INTRODUCTION

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Delusional disorder is a psychiatric disorder in which the central feature is the presence of delusions in the absence of other symptomatology. Since the beginning of psychiatry, delusional disorder has been at the centre of attention and right up to the present, continuing to engender controversy. Delusions have been regarded as the hallmark of insanity in Western cultures, long before psychiatry became a branch of medicine (Berrios, 1991). In contemporary classifications of mental disorders, such as Diagnostic and Statistical Manual, 4th edition (DSM-IV) and International Classification of Diseases, 10th edition (ICD-10), delusions are considered as cornerstone symptoms for the diagnosis of psychotic disorders. Delusional formation is a fascinating and enigmatic psychic process, which has been the object of numerous scientific debates and theoretical models, but of surprisingly few empirical studies (Berrios 1991; Butler & Braff, 1991).

Delusion has been defined as a false belief that is firmly maintained in spite of incontrovertible and obvious proof or evidence to the contrary and in spite of the fact that other members of the culture do not share the belief. The delusional material may be rational, but the belief is not arrived at through normal processes of logical thinking (Rotterstol, 1986). Delusional beliefs may lead to great distress in patients and their relatives. Delusions vary widely in content and composition which can be shaped by many different factors, including social and political events (Sher, 2000). Delusions involve thought contents and, as such, tend to be idiosyncratic and richly varied. They are formed from and coloured by the individual's background, including personal, familial, social and group experiences, educational background, and cultural including religious influences (Benson & Gorman, 1996). Delusions are a common symptom of several mood and personality-related mental illnesses, including schizoaffective disorder, schizophrenia, shared psychotic disorder, major depressive disorder, and bipolar disorder. There are also delusional disorders such as dementia that clearly have organic or physical causes. Systematic study of the phenomenology of delusions, however, is a relatively recent enterprise and many fundamental questions remain unanswered.

Delusional disorder, an uncommon, probably heterogeneous group of illness, has a prevalence of 0.03 percent and incidence 1-3 new cases/100,000 population. Epidemiological data suggests that delusional disorder is a separate condition or is an atypical form of schizophrenia and mood disorders (Kendler, 1980). It is far less prevalent than schizophrenic or mood disorders. The age of onset is later than in schizophrenia although men tend to experience the illness at earlier ages than women (Hsiao *et al,* 1999). The observed sex ratio is different from that of mood disorder, which occurs disproportionately among women.

Numerous attempts have been made to demonstrate an underlying psychological basis for delusions. Delusional thinking may have proved difficult to explain by consistent psychological mechanisms (Oltmanns & Maher, 1988) but the nature of the disorder has led to many suggested psychological explanations (Strauss, 1988). Kraepelin (1989) considered the delusions of paranoia to be the "morbidly transformed expression of the natural emotions of human heart" and more specifically, " a kind of psychological compensation for the disappointments of life." However, anomalous perceptual experiences that lead to thought disorders are often suggested by others (Maher & Ross, 1984). Disturbing social experiences establishing delusional defense mechanisms has been a suggested explanation (Higgins, 1987) and reasons for an individual's vulnerability to delusional belief (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.

As in most psychiatric conditions, there is no evidence of localized brain pathology to correlate with clinical psychopathology in patients with delusional disorder (Manschreck, 2000). On the contrary, delusions can be a feture of a number of biological conditions (many disorders and virtually all brain disorders), suggesting possibly biologic underpinnings for the disorder (Kaplan & Sadock, 1998). Most commonly, neurological lesions associated with temporal lobe, limbic system and basal ganglia are implicated in delusional syndromes. However, other

studies reveal that the patients seldom die early and show no consistent abnormalities on neurological examinations. Certain disorders produce delusions at rates greater than that expected in the general population: for example, epilepsy (especially of the temporal lobe), degenerative dementias (dementia of the Alzheimer's type and vascular dementia), cerebrovascular disease, extra pyramidal disorders, and traumatic brain injury (Cummings, 1992). Imaging studies have begun to yield subtle findings about delusional disorder.

There is no document available regarding the systematic research on delusional disorder. Etiological explanations range from theories based on individual life history factors on the one side (Gabriel, 1987) to biological theories based on organic brain factors on the other (Munro, 1988; Gross *et al.* 1997). Precipitating factors, especially related social isolation, conflicts of conscience, and immigration, are more closely associated to delusional disorder. These characteristics support Kraepelin's view that environmental factors may play an important etiological role. For much of the past century psychodynamic causal explanations held sway in psychiatric practice. Over the past 20-30 years the biological contribution to much mental illness has been rediscovered and biological approaches to treatment and research have enjoyed hegemony over other paradigms (Jones & Kent, 2001).

It has long been suspected that genetics play an important role in the disease processes. In psychiatry a genetic contribution to common disorders, cognition and personality traits is well established and susceptibility loci has been identified for schizophrenia, bipolar affective disorders, autism and Alzheimer's disease. The common neuropsychiatric disorders have a complex genetic etiology, probably involving interaction between genome and environment (Corvin & Gill, 2003). This understanding has largely been based on the classic approach of a high concordance rate for diseases such as schizophrenia, depression and bipolar disorder in monozygotic versus dizygotic twins (Tsuang, 2000). However, such systematic study has not yet been carried out for the delusional disorder. Although familial aggregation of the disease has been proposed by many investigators, the exact role of the hereditary factors in the etiology of delusional disorder remains

controversial (Kendler & Hays, 1981, Schanda *et al*, 1983, Kendler *et al*, 1985, Winokur, 1986).

Since delusional disorder is characterized by mono-symptomatic paranoid symptoms, several investigators suggested that delusional disorder is a naturally occurring model psychosis based on abnormalities of the dopaminergic temporolimbic system (Munro, 1994). Molecular evidence for dopamine hypothesis of delusional disorder has been supported by some studies on D2 receptor variation (Serretti *et al*, 2000) and DRD4 Exon 3 variation (Serretti *et al*, 1998, Serretti *et al*, 2001). However, many other studies do not support relevant contributions of dopamine receptor gene variants to the pathogenesis of delusional disorder (Serretti *et al*, 1999a) and indicate that such variation may be connected with delusional symptomatology, although it does not play a major role in conferring susceptibility to delusional disorder (Morimoto *et al*, 2002).

In the apparent absence of a single pathogenic mutation, the alternative genetic strategy of association becomes increasingly important for psychiatric research (Risch, 1990). In this regard, the Major Histocompatibility Complex (MHC) holds promise of great insights in the understanding of complex disorders with unknown etiology. The HLA (MHC in human) complex is the most diverse and polymorphic genetic system with major functional and medical implications (Charron, 1997). Underlining 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 (Tiwari & Terasaki, 1985). Phenotypes with different etiologies have also been linked to the region, ranging from cancer to sleeping and reading disorders. The discovery of HLA associations with specific diseases implies that at least part of their genetic basis lies in the MHC and suggests that it may possible to determine their etiology. Many studies have shown associations of specific HLA alleles with autoimmune diseases (Heard, 1994) for example, Rheumatoid arthritis was found to be associated with class II HLA DR4 antigen (Nepom *et al*, 1989), insulin-dependent diabetes mellitus with DR3 and DR4 (Tiwari & Terasaki, 1985). A possible immunological etiology has been suspected in some psychiatric complications and

it has been postulated that autoimmune mechanisms may account for psychosis, depression and anxiety (Denburg *et al*, 1997).

Attempts to determine whether HLA linked genetic markers co-segregate with the disease have been investigated in some of the psychiatric diseases like Schizophrenia and A9 (Mercier *et al*, 1977, McGuffin & Stuart, 1986), A28, CW4 (Ivanyi *et al*, 1978), A1, (McGuffin *et al*, 1981, Lahdelma *et al*, 1998), A2 (Luchins *et al*, 1980), DRB1*04(Wright *et al*, 1998), DRB1*0101 (Sasaki *et al*, 1999), Manic depressive disorders and HLA antigens B7, BW16 (Shapiro *et al*, 1977, Lowell *et al*, 1981).

Human leucocyte antigens (HLA) have been demonstrated as the products of the immune response (Ir) and/ or immune suppression (Is) genes (Benacerraf & McDevitt, 1972; Benacerraf, 1981). HLA molecules are cell surface receptor glycoproteins that bind peptides and present them to T cells (Jorgenson *et al*, 1992; Germain and Margulies, 1993). This interaction causes stimulation of the T cell and activation of the immune response. There are class I and class II HLA molecules with different domain organization (Bjorkman *et al*, 1987a; Brown *et al*, 1993). Polymorphic residues in both class I and class II molecules are clustered within the peptide-binding region and are responsible for different peptide specificities observed for different histocompatibility molecules. These residues control the binding of foreign peptides, and indirectly, the immune response to these peptides.

There are no reports available on the role of HLA antigens as well as immune system dysfunction including autoimmune hypothesis in delusional disorder and should be the subject of intensive research for both the association studies as well as linkage analysis using multiple families. This study, however, undertakes to investigate the HLA class-I profile in the sporadic patients with delusional disorder and also in some of the other conditions like Paranoid schizophrenia, mood congruent delusion and early Alzheimer's disease with psychotic features which show delusion as one of the predominant symptoms.

Though linkage and association studies have been the main strategy to map the position of disease genes followed by investigation of potential candidate genes within these genomic regions, the existence of chromosomal alterations may not be ruled out. Identification of several chromosomal aberrations may be especially important given the unknown pathophysiology. The break points of chromosomal abnormalities occurring in the patients with mental illness may be more direct pointers to relevant gene locus (MacIntyre *et al*, 2003). Chromosomal aberrations have long been studied in an effort to identify susceptibility genes in schizophrenia, bipolar disorders etc. Several studies have reported partial trisomy of 5q11-13 (Bassett *et al*, 1988), specific translocations such as t(18;21) (p11.1;p11.1) (Smith *et al*, 1996), inversions such as inv(9) (p11q13) (Toyota *et al*, 2001), deletions at 22q11.1 (Arimani *et al*, 2001; Liu *et al*, 2002), sex aneuploidies (Kunugi *et al*, 1999) in schizophrenic patients and cytogenetic abnormalities on chromosome 18 in bipolar disorder (Mors *et al*, 1997).

There are also no reports available on the aberrations at the chromosomal level in the patients with delusional disorder. In the present investigation, it has also been aimed at delineating the chromosomal profile by full Karyotyping of individuals with such psychotic conditions, which may unravel whether chromosomal abnormalities co-exist with mental illness and mount to an association.

In the present investigation, two etiological approaches were considered for studying the formation of delusion in delusional disorder as well as in other disorders like paranoid schizophrenia, mood congruent delusion and early Alzheimer's disease with psychotic symptoms. Firstly, HLA association studies were employed to understand the immunogenetical/autoimmune etiology of delusional disorder. Secondly, chromosomal studies were considered to find whether chromosomal alterations (if any) involving major gene(s) locus account for the formation of delusion.