC region are normally inherited unchanged from parents, so that one set of allelic variants of the HLA genes present in the parents is present in the same form in the offspring. This phenomenon caused the formation of so called haplotypes where certain alleles of different gene loci tend to segregate together rather than randomly. The two HLA haplotypes in an individual derived after family testing constitute his genotype whereas the total HLA antigen profile is his phenotype. Theoretically, siblings in a family have 25% chance to be HLA identical. 50% chance to be HLA haploidentical (sharing one parental haplotype only) and 25% chance to be HLA unidentical i.e. a total mismatch.

A close study of the different populations have shown that certain combination of HLA alleles occur together more often than would be expected on the basis of their individual gene frequencies. This non-random association of the alleles of two HLA loci found together on the same HLA haplotype is termed linkage disequilibrium and is expressed in terms of delta. It is found to vary among different populations, e.g., haplotype DQ2-DR3-C2C-Bfs-C4AQO-C4B1-B8-Cw7-A1 occurs most frequently among European and North American Caucasians, while among Asian Indians, the haplotype with the highest delta value happens to be DQ2-DR3-C2C-Bfs-C4QO-C4B1-B8-Cw7-A26. Although the reason for these associations is unknown, linkage disequilibrium may be the consequence of natural selection for or against a specific gene combination or it may be due to the fact that the population has not yet reached equilibrium. For very closely linked genes, the rate of approach to equilibrium is slow. The stable relationship between alleles has been taken to suggest that these combinations represent preserved ancient or ancestral haplotypes.

Table-9: HLA Class I and Class II polymorphism: serology vs. molecular (Marsh *et al*, 2002).

HLA Antigens	Serologic Type	No. of Molecular Types	HLA Antigens	Serologic Type	No. of Molecular Types
[redacted] A	A1	9	[redacted] B	B52	4
	A2	58		B53	9
	A3	9		B54	2
	A11	13		B55	12
	A23	9		B56	8
	A24	36		B57	9
	A25	4		B58	6
	A26	18		B59	1
	A29	6		B67	2
	A30	12		B73	1
	A31	8		B78	5
	A32	7		B81	1
	A33	6		B82	2
	A34	4		B83	1
	A36	3			
	A43	1	[redacted] C	Cw1	6
	A66	4		Cw2	5
	A68	22		Cw3	15
	A69	1		Cw4	10
	A74	8		Cw5	5
	A80	1		Cw6	7
				Cw7	16
[redacted] B	B7	31		Cw8	9
	B8	16		Cw12	8
	B13	10		Cw14	5
	B14	6		Cw15	11
	B15	73		Cw16	3
	B18	18		Cw17	3
	B27	24		Cw18	2
	B35	44			
	B37	5	[redacted] DR	DR1	8
	B38	8		DR15	13
	B39	26		DR16	8
	B40	44		DR3	23
	B41	6		DR4	44
	B42	4		DR11	43
	B44	32		DR12	8
	B45	6		DR13	52
	B46	2		DR14	43
	B47	4		DR7	6
	B48	7		DR8	24
	B49	3		DR9	2
	B50	3		DR10	2
	B51	29			

3.2.4. Biologic Functions of the MHC

The products of genes within MHC play a fundamental role in the regulation of immune response. This indication came first from the studies of Benacerraf and coworkers (1967) in guinea pigs using

hapten derivatives of poly L- lysine. The actual position of an 'immune response' (Ir) gene was subsequently mapped within the murine MHC to the I-region in a series of experiments using H-2 recombinants (McDevitt *et al,* 1972). These investigators demonstrated that the response to antigen (T, G)-A-L was under genetic control and linked to the H-2 system. The term immune response (Ir) gene was introduced by Benacerraf and McDevitt (1972) to designate genes determining high or low responsiveness to antigens of limited heterogeneity. The fact that class-II histocompatibility molecules themselves act as immune response factors by binding and presenting the processed antigens to T cells led to the demonstration of association of diseases with HLA linked genes. Later, Rosenthal & Shevach (1973) using a group of synthetic co-polymers composed of L-glutamic acid plus lysine (GL) and L-glutamic acid plus L-tyrosine (GT) demonstrated that immune response in the guinea pig is under Ir gene control. These Ir genes were actually linked to HLA was demonstrated by studies concerning immune responsiveness to streptococcal cell wall antigen (Sasazuki *et al,* 1980).

The role of MHC in the cellular recognition of antigens came with the experiments of Zinkernagel & Doherty (1974) who demonstrated that the killing of lymphocytic chorio-meningitis virus (LCV) infected target cells occurred only when the cytotoxic T lymphocytes (CTLs) and the target cells expressed the same H-2 haplotype. These studies revealed that cytotoxic T cells could recognize a virus infected target cell only in the context of class I molecules, a phenomenon called "MHC restriction". The initiation of cellular and humoral immune responses require successful interaction between T lymphocytes and antigen presenting cells. While class-I MHC molecules are important for the presentation of foreign peptides to cytotoxic T lymphocytes (CTL) and suppressor T

cells; helper T cells recognize the antigen only in association with Class-II molecules.

Underlying its biomedical importance the MHC is associated with more diseases than any other region of the human genome, including most, if not all autoimmune conditions (e.g. Rheumatoid arthritis and diabetes). Phenotypes with different etiologies have also been linked to the region, ranging from cancer to sleeping and reading disorder.

3.2.5. HLA and Disease Associations

The importance of HLA genes in antigen presentation and regulation of immune response results in association of this region with more diseases than any other region of the human genome. The MHC region therefore represents a primary target for disease gene discovery efforts. The concept of disease association was originally suggested by Amiel in 1967 for Hodgkin's disease (Amiel, 1967). He demonstrated a HLA association between an antigen 4C (now B5 + B35 + B18 + B15) and Hodgkin's disease. It opened a new vista in HLA studies. The search for such association increased by an exponential number. A large group of diseases involve genes in the HLA region that are linked to (or associated with) specific class I and class II alleles or combinations of alleles (haplotypes). Genetic studies have shown that persons who have certain HLA alleles have a higher risk of specific autoimmune diseases than persons without these alleles (Klein & Sato, 2000). The associations vary in strength, and in all the diseases studied, several other genes in addition to those of the HLA region are likely to be involved. **Table-10** gives some of the most significant association between HLA antigens and diseases.

Table-10: Association between the presence of various HLA markers and selected autoimmune diseases.

Disease	Associated HLA Marker	Relative Risk
Ankylosing Spondylitis	B27	87.4
Reactive arthropathy	B27	36.0
Rheumatoid arthritis	DR4	4.2
Behcet's syndrome	B51	3.8
Systemic lupus erythematosus	DR3	5.8
Insulin-dependent (type 1) diabetes mellitus	DR3	3.3
	DQB1*0201	2.4
	DR4	6.4
	DQB1*0302	9.5
	DR2	0.19
	DRB*1501	
	DRB*0101	
Idiopathic Addison's disease	DRB1*0602	0.15
Graves' disease	DR3	6.3
Hashimoto's disease	DR3	3.7
Postpartum thyroiditis	DR11	3.2
Celiac disease	DR4	5.3
	DR3	10.8
	DQB1*0201	
	DQA1*0501	
	DR7, 11	6.0-10.0
	DR7, DQB1*0201	
	DR11, DQA1*0501	
Dermatitis herpetiformis	DR3	15.9
Sicca syndrome	DR3	9.7
Myasthenia gravis	DR3	2.5
	B8	3.4
Idiopathic membranous glomerulonephritis	DR3	12.0
Goodpasture's syndrome	DR2	15.9
Multiple sclerosis	DR2	4.1
	DRB1*1501	
	DRB5*0101	
	DQB1*0602	
Pemphigus vulgaris	DR4	14.4
Psoriasis vulgaris	Cw6	13.3
Birdshot retinochoroidopathy	A29	109.0

3.3. MHC AND SUSCEPTIBILITY TO PSYCHIATRIC ILLNESS

The demonstration of major histocompatibility complex (MHC) as T cell restriction element and its linked immune response (Ir) and/or immune suppressive (Is) genes (McDevitt & Chinitz, 1969; Benacerraf, 1981) has resulted in a series of HLA and disease association studies at the population level (Tiwari and

Terasaki, 1985). Since the pathogenesis of most of the psychiatric traits are not well understood, several investigators have searched for an association of the disease with either HLA Class I (HLA-A, -B, -C) or Class II (HLA-DR, -DQ) antigens. Different associations have been reported with HLA antigens and different neuropsychiatric diseases in different populations (**Table 11**). However, none of the studies so far have reported the association of a particular HLA antigen with monosymptomatic psychotic disorder.

Table 11: Neuropsychiatric and neurological disorders and their associated HLA antigens, genes and/or haplotypes:

Disease	HLA antigen, gene or haplotype	Reference
Narcolepsy	DR15-DQ6-Dw2 DR2-DQ1	Olerup *et al*, 1990 Roitt, 1991
Multiple Sclerosis	DRB1*1501-DQA1*0102-DQB1*0602 DR15	Hillert & Olerup,1993 Hensick *et al*, 2002
Myasthenia Gravis	A1-B8-DR3 DQB1*0604	Dawkins *et al*, 1987 Vieira *et al*, 1993
Amyotrophic lateral scleorosis	A3 B35	Kott *et al*,1979 Bartfeld *et al*, 1983
Polymyositis	B8 DR3	Behan *et al*, 1978 Garlepp,1993
Stiff man syndrome	DQB1*0201	Pugliese *et al*, 1993
Chronic immune mediated neuropathies	A3-B7-DR2	Feeney *et al*, 1990
Schizophrenia	A28 A2 A9 A1 DRB1*04 DRB*0101	Ivanyi *et al*, 1978 Luchins *et al*,1980 Mc Guffin & Stuart, 1986 Lahdelma *et al*, 1998 Wright *et al*, 1998 Sasaki *et al* , 1999
Manic depressive disorders	B7, BW16	Shapiro *et al*, 1977 Lowell *et al*, 1981

3.4. CHROMOSOMAL ABERRATIONS & PSYCHIATRIC DISORDERS

Another approach of investigating the specific genetic involvement in psychiatric disorders is to identify associated chromosomal abnormalities. Chromosomal aberrations associated with psychiatric disorders may suggest regions in which to focus the initial search for disease-causing genes by a genetic linkage strategy. There are few reviews of chromosomal abnormalities and psychiatric disorders in the literature. Cytogenetic analysis has identified chromosomal aberrations associated with schizophrenia, interesting regions, which may harbor susceptibility genes. Chromosomal abnormalities associated with various neuropsychiatric disorders are shown in **Table-12**.

Table-12: Showing the association of chromosomal breakpoints and neuropsychiatric disorders.

Disease	Chromosomal Anomaly	References
Paranoid psychosis	Inverted segments 9p11-9q11, Balanced translocation (5p13;6q15)	Axelsson & Wahlstrom, 1984
Schizophrenia	Partial triosomy of 5q11-13 Specific translocations-t(1;7)(p22q22) Sex aneuploidies Inversions -inv(9) (p11q13) Deletions at 22q11.1 Inv (9) and 9qh+	Bassett *et al*, 1988 Gordon *et al*,1994 Kunugi *et al*, 1999 Toyota *et al*, 2001 Arimani *et al*, 2001 Demirhan & Tastemir, 2003
Bipolar disorder	Inv(18) (p11.3; q21.1)	Mors *et al*, 1997