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INFLAMMATION (M LEBOYER, SECTION EDITOR)

# The MHC/HLA Gene Complex in Major Psychiatric Disorders: Emerging Roles and Implications

Monojit Debnath[1] · Michael Berk[2,3] · Marion Leboyer[4] · Ryad Tamouza[4]

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## Abstract

**Purpose of Review** Major psychiatric disorders like schizophrenia and bipolar disorders are etiologically heterogeneous. Gene-environment interactions seemingly constitute the predominant risk mechanism for these conditions. Multiple common and rare genetic variants, sometimes shared, are shown to confer risk to these disorders. Amongst them, the major histocompatibility complex (MHC), known as human leukocyte antigen (HLA) in humans, has emerged as one of the best replicated genetic risk locus of various neuropsychiatric diseases. Herein, we review recent advances regarding MHC's involvement in the immunopathogenetic pathways of major psychiatric disorders and highlight findings that clearly suggest its determining role in the shared aetiology of schizophrenia and bipolar disorder.

**Recent Findings** Converging recent evidence from genome wide association, transcriptomic and imaging genetics studies provide compelling evidence of MHC's involvement in major psychiatric disorders. Some MHC molecules play a cardinal role in neurodevelopment and fine tuning of neuronal plasticity. Dysregulation of MHC expression due to environmental stress or pathological changes could have negative effects on brain and behaviour, including cognition. We highlight possible mechanisms and factors that are crucial in driving MHC-mediated risk of major psychoses.

**Summary** This review further emphasizes the importance of MHC gene complex in the aetiopathology of major psychiatric disorders. Although pleiotropic effects of the MHC locus are well known in various disorders, associations with schizophrenia and bipolar disorder are yet to be definitively validated. This calls for further and systematic research, focusing on the genotype-phenotype correlation in these conditions.

**Keywords** Major histocompatibility complex · Schizophrenia · Bipolar disorder · Immune · Inflammation · Depression · Psychiatry

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✉ Monojit Debnath
monozeet@gmail.com

✉ Ryad Tamouza
tamouza.ryad@gmail.com

[1] Department of Human Genetics, National Institute of Mental Health and Neurosciences, Bangalore, Karnataka, India

[2] School of Medicine, IMPACT Strategic Research Centre, Barwon Health, Deakin University, Geelong, Victoria, Australia

[3] Orygen, The Centre of Excellence in Youth Mental Health, the Department of Psychiatry and the Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia

[4] DHU PePSY, Department of Psychiatry of Mondor Hospital, INSERM, U955, Psychiatrie Translationnelle, Fondation FondaMental, University Paris Est Créteil, Créteil, France

## Introduction

The nexus between the immune system and central nervous system (CNS) has become one of the core issues in understanding the aetiology, course and treatment of neuropsychiatric disorders. Indeed, the separation between these systems is artificial, with notionally immune elements having important signaling and defense roles in response to diverse stressors, apart from classical responses to infection [1]. Some notionally immune components thus perform both the immune and non-immune signaling functions with intriguing regulatory roles on brain development, function and behaviour [2, 3].

The human leukocyte antigen (HLA), an important set of immune molecules in humans, has latterly become the subject of intense research in CNS disorders. The HLA molecules are encoded by several gene loci, located within three sub-regions (class I, class II and class III) of MHC in the short arm of

chromosome 6 (6p21.3–22.1). Both HLA class-I and class-II loci encode the histocompatibility molecules that are known to present peptide antigens to T lymphocytes, while the molecules coded by HLA class-III gene cluster perform both the immune and non-immune functions. The HLA cluster is considered as the most polymorphic and gene-dense region of the human genome [4, 5], encompassing almost 250 genes (spanning a region of > 4 Mb) and more than 17,000 alleles as reported to date (IMGT/HLA Database; http://www.ebi.ac.uk/imgt/hla). Antigen processing and presentation, intercellular recognition and self-versus non-self-discriminations are some of the classical functions of HLA molecules.

Amongst these, HLA-A, HLA-B and HLA-C molecules encoded by the classical HLA class I gene cluster are known to be crucial in the detection and elimination of virus-infected cells, tumor cells and transplanted cells, while their class II counterparts such as HLA-DRB1, HLA-DQB1 and HLA-DPB1, encoded by genes within HLA class-II sub-region, are involved in the initiation and the control of humoral immune responses. Besides these functions, current understanding suggests that many of the genes of the extended MHC super-locus code for molecules that act as ligands, receptors, interacting partners, signaling molecules, cytokines, heat shock proteins and transcription factors. Overall, MHC and MHC-linked molecules are critically involved in determining the susceptibility to or resistance against a myriad of infectious agents [6]. Aberrant expression and inappropriate interactions of MHC/HLA molecules can cause immune dysregulation leading to chronic inflammation and autoimmunity [7]. Although MHC molecules are known for their classical roles in adaptive immunity, their non-classical functions including regulation of development and various physiological processes are becoming increasingly evident [4]. These findings emphasize a series of far more diverse physiological roles of MHC molecules beyond recognition of antigenic peptides from pathogens and self and non-self-recognition.

Although long debated, the functional implications of MHC genes in neuropsychiatric disorders only became apparent with the advent of genome wide association studies (GWAS). The GWAS and the subsequent replication studies in various ethnic populations across geographical boundaries found MHC as one of the strongest risk determinants of various neuropsychiatric disorders including schizophrenia and bipolar disorder [8–10]. In a recent landmark study, the contribution of the MHC region, substantiating implications of the immune system was reconfirmed in schizophrenia [11]. Bipolar disorder, one of the most highly heritable neuropsychiatric disorders with poorly understood aetiology, seems to have shared genetic and immunological underpinnings with schizophrenia [12–14]. Although contradictory, some study findings indicate pleiotropic effects of MHC genes in these disorders [12]. It is interesting to note that many of the MHC-linked autoimmune/inflammatory disorders also co-occur with schizophrenia and bipolar disorder [15, 16]. Taken together, these observations provide suggestive evidence of MHC's involvement in major psychiatric disorders like schizophrenia and bipolar disorder.

Both schizophrenia and bipolar disorder are aetiologically heterogeneous; therefore, significant strides have been made to decipher the role of MHC molecules in neurodevelopment, neuronal plasticity and behavioural aspects of these disorders. Despite these advances, there is a significant lack of information on the implications of MHC genes and their functional interactions with various risk factors/mechanisms of schizophrenia and bipolar disorder. Herein, we have made an extensive effort to garner evidence of MHC's involvement based on both indirect as well as direct evidence in schizophrenia and bipolar disorder. In essence, this updated knowledge will undoubtedly improve our understanding of immune-mediated risks of such disorders.

## MHC Molecules in Major Psychosis: Why Are They Relevant?

### MHC Molecules as Regulator of Neurodevelopment and Neuronal Plasticity

It is now evident that neurons express MHC molecules, the expression of which is dynamically regulated during development [17–19]. Though MHC class I molecules are mainly expressed by neurons, in the healthy brain, low level expression of these molecules have also been reported in non-neuronal cells such as astrocytes and microglia [20–22]. Animal and *in vitro* studies have revealed that MHC class I molecules have a variety of non-immunological functions such as neurodevelopment, neuronal and synaptic plasticity, learning, memory and behaviour [2, 23–25]. Notably, MHC class I molecules display spatio-temporal expression during human hippocampal formation [19] and their expression is also required for the activity-dependent synaptic rearrangements during normal neural development [23, 26]. MHC class I molecules are also implicated in the normal developmental remodelling of glutamatergic synapses [27]. Altered expression of MHC molecules leads to deleterious consequences on developing brain [23, 28, 29]. In a murine model, increased neuronal classical MHC class I expression was shown to affect the establishment of neural circuitry and repair [28]. Additionally, genetically deficient MHC class I mice exhibited incomplete synaptogenesis in the developing visual system and enhanced long-term potentiation (LTP) of synaptic transmission in the hippocampus [23].

The mechanisms whereby MHC class I molecules regulate neural and synaptic functioning as well as plasticity are inadequately known. One of the underlying mechanisms through

which MHC molecules might influence synaptic plasticity is by disrupting N-methyl-D-aspartate receptor (NMDAR)-mediated signaling pathways. Indeed, the MHC class I molecules are critical modulators of NMDAR function and NMDA-induced AMPA receptor trafficking in the mammalian CNS [27]. In the case of MHC class-I-deficient synapses, NMDAR-mediated responses are enhanced, even in the absence of significant changes in NMDAR levels, distribution, or subunit composition. Differences in the levels of MHC molecules affect NMDAR dependent LTP, a critical process in learning and memory. The dual functions of MHC molecules have made them as molecule of choice in understanding the neurobiological trajectories for brain and behaviour. It is noteworthy that the disruption of the expression of MHC molecules and/or variation within the MHC impact neurodevelopment, neuronal plasticity, brain structure and cognition [23, 24, 30]. These observations suggest pathophysiological role of MHC gene complex in CNS disorders. Schizophrenia and bipolar disorder are increasingly considered as neuro-developmentally influenced disorders [31–33]. Understanding the neurodevelopmental underpinnings of these disorders is thus one of the dominant current research paradigms. As MHC molecules play a significant role during neurodevelopment, a pathologic role of MHC molecules in major psychoses seems probable.

## MHC at the Crossroads of Gene-Environment Interactions, Serving as a Bridge Between Infectious Events and Immune Dysfunction in Psychosis

The gene-environmental conundrum of risk of major psychiatric disorders has taken centre stage in decoding the aetiologies of these complex and debilitating illnesses. Environmental factors have important impacts on the onset, course and expression of schizophrenia as well as of bipolar disorder. Several environmental factors such as prenatal infections, hypoxia, or stress as well as obstetric complications during neurodevelopment play a role in these disorders [32]. Among others, infection is a well-known environmental risk factor for these disorders [34]. Prenatal viral, bacterial, or protozoan infections enhance the risk of major psychoses in offspring and have emerged as predominant risk determinants [35, 36]. Gestational exposure to influenza has been shown to lead to a fourfold increase in the risk of bipolar disorder in adult offspring [37]. Findings from animal studies suggest that maternal infection can lead to cognitive deficits in schizophrenia and bipolar disorder [38]. Viral infections such as herpes simplex virus type 1 infection seem to be associated with cognitive impairment in bipolar patients [39]. In a recent study, cytomegalovirus seropositivity was associated with decreased hippocampal volume and verbal memory in bipolar disorder [40]. Interestingly, the effects of such factors seem to be contingent on the genetic architecture of the host [41].

These environmental risk factors interact with the maternal and offspring genomes and lead to increased rates of congenital malformations and behavioural abnormalities in offspring. Maternal genotypes can have profound impact on the in utero microenvironment, affecting prenatal development and potentially disrupting long-term mental health in the offspring. In the whole process, there is a complex interplay between host genetic factors, immune components and infectious agents. Although the number of genes conferring risk to neuropsychiatric diseases like schizophrenia and bipolar disorder has reduced following genome wide scan studies, the genes showing strongest signals were seen to belong to immune function-related pathways [11]. Amongst them, genes residing in the MHC locus have proved to be instrumental in interacting with the environmental triggers and subsequently modulating their effects. Amongst the various host genes, HLAs have proven to be crucial as these molecules play a critical role in mounting the immune response to infection via their ability to process and present microbial peptides to specific immune cell subsets.

Susceptibility to or resistance against particular microbes depends on the inherited set of HLA genes. The association between genomic variations within HLA region and herpes simplex virus, type 1 (HSV-1) and cytomegalovirus (CMV) exposure was reported in schizophrenia [42, 43]. Interestingly, in a German population, schizophrenia patients carrying HLA-A10 genotype were shown to be more prone to develop Chlamydial infection [44]. In another study, multiple SNPs located within the HLA region were found to interact with HSV1 in individuals with schizophrenia [41]. Further to this, a recent seminal study on MHC class III region genes demonstrated the involvement of complement pathway in the risk and pathogenesis of schizophrenia. This study has established a relationship between the effect of genetic variation and expression changes of complement C4 component and excess of synaptic pruning during developmental windows in schizophrenia risk [45••]. Considering this functional link, the complement system has been proposed to be a gateway to gene-environmental interactions in the pathogenesis of schizophrenia [46].

## MHC/HLA as a Connecting Link Between Autoimmunity and Psychosis

The HLA system has appeared as the most predominantly associated gene cluster in common autoimmune diseases such as type 1 diabetes (T1D), rheumatoid arthritis (RA), celiac disease (CD) or systemic lupus erythematosus (SLE) [47]. These conditions have been linked with genes located either in the HLA class-I or HLA class-II regions or both, as evidenced by a recent study on T1D [48]. Interestingly, some of the HLA alleles were seen to confer susceptibility to many autoimmune diseases while others were protective. The basis of such differential association lies in the specificity of

peptide-binding functions of HLA molecules, which in turn determine the nature of immune responses.

Many of such autoimmune/inflammatory disorders co-occur with schizophrenia and bipolar disorder [16, 49]. Interestingly, the pattern of association of autoimmune diseases with schizophrenia and bipolar disorders shows clear differences. In a recent study, the prevalence of hyperthyroidism, rheumatoid arthritis and polymyalgia rheumatic was found to be more frequent, while systemic lupus erythematosus was less associated with bipolar disorder than schizophrenia [50]. Autoimmune diseases in combination with infection also increase the risk of major psychosis [51]. It is noteworthy that exposure to neurotropic infectious organisms can drive inflammation and autoimmunity and thus may influence psychosis development. For example, *Toxoplasma gondii*, a parasitic protozoan has not only been reported as a putative risk factor of schizophrenia and bipolar disorder but also been associated with cognitive deficits [52–54]. The underlying mechanism by which pathogens could induce autoimmunity and alter behaviour has been studied in animal models, as exemplified by the development of anti-NMDAR autoantibodies with consequent altered behaviour in mice infected with *T. gondii* [55].

Though these findings further highlight the emerging role of infection and autoimmunity in major psychiatric disorders, direct evidence pointing to a role of autoimmunity in these disorders has come from studies showing the presence of a wide spectrum of autoantibodies against neuronal surface antigens in the CNS [56]. One of the most important discoveries has been anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis, a synaptic autoimmune disorder where autoantibodies target NMDARs in the brain [57]. Antibodies directed against NMDAR have been reported in both schizophrenia and bipolar disorders and this finding is supported by a meta-analysis [58–60].

It is interesting to note that genes clustered within the MHC region have consistently been associated with most autoimmune diseases like rheumatoid arthritis and multiple sclerosis that co-occur with schizophrenia and bipolar disorder [61, 62]. Importantly, some of the studies involving MHC regions have suggested shared aetiology or genetic pleiotropy between major psychosis and autoimmune disorders. Genomic studies including SNPs within MHC region suggest a relationship with respect to pathogenesis of schizophrenia and rheumatoid arthritis [63]. The presence of the HLA-DRB1*03 allele has been proposed to be a common aetiology for co-morbid Graves' disease, type 2 diabetes and schizophrenia [64]. It is noteworthy that HLA-DRB1*03 allele belongs to the so-called 8.1 ancestral haplotype (HLA-A*01, HLA-B*08, DRB1*03, DQB1*02) which is widely associated with autoimmune disorders and also with altered cytokine production in healthy individuals. The association of "8.1 ancestral haplotype" with schizophrenia, as shown in a recent study, adds further strength towards this connecting link between autoimmunity and psychosis [65••]. Interestingly, a study examining the involvement of genetic regions for pleiotropy between psychiatric and immune disorders demonstrated a significant role of MHC region amongst diseases like schizophrenia and bipolar disorder with rheumatoid arthritis and Crohn's disease [66]. These studies suggest a crucial role of MHC genes in establishing a connecting link between psychoses and autoimmune disorders and further emphasize the role of MHC genes in pathogenetic pathways of psychiatric disorders.

## MHC and Major Psychiatric Disorders: a Review of Evidence

The earliest support implicating HLA as a susceptibility locus for psychoses dates back to the early seventies of the last century [67, 68] and was re-confirmed by several subsequent studies [9, 69]. Following this, there was a surge of data from genome wide association, transcriptomic, epigenetic and imaging genetics studies providing compelling evidence of the involvement of MHC genes in major psychiatric disorders [70–73].

### Genetic Association Studies

The divergent function of the MHC in the development, function and integrity of the brain has made it a key molecule in biological psychiatry. Recent GWAS have provided crucial clues about the implication and functional dichotomy of MHC genes in major psychoses. The MHC region appears to be one of the best replicated risk determinants for schizophrenia by GWAS [12, 74]. Support for the involvement of MHC region in bipolar disorder from GWAS data has also come from a recent study [75]. A combined GWAS study indicates that MHC was the most significantly associated region in schizophrenia while the association was considerably weaker in bipolar disorder [76]. In a GWAS, HLA-C*01:02 was implicated as a risk factor for schizophrenia while DRB1*03:01 and B*08:01 were protective [77], indicating differential functions of HLA molecules in psychiatric disorders also. Despite dozens of GWAS consistently showing association of MHC with schizophrenia, however with variations across ethnic groups, a causal link/mechanism is yet to be established. Excess of homozygosity in the classical MHC region has been shown to confer significant risk to schizophrenia [78]. Although a recent study provides evidence of MHC role in schizophrenia across populations, it however emphasized the involvement of population-specific mechanisms for the MHC region [10].

### Gene Expression Studies

The expression of MHC genes appears altered in many CNS disorders, including major psychoses. HLA-DRB1 showed significant downregulation in both the dorsolateral prefrontal cortex (DLPFC) and peripheral blood cells in schizophrenia patients [79]. In addition to this, significantly upregulated MHC class I mRNA expression in hippocampus and reduced expression in DLPFC were demonstrated in post mortem brain of schizophrenia patients [80, 81]. An expression quantitative trait loci QTL (eQTL) analysis based on meta-analysis of GWAS data also supports involvement of the MHC region in schizophrenia susceptibility [82]. Gene expression studies in bipolar disorder also indicate possible involvement of MHC regions in its pathobiology. A study examining the expression levels of more than 12000 genes in Brodmann's area 46 (BA46) of the post-mortem brain of bipolar patients, observed decreased expression of HLA-DRA [83]. Further to this, reduced expression of HLA-DPA1 and CD74 was reported in hippocampus, amygdala and DLPFC regions in both schizophrenia and bipolar disorder patients [84]. The implications of the altered expression of MHC genes in major psychoses are not very clear. A recent eQTL study indicated that expression of some genes like TRIMP26, RNF5 and HLA-DRB3, located within the MHC region, were shown to be regulated by schizophrenia risk variants [82]. These findings suggest that MHC-linked risk variants might modulate disease status by influencing gene expression.

### Epigenetic Studies

In addition to genetic and environmental risk factors, epigenetic processes play an additional role in mediating susceptibility to psychiatric disorders. Epigenetic changes leading to differential gene expression have been associated with brain development, cognitive processes, learning and memory. Epigenetic studies, though limited in number, indicate significant effects in both schizophrenia and bipolar disorder. In a methylation study of MHC region in healthy individuals, a bimodal pattern with inter-individual and tissue-specific variation of DNA methylation profile in the MHC region was demonstrated [85]. In an epigenome-wide study, DNA methylation differences were observed for CpG sites upstream of HLA complex group 9 (HCG9) gene in post mortem brain tissue of schizophrenia and bipolar patients [86]. HCG9 is located within MHC class I region and is a part of gene family that codes for ligands for natural killer cell receptors [87]. Subsequent to this, a follow-up study on multiple tissues including blood, sperm and brain further demonstrated hypomethylation of HCG9 in bipolar disorder [88]. Lastly, a recent study on HCG9 suggests significant differences in epigenetic modification between schizophrenia and bipolar disorder, implying that this might provide clues in deciphering the heterogeneous causes of psychiatric disorders [89].

### Converging Evidences from Neuroimaging, Psychopathology and Treatment Response Studies

Considering the impact of MHC genes and molecules on core features as well as brain abnormalities, the MHC region has emerged as a crucial genetic determinant for neuropsychiatric disorders. Given the role of MHC proteins in synaptic development and functions, both the presence and key roles of such proteins in brain functioning and structure, especially the hippocampus, seem inevitable. Albeit limited, preliminary data indicate influence of MHC genes on schizophrenia psychopathology including cognitive attributes. One of the SNPs (*rs*6904071) within MHC region was associated with delayed episodic memory [30]. In a recent study, we have shown significant association between HLA-G 14 bp Ins/Ins genotype and third person auditory hallucination [90]. In addition to this, the AA genotype of HLA-G +3187 A > G (rs9380142) SNP was found to be associated with the life time presence of first rank symptom in schizophrenia [90].

Neuroimaging studies have provided further evidence towards the determining effect of MHC gene variants on brain morphometry in patients with schizophrenia. One of the SNPs (*rs*6904071) in MHC region was linked to decreased hippocampal volume [30]. In addition to this, another SNP (*rs*2596532) in the MHC region was associated with cerebral ventricular volume [72]. In a recent study, a genetic variation within the HLA region was shown to influence volume and asymmetry of the human thalamus and the HLA SNPs including rs17194174 linked to these events were found to be associated with schizophrenia susceptibility [91•].

Albeit limited, host genetic factors are shown to influence antipsychotic treatment responses in schizophrenia. A genetic overlap between schizophrenia pathogenesis and mechanism of action of antipsychotic drugs has also been suggested [92]. In a recent study, HLA molecules were found to influence antipsychotic treatment response in schizophrenia. A double amino acid change at 62 and 66 positions of the peptide binding groove of the HLA-A molecule was associated with better response to antipsychotic treatment in schizophrenia patients [93]. In addition to this, several antigen genes in the HLA gene complex were shown to mediate lithium treatment response in schizophrenia and bipolar affective disorders and susceptibility to schizophrenia [94].

## MHC in Major Psychiatric Disorders: Shared Immunopathogenesis Versus Differential Involvement

There is a long-standing debate as to whether schizophrenia and bipolar disorder are separate disease traits or different manifestations of a common or overlapping underlying pathophysiological process. Evidence derived from multiple

genetic studies suggests an overlap in susceptibility genes and diseases associated pathway between schizophrenia and bipolar disorder, implying that the genetic contribution to schizophrenia and bipolar disorder is likely to be shared at least in part [14, 95, 96]. Several studies have also demonstrated epidemiological and environmental similarities, for example, association with infection, early life stress and substance abuse between schizophrenia and bipolar disorder, although these are risks for other psychiatric disorders and for that matter some non-communicable medical disorders [97, 98]. In addition, imaging studies have also pointed similar neuropathological abnormalities in schizophrenia and bipolar disorder, although again there are clear points of difference [99, 100].

Incidentally, immunological studies also suggest similar immune profile in most neuropsychiatric disorders including depression, schizophrenia and bipolar disorder [13]. The association of the MHC locus with schizophrenia is consistently replicated across diverse ethnic populations. On the contrary, the MHC locus is less intensively studied in bipolar disorder and depression [101], and the association so far tested in a limited number of studies is also not very robust. However, preliminary data suggesting MHC as a shared risk locus between schizophrenia and bipolar disorder seem encouraging. In a landmark GWA study, Purcell (2009) proposed the contribution of common polygenic variation to the risk of schizophrenia and bipolar disorder, and the MHC region was suggested to be a key part [102]. Recently, in a combined (bipolar disorder + schizophrenia) GWA study, MHC was one of loci that reached genome wide significance [76]. Furthermore, in a replication study in Japanese populations, two risk variants of schizophrenia located within MHC region (rs7759855 in zinc finger and SCAN domain containing 31 [ZSCAN31] and rs1736913 in HLA-F antisense RNA1 [HLA-F-AS1]) identified by GWAS appeared significant in schizophrenia and bipolar patients [12]. Interestingly, a study examining quantitative trait locus and brain expression of MHC class II genes, HLA-DPA1 indicated shared immune alterations in psychiatric disorders including schizophrenia and bipolar disorder [84]. Whether this truly reflects shared pathophysiological pathways, or the pleomorphic roles of the HLA system in mediating adaptive responses to diverse environmental stressors affecting equally diverse disease endpoints remains to be clarified.

Some data do not support a shared aetiology model of schizophrenia and bipolar disorder. Differences with respect to some environmental factors, neuropathological and other changes are seen in these conditions. For example, obstetric events appear to increase the risk of schizophrenia in multiple studies, while these events do not confer similar risk to bipolar disorder. Neuroimaging findings reveal that schizophrenia is associated with extensive gray matter reductions while generalized gray matter reductions have not consistently been reported in bipolar disorder [103]. In addition to this, neuropsychological traits deficits like lower IQ, executive function and verbal memory are more common in schizophrenia than bipolar disorder [104]. In contrast, those with the highest early academic attainment seem to be at greatest risk for developing bipolar disorder [105]. These observations indicate that differences in neurodevelopment possibly distinguish schizophrenia from bipolar disorder [106].

Data from a recent GWAS suggest significantly different polygenic risk score between bipolar disorder and schizophrenia that essentially discriminates these disorders at the level of molecular genetic variation [76]. In a GWAS in a Swedish population, a significant association of the MHC region was reported only in schizophrenia but not in bipolar disorder [74]. A recent study analysing the genetic pleiotropy amongst schizophrenia, bipolar disorder and multiple sclerosis observed that the same HLA alleles with opposite directionality of effects were involved in schizophrenia and multiple sclerosis; however, such effects were not seen in bipolar disorder and multiple sclerosis [65]. We have recently demonstrated that 14bp insertion/deletion polymorphism of HLA-G, non-classical MHC class I molecules confer protection against bipolar disorder while the same genotype was seen to be associated with the risk of schizophrenia [90, 107]. Some copy number variants in the genomic region that codes immune function-related proteins like immunoglobulins and T cell receptors were found to associated more with schizophrenia than bipolar disorder, suggesting differential involvement of these variants [108]. These findings suggest that immune, especially MHC signals may differentially determine schizophrenia and bipolar disorder susceptibility. The precise reasons for such differences are not properly understood. However, some of the risk variants can act as “modifier genes” for other disorders and may have significant impact on clinical dimension.

## Conclusion

Both schizophrenia and bipolar disorder have been separately linked to chronic low grade inflammation by many studies. Both disorders share increased medical comorbidities with a similar inflammatory foundation such as cardiovascular disease and diabetes. However, it was proposed that inflammation may have a greater association with schizophrenia while stress signaling may have a greater association with bipolar disorder. The combined analysis indicated that significantly greater number of individuals with schizophrenia had high inflammation/stress than bipolar disorder [109], implying that this may partially explain some of the heterogeneity in schizophrenia and bipolar disorder. Taken together, these observations clearly suggest some biological and clinical differences between bipolar disorder and schizophrenia.

The heightened inflammation in schizophrenia and bipolar disorder may be, at least in part, determined by genes encoding immune effectors such as cytokine and MHC-

linked loci in some individuals. The MHC region has been shown to be nominally associated with bipolar disorder and knowledge of the genetic overlap in the MHC locus is also inadequate. However, based on the associations with various risk factors/mechanisms like infection, autoimmunity and inflammation, involvement of MHC genes seems likely in bipolar disorder [110]. Further, stress is more robustly associated with the risk and progression of bipolar disorder and stress modulates the expression of MHC genes. MHC being a complex locus with extensive linkage disequilibrium phenomena, the association with various psychoses may not be straightforward. The risk may involve multiple MHC variants or interaction between MHC as well as other genes. Therefore, an extensive multi-level characterization of the MHC region can lead to a comprehensive understanding of its role in the pathogenetic pathways of bipolar disorder.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no competing interests.

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- •• Of major importance

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