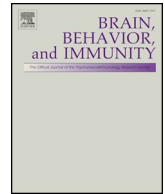




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Understanding the genetic contribution of the human leukocyte antigen system to common major psychiatric disorders in a world pandemic context



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ABSTRACT

The human leukocyte antigen (HLA) is a complex genetic system that encodes proteins which predominantly regulate immune/inflammatory processes. It can be involved in a variety of immuno-inflammatory disorders ranging from infections to autoimmunity and cancers. The HLA system is also suggested to be involved in neurodevelopment and neuroplasticity, especially through microglia regulation and synaptic pruning. Consequently, this highly polymorphic gene region has recently emerged as a major player in the etiology of several major psychiatric disorders, such as schizophrenia, autism spectrum disorder and bipolar disorder and with less evidence for major depressive disorders and attention deficit hyperactivity disorder. We thus review here the role of HLA genes in particular subgroups of psychiatric disorders and foresee their potential implication in future research. In particular, given the prominent role that the HLA system plays in the regulation of viral infection, this review is particularly timely in the context of the Covid-19 pandemic.

1. Introduction

Since the first description of an association between human leukocyte antigen (HLA)-B and Hodgkin lymphoma (Amiel, 1967) the highly polymorphic HLA gene cluster has been linked to a wide array of immune/inflammatory disorders, including now psychiatric disorders (Debnath et al., 2018). Recently, a strong association between schizophrenia and the Major Histocompatibility Complex (MHC), which hosts the HLA gene cluster, was reported by the Psychiatry Genomic Consortium (Ripke et al., 2014). This finding extends the long-standing observation of links between HLA and psychiatric disorders (Eberhard et al., 1975). Given the prominent role of HLA gene cluster in the regulation of immuno-inflammatory processes, as well as in neurodevelopment and neuroplasticity, through microglia regulation and synaptic pruning (Mokhtari and Lachman, 2016), it was expected that HLA alleles would play a major role in the pathophysiology of psychiatric disorders. Convergent results now show that this is particularly relevant for Autism Spectrum Disorders (ASD), schizophrenia or bipolar disorders, all known to be associated with chronic low-grade inflammation and comorbid autoimmune diseases (Pape et al., 2019). The HLA system is expected to influence both the early development and the course of psychiatric disorders.

The MHC is a four megabases region located on the short arm of the

chromosome 6 (6p21.3–22.1) and is one of the most polymorphic and gene dense regions of the human genome (Trowsdale and Knight, 2013). This region hosts the HLA gene cluster, which is physically divided into three functionally distinct sub-regions:

- i) the HLA-class I region 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 three classical HLA genes act to regulate antigen presentation to CD8+ T-lymphocytes, whilst the non-classical genes are mainly implicated in different immunomodulatory functions;
- ii) the HLA class II region encompasses the HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, HLA-DRB1, HLA-DRB3, HLA-DRB4 and HLA-DRB5 genes which are involved in antigen presentation to CD4+ T-lymphocytes; and
- iii) the class III region which encompasses gene loci involved in inflammatory responses, leukocyte maturation and in 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 cells and tumoral cells through cell-mediated cytotoxic processes, their HLA class II counterparts modulate humoral immune responses (Klein and Sato, 2000). Both gene sets are highly polymorphic with more than 26,000

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alleles reported to date, although each locus has only around 10 to 20 dominant alleles (IMGT/HLA Database, 2020), the main function of which is to present self or foreign antigens to T cell receptors (TCR) on effector cells.

The HLA molecules have long been appreciated to be involved in fine tuning of inflammatory processes as well as in the development of immuno-mediated pathophysiological processes including autoimmunity, a frequent comorbidity of psychiatric disorders (Khandaker et al., 2017). Recent data also show that HLA molecules modulate the development and function of the Central Nervous System (CNS), including core functions such as neuronal/synaptic plasticity, learning, memory and behavior (Boulanger, 2009), as well as more direct modulation of neuron-neuron interactions and neuro-signaling (Sterner et al., 2012). The highest HLA expression levels are detected in post-synaptic hippocampal neurons (Goddard et al., 2007). 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 (Huh et al., 2000).

Despite evidence of prominent immune implication in a significant subset of major psychiatric disorder patients such as schizophrenia, bipolar disorder or depression (Khandaker et al., 2017) or autism spectrum disorder (Meltzer and Van de Water, 2017), deciphering the mechanistic link between the HLA system and these disorders was difficult, primarily because of the complex genetic architecture of the HLA system. Recent technological advances now allow a more precise characterization of the HLA gene cluster and the identification of its etiological or protective role in psychiatric disorders. It thus timely to review the role of HLA genetics in major psychiatric disorders and to describe future research directions including the regulation of the impact of viral infections on aetiology and course of psychiatric conditions in the context of a world pandemic.

2. HLA complexity and diversity

Since the discovery of the HLA system by Jean Dausset (Dausset and Brecy, 1957), the analysis of HLA polymorphisms has undergone successive technological improvements over 20 years, leading to the gradual incorporation of DNA-based molecular approaches, including the high throughput and cost-effective Next Generation Sequencing (NGS) which provides reliable and extensive HLA genotyping. However, fine-tuned analysis and understanding of the HLA diversity in genetic studies still requires specialized training either in terms of histocompatibility testing or imputation analysis.

Despite such advances and expertise, HLA investigation in disease association studies still faces a number of challenges, including: (i) the extreme rate of polymorphism; (ii) the ethno-geographical-dependent distribution of HLA alleles; (iii) the disease-dependent variable pertinence of a given HLA allele e.g. 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 as distinct alleles may have shared functions; and (iv) the variability of allele expression (Ramsuran et al., 2018; D'Antonio et al., 2019; Aguiar et al., 2019). It thus should be stressed that while the candidate gene approach, which may ignore the degree of contribution of other interacting loci to the phenotype, is not a satisfactory way to fully underscore the HLA genetic diversity, Genome-Wide Association Studies (GWAS) followed by HLA imputation-based methods, at least in Caucasian and Asians, may provide clues towards understanding the HLA genetic contribution to psychiatric disorders. Unfortunately, at the present time, only few post-GWAS HLA imputation-based studies have been undertaken.

An approach to overcome these difficulties is to understand the evolution-based shaping of present-day HLA diversity as 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 (Price et al., 1999;

Dawkins et al., 1999). These AHs were selected under diverse geographic-specific environmental pressures, then conserved and fully or partially transmitted to successive generations (Dawkins et al., 1999). Consequently, study of AH distribution in disease association studies have clarified why apparently distinct HLA alleles exhibit association with a given disorder. Indeed, these alleles, linked to AHs, allow to stratify the patients into an immuno-inflammatory subset for AH associated with steady state inflammation even among healthy subjects. For example, HLA-8.1AH is the most associated AH with immune-related disorders, including infections and autoimmunity, whilst also being characterized by a steady state pro-inflammatory background in healthy individuals (Price et al., 1999; Gambino et al., 2018). Such properties may explain why the 8.1AH can be protective against pathogens and therefore positively selected, while also having a negative health impact due to the association of chronic pro-inflammatory status with high risk for autoimmunity (Crespi and Go, 2015).

HLA functional diversity can also be investigated via allele-dependent expression status which reflects the influence of HLA alleles *per se*. For example, single nucleotide polymorphisms (SNP) categorize the HLA-DPB1 and HLA-C alleles into highly and lowly expressed variants (Petersdorf et al., 2015; Thomas et al., 2009; Apps et al., 2013). HLA-peptide combination is mediated by the polymorphic 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, whilst simultaneously preventing auto-immune processes (Creusot et al., 2002; Woodsworth, Castellarin and Holt, 2013; Morris and Allen, 2012). Different mechanisms may underpin HLA associated diseases, including: 1) atypical HLA-peptide-TCR binding orientation; 2) low affinity peptide binding that facilitates thymic escape; 3) TCR-mediated stabilization of weak-peptide-HLA-interaction; and 4) presentation of peptides in a different binding register. Other mechanisms that may generate autoreactive T cells are driven by epitope variation, including molecular mimicry (Yin, Li and Mariuzza, 2012).

Thus, while GWAS identified the MHC/HLA genetic cluster as being a pivotal region, specific HLA-dedicated expertise started to uncover meaningful functional haplotypes associated with specific psychiatric entities. HLA analysis in psychiatric disorders will help not only to identify homogeneous subgroups, HLA based, but also to decipher their underlying mechanisms.

3. HLA diversity and common major psychiatric disorders

Recent GWAS and haplotype-based studies have revived and strengthened interest in the roles of the immune system in psychiatric disorders. This section reviews investigations of HLA gene candidate association in schizophrenia, bipolar disorders and Autism Spectrum Disorders, focusing on the risk/protection that HLA alleles/haplotypes may confer on specific sub-groups.

3.1. Schizophrenia

Accumulating evidence from epidemiological, immunological, genetic, and imaging studies strongly indicate a role for MHC in schizophrenia risk (Debnath et al., 2018), dating from the 1970's (Eberhard et al., 1975; Cazzullo and Smeraldi, 1979). Previous work has shown a number of associations across different ethnic populations, including the HLA-A9, HLA-A10, HLA-DRB1, and HLA-DQB1 alleles (Debnath et al., 2018). In 2009, three GWAS and a meta-analysis of these GWAS were published in Nature, revealing a strong association between the MHC region and schizophrenia, although without any precision as to the specific location (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009). Subsequent studies using GWAS subjected to HLA imputation of classical HLA alleles, revealed a marked dominant protective effect conferred by HLA-A*01, B*08 and DRB1*03 (Donnelly et al., 2012). These

alleles are all derived from the so-called 8.1 “autoimmune” ancestral haplotype (8.1AH) (A*01 ~ B*08 ~ Cw*07 ~ DRB1*03 ~ DQB1*02). The 8.1 AH is the most associated HLA haplotype with inflammatory processes and autoimmune diseases, including type1 diabetes, celiac disease, Grave’s disease, and myasthenia gravis (Price et al., 1999), a situation that may appear at first sight contra-intuitive according to the protecting effect conferred against schizophrenia risk.

A deeper exploration of the HLA region further revealed a major contribution to schizophrenia risk mediated by increased complement C4A gene copy number with consequent C4-dependant neuro-synaptic pruning (Sekar et al., 2016). The complement system is not only in first-line defense against pathogens but also a major contributor to synaptic pruning during neurodevelopment (Druart and Le Magueresse, 2019). However, it is important to signal that the Sekar’s study not only suffer from absence of replication especially in ethnically-distant population groups such as Asians (Lam et al., 2019) but also from the complexity of long-range imputation statistics and absence of direct inference of C4 haplotypes along their respective expression status. It is evident that the full sequencing of the C4 cluster may help genetic dissection of this complex region. Besides these considerations, recent investigations have established a link between the C4 locus and classical HLA haplotype diversity in the modulation of schizophrenia risk. Indeed, the protective status conferred by the 8.1AH haplotype plausibly arises from this haplotype naturally lacks the C4 locus. We recently showed that a 8.1 AH-derived HLA haplotype was significantly less frequent in schizophrenia patients with early onset, whilst gradually increasing in frequency with the age of schizophrenia onset (Tamouza et al., 2020a, b). This would suggest that 8.1 AH, via decreased C4 expression, leads to less synaptic pruning and cortical thinning, thereby delaying the age of schizophrenia onset, whilst concurrently potentially favoring heightened autoimmune processes due to its pro-inflammatory properties. In contrast, we hypothesized that schizophrenia 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, increased synaptic pruning and cortical thinning, whilst being less prone to develop autoimmune disorders. This is in line with previous observations that carriers of MHC-linked risk variants (rs2596532) have larger ventricles (Agartz et al., 2011).

Even if it is assumed that the above-mentioned mechanisms, if proven, would be not the unique disease process, overall HLA data may highlight the possibility that HLA genetics will help to identify homogeneous sub-groups of schizophrenia patients.

3.2. Autism spectrum disorder

Although GWAS clearly indicate that the MHC region confer an increased Autism Spectrum Disorder risk, candidate gene analysis of potential associations between HLA genetic diversity and Autism Spectrum Disorder have provided only fragmented data without any strong functional associations (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Wang et al., 2013). However, recent HLA haplotype-based analysis have identified both risk and protective HLA haplotypes regarding autism (Bennabi et al., 2018): (i) the celiac disease-associated HLA-DRB*11 ~ DQB1*07 haplotype is associated with autism risk, especially in patients with high scores for social and non-verbal functioning, the two proxies of disease severity, as well as being parsimonious with the role of gastro-intestinal alterations in patients with autism (Vuong and Hsiao, 2017; Hughes et al., 2018), (ii) as in schizophrenia, a protective status is conferred by the HLA 8.1 AH, and as such expected to be associated with decreased complement C4 and synaptic pruning especially as cortical thickness abnormalities were amply documented in autism (Braden and Riecken, 2019; Levman et al., 2019; Pereira et al., 2018) along with an MRI-demonstrated decrease of cortical thickness (Laidi et al., 2019), but raised levels of steady state pro-inflammatory activity; and iii) in a subset of patients with regressive autism, a subgroup known to have particularly pronounced

immune dysfunctions, protection was afforded by a class II sub-haplotype, namely HLA-DPA1*01 ~ DPB1*04 (Tamouza et al., 2020a, b). Of interest another HLA-DPB1 allele, namely DPB1*15:01 recently demonstrated to confers protection against intellectual disability and autism in a large survey from northern Europe (Nudel et al., 2019). However, it is worthy to keep in mind that recent very large GWAS failed to detect MHC-linked signals (Grove et al., 2019), a finding possibly reflecting disease heterogeneity and/or scarcity of post-GWAS HLA imputation studies in ASD.

Overall, these data give some indication of the role that HLA haplotypes may play in the abnormal neurodevelopment as well as in the systemic and gastro-intestinal inflammatory processes at work in Autism.

3.3. Bipolar disorders

We recently reported an association between an 8.1 AH derived HLA haplotype and bipolar disorder, specifically in patients with severe forms of the disorder defined by rapid cycling and/or personal history of suicidal behaviors (Tamouza et al., 2018). This association might also underline the well-known high frequency of auto-immune disorders in bipolar patients, including elevated levels of anti-thyroid or other organ-specific autoantibodies (Padmos et al., 2004; Jeppesen and Benros, 2019). We also found that two haplotypes namely HLA 57.1 AH and 7.1 AH were specifically associated with bipolar disorder having first episodes defined by hypomanic episode or psychotic symptoms. This is of importance as these two haplotypes are also linked to common inflammatory conditions, and might thus contribute to the pro-inflammatory processes observed in bipolar disorder. Although these data, observed in phenotypically well-defined subgroups of patients, may constitute interesting tags of the MHC implication in BD, here again, a recent GWAS did not allowed to uncover any MHC-derived signal (Stahl et al., 2019).

The contrasting effect of 8.1 AH, being protective in schizophrenia and autism but conferring severity in bipolar disorder, is interesting. Andreassen et al. (2015) reported that the same HLA allele was shared between schizophrenia and multiple sclerosis (MS), but not between MS and BD. Despite the large overlaps of genetic as well as clinical features in bipolar disorder and schizophrenia, these data are suggestive of temporal differences in HLA-dependent immunogenetic influences on neurodevelopmental processes (Andreassen et al., 2015; Bergen et al., 2012). These two psychiatric disorders may be differentiated by opposite effects mediated by the 8.1 AH possibly through specific complement C4-mediated synaptic pruning processes. The role of HLA-driven changes to the temporal neurodevelopmental specificities of bipolar disorder and schizophrenia will be important to clarify in future research.

3.4. Other common psychiatric disorders

Beside schizophrenia, autism spectrum disorders and bipolar disorders, major depressive disorders and attention deficit hyperactivity disorders are also major, common and frequent psychiatric conditions but suffer from scarcity of published/robust data implicating HLA genetics. Concerning major depressive disorders results from number of small studies, using broad serological typing (now considered as obsolete), generated inconsistent data. Besides, a very recent GWAS failed to identify any HLA-related signals in MDD (Glanville et al., 2020). This is also true for ADHD where few previous studies indicated potential association with the MHC non-classical complement C4b, but again, a recent large GWAS did not allow to detect any association between ADHD and HLA (Nudel et al., 2019).

Such observations in disorders admitted to be underpinned by immuno-inflammatory processes, either for MDD (Miller et al., 2009; Medina-Rodriguez et al., 2018) or ADHD (Dunn et al., 2019), may reflect the extreme heterogeneity of psychiatric disorders in a highly

polygenic context where the MHC/HLA contribution may thus be difficult to unmask.

Indeed, given the pivotal role of the HLA system in almost all immune processes and now the well-documented immune implication in psychiatric settings, at least for subsets of patients, the absence of MHC/HLA-tagging signals could be likely related to the heterogeneity of psychiatric disorders, to effect sizes given the high rate of polymorphism of the HLA cluster and to the scarcity of post-GWAS HLA imputation studies

4. HLA alleles and “autoimmune psychosis”

Following the initial description of “autoimmune limbic encephalitis” by Dalmau in 2008 (Dalmau et al., 2008), the concept of “auto-immune psychosis” emerged (Ellul et al., 2017; Pollak et al., 2020). In patients having pure psychiatric presentations, antibodies directed against the N-methyl-d-aspartate receptor (NMDA-R) have been shown to disrupt receptor function/signaling through a mechanism distinct from that occurring in NMDA-R limbic encephalitis (Jézéquel et al., 2017). Recent, but unfortunately few studies have addressed the relationship between autoimmune encephalitis and HLA polymorphisms. The HLA-B*07:02 was found to be associated with anti-NMDA-R encephalitis in German population-groups (Mueller et al., 2018), whilst among Chinese patients this association involved the HLA class II DRB1*16:02 allele (Shu et al., 2019; Chen et al., 2020). HLA is also thought to be implicated in anti-NMDA-R encephalitis occurring one month after a pulmonary infection in a 3-year-old boy with a chromosomal deletion in the HLA-DP cluster (Verhelst et al., 2011). In this case, one could postulate that HLA-dependent altered immune response failed to resolve the infectious event compromising the tolerogenic process and activating autoimmune processes. Nevertheless, the potential genetic association between HLA polymorphism and anti-NMDA-R encephalitis awaits confirmation. More consistently, other auto-antibodies 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 (Mueller et al., 2018). In addition, another study, besides replicating the above-mentioned HLA association with LGI1-mediated encephalitis, described an additional association between the HLA-DRB1*11:01 ~ DQA1*05:01 ~ DQB1*03:01 haplotype and anti-contactin-associated protein-2 (CASPR2) encephalitis (Binks et al., 2018). Further, it has been recently suggested that the genetics of the HLA cluster may help to stratify anti-CASPR2-related clinical subtypes (Muñiz-Castrillo et al., 2020; Binks and Irani, 2020). Whether and how the HLA system is involved in the autoimmune encephalitis/psychosis remains an open question and will be an important avenue for future research, especially given the heightened levels of autoantibodies against the NMDA-R in 20% of patients diagnosed with schizophrenia (Jézéquel et al., 2017).

5. HLA and treatment responses

HLA genetic diversity is also implicated in the modulation of treatment responses in psychiatric conditions, including in the regulation of adverse drug reaction (ADRs) and treatment efficacy. Both candidate gene studies and GWAS have shown that clozapine-induced agranulocytosis is partly mediated by class I and II HLA alleles (Numataa et al., 2018). In a study of treatment response to antipsychotic, we showed that a double amino-acid change in the HLA-A peptide-binding groove was associated with a better response to treatment with Risperidone in patients with schizophrenia (Le Clerc et al., 2015). A recent large survey showed that treatment response to lithium in BD is strongly influenced by both schizophrenia-linked polygenic score and the MHC/HLA genetic diversity (Amare et al., 2018). In the latter context the authors identified signals related to antigen presentation pathway (HLA-DM region), the main function of HLA molecules. Such observation could be in line with the notion that differences in the heritability between schizophrenia and BD may lie in the MHC cluster (Andreassen et al., 2015).

6. HLA, HERV and schizophrenia

The Human Endogenous Retroviruses (HERVs) are ancient retroviral-derived fragments integrated into the human genome, representing 8% of its totality. The majority of HERVs are not expressed, although some of the undisrupted HERV sequences can be reactivated under certain triggering conditions, including early infections, with consequent expression of proteins harboring viral properties. Such reactivation is relevant to the etiology of various autoimmune/inflammatory disorders, including multiple sclerosis and rheumatoid arthritis, where two types of HERV family, namely HERV-W and HERV-K, are respectively implicated (Greenig, 2019). Given the role of gene and environment interactions in HERV reactivation, and its capacity to induce pro-inflammatory and neurotoxic proteins, HERV has been the focus of studies in psychiatric disorders. We and others have found associations between the HERV-W type and both schizophrenia and BD at protein and/or at DNA/RNA levels, further influenced by copy number variations (Perron et al., 2012; Leboyer et al., 2013). Recent data show HERV-K to be a potential risk component for schizophrenia. It is worth mentioning that Sekar et al demonstrated that complement C4 long allele, harboring insertion of HERV-K, expressed higher levels of C4A molecules, thereby increasing the risk of exaggerated synaptic pruning, cortical thinning and early onset (Sekar et al., 2016). This is an interesting area of investigation as clearly different HERV family members can be associated with the same disease, although with different disease pathways.

7. Non-classical HLA and psychiatry

All living organisms have to constantly learnt to deal with environmental insults in order to survive, including various types of pathogens. Given the extreme diversity of these environmental insults, evolutionary forces have gradually shaped powerful biological systems characterized by a large number of genes with high allelic diversity adapted to handle these challenges, *viz* the different wings of the immune system. Upon interaction with a given trigger, the immune system first mounts non-specific pro-inflammatory processes and then, if necessary, more adaptive cellular processes directed against the triggering event. In parallel with the shaping of the immune response, counteracting immune-modulatory genetic strategies, limiting uncontrolled inflammation, have emerged and have been positively selected by evolutionary constraints.

The HLA-class I classical and non-classical molecules represent one of the best examples of such Janus-faced system. Indeed, 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 (heterozygote advantage) to cope up with a large variety of environmental pathogens and (ii) the non-classical HLA-E, G and F genes, remarkable due to a very low rate of diversity that reflect broader properties, such as immunomodulation.

Among the latter, the non-classical HLA-G encode cell surface molecules exerting powerful immunomodulatory functions, demonstrated to be essential for the establishment and tolerance between the maternal immune system and the semi-allogeneic fetus at the fetal-placental interface (Ferreira et al., 2017). These characteristics drove the study of various immune-related disorders, especially in pregnancy and early post-natal life, as the powerful effects of HLA-G have major impact during crucial neurodevelopmental windows. We and others have demonstrated the association of both HLA-G polymorphism and/or expression in psychiatric disorders including Autism Spectrum Disorders, schizophrenia and bipolar disorder, within an early developmental context. In consecutive articles, Guerini et al., demonstrated that genetically determined low expression of the tolerogenic HLA-G molecules at the fetal-mother interface, possibly led to prenatal immune activation, is associated with ASD risk (Guerini et al., 2015, 2018a,

2018b, 2019). Schizophrenia is also widely believed to be a neuro-developmental psychiatric disorder, although the role of HLA-G polymorphism and expression has been less investigated. However, available data does indicate that low levels of HLA-G, either circulating or genetically determined, may influence disease onset and phenotype (Rajasekaran et al., 2015, 2016a,b; Shivakumar et al., 2018). In two studies performed on bipolar disorder patient populations of distant ethnicity, namely French and south Indian Tamils, data shows that in contrast to autism and schizophrenia, genetically determined HLA-G low expression confers protection against bipolar disorder, suggesting the role of distinct HLA-G effects in the aetiology of these disorders (Debnath et al., 2013; Sundaresh et al., 2018). It is hence possible that in bipolar disorder, the protection conferred by low grade immunomodulation may favor a more efficient and intense pro-inflammatory, anti-infectious response, but outside the neurodevelopmental window.

8. HLA and viral infections, including Covid-19

At the time of writing this review, the Covid-19 pandemic was devastating the health and economies of countries worldwide, highlighting the powerful influence that viruses have had and have on animal and plant life over the course of evolution. There is an increasing appreciation of the role of viruses in wide array of diverse medical conditions, including cancers and neurodegenerative conditions, but also in psychiatric conditions (Avramopoulos et al., 2015). Direct impact of viruses on the central nervous system was illustrated in contemporary history by clinical situations in neuro-psychiatric settings after pandemics such as the Spanish flu or the more recent H1N1. While an increased frequency of psychosis (Yudofsky, 2009) and encephalitis lethargica/parkinsonism (Limphaibool et al., 2019; Hoffman and Vilensky, 2017) were observed following the Spanish flu pandemic, a raised rate of narcolepsy was described after H1N1 pandemic likely triggered by the Pandemrix® vaccination (Sarkanen et al., 2018). More recently, comforting early reported deleterious effects of viral infections on CNS, large nationwide studies demonstrated association between maternal viral infectious events during the first trimester and subsequent psychiatric diseases in the offspring (Brown and Derkits, 2010). It is worth reminding here again, as for the vast majority of viral infections, that the HLA system is pivotal in the anti-infectious immune response processes, very likely in the present pandemics too. In the current context, it is important to note that variations in HLA/MHC act to regulate viral infections, including influenza infection in humans (Dutta et al., 2018). Influenza and other infections prenatally can also increase risk of schizophrenia and autism spectrum disorders in the offspring, suggesting that HLA/MHC genetic variations may interact with prenatal infection in the etiology of major psychiatric disorders, although complicated by the immune-suppression that occurs in pregnancy (Shah et al., 2019).

The devastating influence of the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 virus that has led to the Covid-19 pandemic raises the question as to the role of HLA/MHC in the regulation of the inflammatory processes which is an integral aspect of SARS-CoV-2 infection, usually referred to as the 'cytokine storm'. This will also be important to investigate in the distinct sub-groups of major psychiatric disorder patients carrying particular variations of their HLA alleles.

Although the literature concerning the immunogenetic aspects of previous pandemic waves of SARS or MERS-Cov (middle east respiratory syndrome) is relatively low, data do show that HLA plays a major role in viral infection regulation, and this is also relevant to analyze risk/protection of major psychiatric disorders in the pandemic context. The available data on HLA diversity show associations with HLA-class II alleles, notably the HLA-DRB1*03 variant in two studies from Taiwan (Wang et al., 2011), and Hong Kong (Ng et al., 2004). As noted, this variant belongs to the HLA 8.1 AH in European or in Asian geographical areas. As compared to the canonical HLA 8.1 AH, their

equivalent in Asia, share all the HLA-DRB1*03 allele and can differ regarding the diversity of the other loci. For example, Indians share with the European 8.1 AH, HLA-B*0801, HLA-DRB1*0301 and HLA-DQB1*02 alleles and differs for HLA-Cw*07 and HLA-DRB3 while Chinese share the DRB1*03 and differs by HLA-B58 (Witt et al., 2002). This observation strongly suggests that DRB1*03 has survived under distinct environmental pressures, possibly as a consequence of the functional weight of such conserved haplotypes. Concerning the present pandemic, nothing is presently known concerning the relationship between HLA genetic diversity and SARS-CoV-2 infection except an *in silico* prediction of viral peptide-MHC class I binding affinity for SARS-CoV-2-derived peptides across a number of HLA-A, -B and C genotypes (Nguyen et al., 2020). As acknowledged by the authors, among many other limitations, peptide-MHC binding affinity cannot be alone a predictor of subsequent T-cell responses.

The psychiatric inpatient population-group is at high risk for any epidemic threat. Increased vulnerability not only arises due their psychiatric condition, associated stressors, and confinement with other patients but also from their comorbid somatic disorders including, cardiovascular disorders, metabolic syndrome, diabetes, autoimmune disorders and respiratory tract dysfunctions. All of these common comorbidities are risk factors for severe Covid-19 infection and almost all are linked to HLA genetic diversity (Trowsdale and Knight, 2013). As with influenza viruses, the most deleterious event in Covid-19 does not seem to be the infectious agent *per se*, but the overwhelmed reactive inflammation arising from the 'cytokine storm'. Future research will have to determine whether variations in HLA genetic diversity modulate the susceptibility to severe infection and fatality in major psychiatric disorders subjected to the SARS-CoV-2 pandemic.

9. Future research directions

The data reviewed above and the long evolutionary history of HLA-equivalent loci, including in non-vertebrates (protochordate), highlight the important role of HLA in coordinating the immune responses in human health and disease (De Tomaso et al., 2005). Clearly, present knowledge of the intimate role of HLA diversity in psychiatric conditions requires further investigation, especially in different ethnic populations, given that the vast majority of the studies have been performed in populations of European and Asian ancestries. Undoubtedly further investigation is required in people from Africa, given that the rate of the genetic diversity is the highest in Africans amongst all human ethnic groups. In this context, a recent study of a sample 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 relevant to the origins of schizophrenia (Gulsuner et al., 2020). Future studies of long-established 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.

10. Conclusion

As highlighted in this review HLA diversity is integral to variations in the immune responses that form biological underpinnings, among others and likely in subsets of patients, of a wide array of psychiatric presentations as well as to how we, and other animals, have interacted with viruses over the course of evolution.

11. Search strategy and selection criteria

Relevant papers were identified through PubMed searches of articles published in English from Jan 1, 1955, up to April 30, 2020, using the following search terms (alone or in combination): "HLA, MHC, psychiatry, polymorphism, immunogenetics, immuno-psychiatry, Covid". Additional

studies were identified from our own files. The final reference list was generated on the basis of their relevance to the topics covered in this review.

12. Funding sources

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Author contributions

RT: designed the search strategy and performed it, wrote the manuscript and take the primary responsibility to submit the review. RK and ML: participated to the search strategy, critically reviewed and edited the manuscript. All authors approved the final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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