The Human Leukocyte Antigen System in Psychiatry: Where Do We Stand?

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10.1 The HLA System

Since the first description of an association between HLA-B and Hodgkin lymphoma [1], genetic association between the highly polymorphic human leukocyte antigen (HLA) gene cluster and a large variety of immune/inflammatory disorders, ranging from infections to cancer, have consistently been observed [2]. Recently, a strong association between schizophrenia and the major histocompatibility complex (MHC) that hosts the HLA gene cluster was reported by the Psychiatry Genomic Consortium [3], extending the previous observation that dates back to 1975 [4]. Given the prominent role of HLA gene cluster in the regulation of immune-inflammatory processes, a genetically determined dysfunctional HLA system or

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M. Berk et al. (eds.), *Immuno-Psychiatry*, https://doi.org/10.1007/978-3-030-71229-7_10

context-dependent inappropriate/aberrant response of the MHC complex very likely plays a major role in psychiatric settings. Indeed, a large subset of patients with autism, schizophrenia, or bipolar disorders have consistently been associated with immune dysfunction in a background of chronic low-grade inflammation and comorbid autoimmune diseases. The implication of HLA-related immune processes in psychiatric disorders could be related to its role in brain development as they regulate processes like microglia activation and synaptic pruning [5].

The MHC is a 4 Mb region located on the short arm of chromosome 6 (6p21.3-22.1) and is one of the most polymorphic and gene dense regions of the human genome [6]. This region hosts the HLA gene cluster, physically divided into three functionally distinct sub-regions:

1. The HLA-class I region that includes the classical HLA-A, HLA-B, and HLA-C genes as well as the non-classical HLA-E, HLA-F, and HLA-G loci; the former three are involved in antigen presentation to T CD8+ lymphocytes while the latter are mainly implicated in immunomodulatory functions.
2. The HLA class II region encompasses the HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DRB1, HLA-DQB1, HLA-DQB2, HLA-DRA, HLA-DRB1, HLA-DRB2, HLA-DRB3, HLA-DRB4, and HLA-DRB5 genes which are involved in antigen presentation to T CD4+ lymphocytes.
3. The class III region consists of genes involved in inflammatory responses, leukocyte maturation, and some of the genetic components of the complement cascade.

While the encoded molecules of the HLA-A, -B, and -C genes play an essential role in the detection and elimination of virus-infected and tumoral cells through cellular-mediated cytotoxic processes, their HLA class II counterparts modulate humoral immune responses. Both gene sets are highly polymorphic with more than 26,000 alleles reported to date [7], the main function of which is to present self or foreign antigens to the T cell receptors (TCR) on the effector cells.

Since long, the HLA molecules are known to be involved in fine-tuning of the inflammatory processes, and any of their dysfunctions can cause a variety of immuno-pathological events including autoimmunity, a frequent comorbid condition in psychiatric disorders [8]. In recent years, evidences mount to show that the HLA molecules also play a role at a central level. Indeed, they modulate some of the core functions of the central nervous system (CNS) such as neurodevelopment, neuronal/synaptic plasticity, learning memory, and behavior [9]. In fact, neurons influence neuron-neuron interactions and neuro-signaling [10]. Their highest levels of expression were detected in post-synaptic hippocampal neurons [11]. Moreover, the HLA molecules are pivotal for the anatomical integrity of the CNS as exemplified by the enlarged ventricles observed in HLA-class I deficient murine models [12].

Despite evidences for the prominent immune dysfunctions in a significant subset of patients affected by major psychiatric disorders likely via the involvement of HLA molecules in neurodevelopment and neuronal function, further supported by HLA genetic association studies (that provide tags, but not direct proof), difficulties in deciphering the mechanistic link between the so-called classical HLA diversity

(alleles corresponding to antigen-presenting molecules), and these disorders persist essentially due to the complex genetic architecture of the HLA system. Given the recent technological advances, it is now possible to perform a precise and deep characterization of the HLA gene cluster to understand the pathophysiological underpinnings of its diversity in conferring susceptibility to or protection against psychiatric disorders. In this review, we will discuss the current knowledge and prospects of HLA genetics in major psychiatric disorders.

10.2 The Genetic Complexity of the HLA Region

Since the discovery of the HLA system by Jean Dausset [13], the analysis of HLA polymorphism has undergone successive technological improvements over 20 years incorporating gradually DNA-based molecular approaches including the high throughput, and cost-effective next-generation sequencing (NGS) for reliable HLA genotyping, that could cover all the known HLA alleles. Nevertheless, such fine-tuned analysis and understanding of the potential of HLA diversity in genetic studies requires specially trained "histocompatibility expertise."

Despite such advances and available expertise, HLA and disease association studies are still hampered by several limitations including (i) the extreme rate of polymorphism, (ii) the ethno-geographical-dependent distribution of HLA alleles, (iii) disease-dependent variable pertinence of a given HLA allele. For example, the HLA-B27 association is prominently evident for Ankylosing Spondylitis while for other multi-genic and multifactorial disorders, evidence of disease association may not be that apparent because distinct alleles may have shared functions and (iv) further complexity of HLA polymorphism resides in the variability of allele expression [14–16]. Given these aspects, both the candidate gene approach which may ignore the degree of contribution of other interacting loci to the phenotype and the Genome-Wide Association Studies (GWAS) which covers imperfectly the extreme polymorphism of HLA loci (only 60% of the diversity accounted for) limit the power of HLA imputation-based methods.

To overcome these difficulties, one possible approach is to understand the evolution-based shaping of the present day HLA diversity stemming from a limited but manageable number of ancestral haplotypes (AH). Various genetic events, viz., crossing-overs, recombination and point mutations, have participated in that evolution [17, 18]. These AHs were selected under diverse geographic-specific environmental pressure, then conserved, and fully or partially transmitted to generations [18]. Hence, the study of the distribution of AHs in disease association studies has clarified issues raised by the scattered HLA allele association in a given disease and further allowed to predict, by features of commonality of these alleles, potential mechanisms in the disease process. One of the best examples is represented by the HLA-8.1AH, which is recognized as the most associated AH with immune disorders including infections, inflammation and autoimmunity, while being characterized by a steady-state pro-inflammatory background in healthy individuals [17, 19]. Consequently, such properties may explain why the 8.1AH was found to be

protective against pathogens, a status likely due to positive (balancing) selection, however with a price to be paid by its inherent pro-inflammatory properties that could favor risk for chronic inflammation and autoimmunity [20].

Another way to apprehend the HLA functional diversity is to study allele-dependent expression status. Indeed, such diversity reflects the influence of HLA alleles per se. For example, single nucleotide polymorphisms (SNP) categorizing the HLA-DPB1 and HLA-C alleles into high and low expressed variants were shown to be strongly associated, respectively, with graft-versus host disease after hematopoietic stem cell transplantation and HIV infection [21–23].

Immersing further, it is relevant to note that the specific recognition of HLA-Peptide combination is mediated by the per se polymorphic T cell receptors (TCRs) on CD8+ T cells which bind class I molecules and on CD4+ T cells which bind class II molecules. The specificity of HLA-peptide-TCR tripartite interactions is fundamental in enabling the adaptive immune system to mount an efficient and appropriate response against infection while simultaneously being capable of preventing autoimmune processes [24–26].

Different mechanisms have been found in HLA-associated diseases such as atypical HLA-peptide-TCR binding orientation, low-affinity peptide binding that facilitates thymic escape, TCR-mediated stabilization of weak-peptide-HLA-interaction, or presentation of peptides in a different binding register [27], altogether adding a supplementary level of diversity.

Thus, while the GWAS allowed detection, among hundreds of genes, of the MHC/HLA genetic cluster as a pivotal region, specific HLA-dedicated expertise is needed to uncover meaningful functional haplotypes associated with disease subgroups of interest. It may even allow retro-stratification, based on their HLA type, into subgroups of the psychiatric patients who are essentially classified into clinical categories. Indeed, molecular retro-stratification may generate homogeneous subgroups, thus providing better insight into the pathophysiological underpinnings of these complex genetic disorders.

10.3 HLA Diversity in Major Psychiatric Disorders

In this section, we review the previously studied HLA gene candidate association in major psychiatric disorders, especially the risk/protection conferred by them not only on the disease category per se but also on specific sub phenotypes of a given disorder.

10.3.1 Schizophrenia (SZ)

Accumulated evidence from epidemiologic, immunological, genetic, imaging studies strongly argues in favor of the proposition that MHC confers risk to schizophrenia [28]. The first evidence supporting HLA as a schizophrenia susceptibility locus dates back to papers published in the 1970s [4, 29]. Since then, several associations

have been reported in different ethnic populations, for example, the HLA-A9, HLA-A10, HLA-DRB1, HLA-DQB1 alleles [28]. In 2009, three GWAS and meta-analysis of these GWAS published in the same issue of *Nature* revealed strong association between the MHC region and schizophrenia [30–33]. These studies clearly established that the HLA hosting MHC is the strongest region of association with SZ, but without any precision on the location of a potential at risk loci albeit possible involvement of the HLA gene cluster.

Later, GWAS subjected to HLA imputation of classical HLA alleles strikingly revealed a dominant protective effect conferred by some HLA alleles namely, HLA-A*01, B*08, and DRB1*03 (Donnelly et al. 2012), all derived from the so-called 8.1 "autoimmune" ancestral haplotype (8.1AH) (A*01 ~ B*08 ~ DRB1*03 ~ DQB 1*02). This latter is the most associated HLA haplotype with inflammatory processes and autoimmune diseases including Type1 diabetes, celiac disease, Grave's disease, and myasthenia gravis [17].

Further dissection of the MHC/HLA region revealed a major contribution to SZ risk is represented by an elevated expression of the complement C4A molecules. Such raised gene expression is apparently due to increased C4A gene copy number. This fits very well with the plausible (experimentally demonstrated) contribution of C4A to exaggerated C4-dependant neuro-synaptic pruning [34]. The complement system is a set of immune proteins involved not only in first-line defense against pathogens but also as a major contributor of synaptic pruning during neurodevelopment [35]. Recent observations established a link between the C4 locus and classical HLA haplotype diversity in the modulation of risk to develop schizophrenia. Indeed, the protective status conferred by the above-mentioned 8.1 AH haplotype is likely related to the fact that this haplotype naturally lacks the C4 locus. We recently showed that one of the 8.1 AH-derived HLA haplotypes was significantly less frequent in SZ patients with early onset but gradually increased in frequency with the age at the onset of SZ (12.7% after 30 years, Pc = 0.008) [36]. This is probably explained by the fact that carrying the 8.1 AH decreased the C4 expression which leads to less cortical thinning (synaptic pruning), thus delaying the age at the onset of SZ while potentially favoring autoimmune processes due to its pro-inflammatory properties. By contrast, SZ patients not bearing 8.1 AH-derived HLA haplotypes have an active C4 complement and may suffer from a more severe form of the disorder, characterized by early age at onset, associated to increased synaptic pruning leading to cortical thinning. Simultaneously these SZ subjects will be expected to be less prone to develop autoimmune disorders. This is in line with previous observations that carriers of MHC-linked risk variants (*rs*2596532) have larger ventricles [37].

Altogether, these observations highlight the possibility that the HLA genetics will help identifying homogeneous sub-groups of patients with schizophrenia.

10.3.2 Autism Spectrum Disorder (ASD)

Several case-control-based analyses of potential associations between the HLA genetic diversity and autism spectrum disorders (ASD) provide only fragmented data without any functional clues albeit GWAS studies confirmed the ASD risk conferred by the MHC region [38, 39]. Recent HLA haplotype-based analysis brought further precisions by identifying both at risk for and protective HLA haplotypes against ASD [40]. More precisely: (i) the celiac disease-associated HLA-DRB*11 ~ DQB1*07 was found to be associated with the risk to develop ASD and in particular in those with higher scores for social and non-verbal functioning, the two proxies of disease severity, and also interestingly in agreement with the concept of gastro-intestinal involvement in ASD [41, 42], (ii) as in SZ, here again a protective status conferred by the HLA 8.1 AH. To remind, this haplotype lacks the synaptic pruning complement C4 component and confers raised degree of steady-state pro-inflammatory status, and (iii) in a subset of regressive autism, a subset of ASD characterized by immunological features, protection was shown to be conferred by a class II sub-haplotype, namely, HLA-DPA1*01-DPB1*04 [43].

10.3.3 Bipolar Disorder (BD)

Along the report of pharmacogenetic association of HLA antigen with response to lithium [44], ancestral haplotype derivation from observed HLA allelic combinations revealed an association between the 8.1 AH and bipolar disorder (BD), and in particular with BD subgroup having rapid cycling and/or history of suicidal behaviors [45]. Such association likely bears pathophysiological relevance since the pro-inflammatory 8.1 AH favors autoimmune processes. This is in line with the well-known association of BD with comorbid autoimmune conditions [46, 47]. This study also reported associations between disease onset by hypomanic episode or by psychotic symptoms, and HLA 57.1 AH and 7.1 AH, both previously associated with common inflammatory disorders. Consequently, it is likely that in BD, HLA-mediated pro-inflammatory processes are at work.

An interesting observation is the contrasting effect of the 8.1 AH; in SZ and ASD it is protective while in BD it confers increased risk to develop severe forms of BD. Similarly, Andreasen et al. [48] reported that the same HLA allele was shared between SZ and multiple sclerosis (MS), but not between MS and BD. Despite a large overlap of the genetic and some clinical features between BD and SZ, it is possible that their neurodevelopmental differences may be related to temporal differences in HLA-dependent immunogenetic influences [48, 49]. In summary given the relationship between the 8.1 AH and complement C4-mediated synaptic pruning on the one hand and the established shared genetic inheritance between SZ and BD, on the other, it is possible that the 8.1 AH-associated immunogenetic processes contribute to temporal neurodevelopmental specificities between these disorders.

10.4 Other Implications in Psychiatric Settings

10.4.1 HLA and "Auto-Immune Psychosis"

After the initial description by Dalmau in 2008 of "autoimmune limbic encephalitis" [50], the concept of "auto-immune psychosis" emerged [51]. Indeed, in typical psychiatric setting antibodies directed against the NMDAr disrupt the receptor function/signaling through a mechanism different from that occurs in NMDAr limbic encephalitis [52]. Only few studies have addressed the potential relationship between autoimmune psychosis/encephalitis with HLA polymorphism. While the HLA-B*07:02 was found associated with anti-NMDAR encephalitis in German population-groups [53], in Chinese patients such association involve the HLA class II DRB1*16:02 allele [54]. Potential implication of HLA in anti-NMDAR encephalitis was further suspected by the appearance of anti-NMDAr encephalitis a month after pulmonary infection in a 3-year-old boy with chromosomal deletion in HLA-DP cluster [55]. In this case, one could postulate that HLA-dependent altered immune response failed to resolve the infectious event compromising the tolerogenic process with consequent occurrence of autoimmunity.

Other autoantibodies for brain receptor targets have recently been described. In particular, a German study described a strong association between anti-leucine-rich glioma-inactivated1 (LGI1) encephalitis and the HLA-DRB1*07:01, DQA1*02:01 haplotype [53]. Whether and how the HLA system is involved in the autoimmune encephalitis/psychosis remains an open question.

10.4.2 HLA and Treatment Responses to Psychotropic Compounds

The HLA genetic diversity is also implicated in the modulation of treatment responses in psychiatric settings either in terms of adverse drug reaction (ADRs) or treatment efficacy. In the context of ADRs both candidate gene studies and GWAS demonstrated that clozapine-induced agranulocytosis is partly mediated by HLA alleles belonging to both HLA-class I and class II specificities [56]. In terms of efficacy of treatment response, we showed that a double amino-acid change in the HLA-A peptide-binding groove was associated with better response to psychotropic treatment in patients with SZ [57]. A recent large survey showed that treatment response to lithium in BD is strongly influenced by both SZ-linked polygenic score and the MHC/HLA genetic diversity [44]. The latter finding may be in line with the assumption that a major difference in the shared heritability between SZ and BD likely lie in the MHC cluster [48].

10.4.3 HLA and Human Endogenous Retrovirus Elements (HERV)

The human endogenous retroviruses (HERVs) are ancient retroviral-derived fragments integrated in human genome representing 8% of it. A majority of them are not expressed, but some of the undisrupted HERV sequences can be reactivated under certain triggering conditions, such as early infections, with consequent expression of proteins harboring viral properties. Such reactivation is known to be associated with various autoimmune/inflammatory disorders such as multiple sclerosis or rheumatoid arthritis implicating, respectively, two types of HERV family, namely, HERV-W and HERV-K [58].

Given the likely gene and environment framework of HERV reactivation leading possibly to the production of pro-inflammatory and neurotoxic proteins, HERV was the focus of studies in psychiatric disorders revealing associations especially between the HERV-W type and both SZ and BD at protein and/or at DNA/RNA levels further influenced by copy number variations [59, 60]. More recently, one of the HERV members, namely, HERV-K, as a potential risk component for SZ was envisaged. Indeed, Sekar et al. demonstrated that complement C4 long allele harboring the insertion of HERV-K expressed higher levels of C4A molecules with presumable exaggerated synaptic pruning, and cortical thinning [34]. It is thus amazing that different types of the HERV family members can be associated with the same disease and may represent different disease pathways. Finally, within the context of the present review, it is important to remind that the complement C4 is located in the HLA-class III region and that the HLA-8.1 ancestral haplotype is believed to exert a protective effect against SZ risk possibly because it is devoid of C4A gene.

10.4.4 Another Facet of the HLA Diversity: The Non-classical HLA-Class I Loci

Given the extreme diversity of environmental stressors, including infections, evolutionary forces have gradually shaped a highly multigenic and polymorphic biological system to handle these challenges: the immune system. Upon interaction with a trigger, the immune system mounts non-specific pro-inflammatory processes, if necessary, by adaptive cellular processes specific for the triggering event. Such sequence of events could at times be deleterious in case of uncontrolled inflammatory processes. Thus, in parallel, counteracting immune-modulatory genetic strategies have emerged and were positively selected by evolutionary constraints.

One of the best example of such “Dr Jekyll and Mr Hyde” biological system is represented by the HLA-class I classical and non-classical molecules. Within the same HLA-class I region lie (i) the classical HLA-class I-A, -B, and -C loci characterized by an extreme polymorphism essential for their antigen-presentation functions and maintained by balancing selection to cope up with a large variety of environmental pathogens and (ii) the non-classical HLA-E, G, and F genes

remarkable by a very low rate of diversity that reflect more broad properties such as immunomodulation.

Among these latter, the non-classical HLA-G encodes cell surface molecules exerting powerful immunomodulatory functions, first demonstrated essential for the establishment and tolerance between the maternal immune system and the semi-allogeneic fetus at the fetal-placental interface [61]. These characteristics thus opened the way to study various immune-related disorders, especially those possibly starting in early life, in particular during pregnancy when neurodevelopmental windows are critical. In this context, we and others have demonstrated the likely implication of both HLA-G polymorphism and expression in psychiatric disorders including autism, SZ, and BD. In consecutive articles Guerini et al. demonstrated that genetically determined low expression of the tolerogenic HLA-G molecules at the fetal-mother interface, possibly leading to prenatal immune activation, is associated with ASD risk [62–65].

In addition, in SZ, another neuro-developmental psychiatric disorder, even if the potential influence of HLA-G polymorphism and expression was less investigated, it seems that low levels of HLA-G either genetically determined or at circulating level may influence disease onset and phenotype [66–69]. In bipolar disorders two studies performed on patient population of distant ethnicity, i.e., French and south Indian Tamils revealed that contrary to ASD and SZ, genetically determined HLA-G low expression confer protection against the BD which can suggest a possible difference mediated by HLA-G in the ontogeny of such disease [70, 71]. It is hence possible that in BD the protection conferred by low-grade immunomodulation may rather favor more efficient and intense pro-inflammatory anti-infectious response but outside the neurodevelopmental window.

10.5 Future

These findings and the fact that, predating human lineage, HLA-equivalent loci are found in non-vertebrates and still retained accumulating diversity are the indisputable proof of the pivotal role of HLA in human health and disease [72].

Accordingly, the potential involvement of the HLA system in psychiatric disorders makes them eligible to integrate the pool of immune disorders. However, the present knowledge concerning the intricacies between HLA and psychiatry is without any doubt the tip of the iceberg as, for example, the vast majority of the studies was focused on populations of European and Asian, ancestries leaving aside the African continent where the rate of the genetic diversity is the highest among humans. In this context, a recent study of SZ patients from south Africa, namely, the Xhosa population-group, revealed not only that the observed overall genetic diversity was more important than that of non-African populations but importantly uncover mutational events that could be hypothesized to be founder SZ causing variants, latter on submitted to further variations, and genetic dilution after migration out of Africa as we see in present day Europeans and Asians [73]. Studying further such ancient populations from where the human genome was shaped by

various environmental pressures over time including a variety of social and microbial pressures will be pivotal for the understanding of psychiatric disorders.

Hence, we are at the beginning of the of HLA and PSYCHIATRY history.

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