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The immunogenetics of neurological disease

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Summary

Genes encoding antigen-presenting molecules within the human major histocompatibility complex (MHC) account for the highest component of genetic risk for many neurological diseases, such as multiple sclerosis, neuromyelitis optica, Parkinson's disease, Alzheimer's disease, schizophrenia, myasthenia gravis and amyotrophic lateral sclerosis. Myriad genetic, immunological and environmental factors may contribute to an individual's susceptibility to neurological disease. Here, we review and discuss the decades long research on the influence of genetic variation at the *MHC* locus and the role of immunogenetic killer cell immunoglobulin-like receptor (*KIR*) loci in neurological diseases, including multiple sclerosis, neuromyelitis optica, Parkinson's disease, Alzheimer's disease, schizophrenia, myasthenia gravis and amyotrophic lateral sclerosis. The findings of immunogenetic association studies are consistent with a polygenic model of inheritance in the heterogeneous and multifactorial nature of complex traits in various neurological diseases. Future investigation is highly recommended to evaluate both coding and non-coding variation in immunogenetic loci using high-throughput high-resolution next-generation sequencing technologies in diverse ethnic groups to fully appreciate their role in neurological diseases.

Keywords: immunogenetics; neurological disease.

Introduction

Rare or common neurological diseases are associated with an impaired central nervous system (CNS) and/or peripheral nervous system (PNS). Neurological disease impacts approximately 1 billion individuals around the world, comprising individuals of all age groups and races, in diverse geographical locations and with diverse socio-economic status.[1] Together, neurological diseases represent 7·1% of the total global burden of disease, evaluated in disability-adjusted life years, across all causes and ages.[2]

Despite significant progress in the management of many neurological diseases, we are still lacking complete and coherent models of pathogenesis, and as a result the repertoire of available therapies is imperfect. Recent advances in genomic sciences have set in place the foundation for understanding and decoding the rules of inheritable risk for chronic neurological diseases, which may translate into improved prognosis of outcomes and new therapeutic options. The genetic signals associated with susceptibility to the majority of neurological diseases remains inadequately explained due to the heterogeneous and multifactorial nature of these complex traits.[3] Myriad genetic, immunological and environmental factors may contribute to an individual's susceptibility to neurological disease. However, the clear implication of genetic factors in the causation of many neurological diseases has been gleaned from heritability studies in families, twins and adopted individuals.[3] Familial studies have reported increased incidence of several neurological diseases in offspring or siblings of affected individuals, twin studies have reported higher disease concordance in monozygotic than in dizygotic twins and studies in adopted individuals have suggested a high disease concordance in monozygotic twins raised in diverse environments.

Genes encoding antigen-presenting molecules within the human major histocompatibility complex (MHC) account for the highest component of the genetic risk for many neurological diseases. Risk or protection for a variety of neurological diseases, including multiple sclerosis, neuromyelitis optica, Parkinson's disease, Alzheimer's disease, schizophrenia, myasthenia gravis and amyotrophic lateral sclerosis, has been mapped to this region (Fig. 1). However, the precise mechanisms underpinning these

effects in these neurological diseases remain elusive. Here, we aim to review and discuss the decades long research on the influence of genetic variation at immunogenetic loci in neurological disease. We focus primarily on the well-studied loci of the *MHC*, and later turn our attention to the killer immunoglobulin-like receptor (*KIR*) complex, whose protein products functionally interact with some loci of the *MHC*.

The human major histocompatibility complex region and neurological disease

The balance of innate and adaptive immunity is now appreciated as an important component in the determination of neurological disease outcome. The molecules encoded by the major histocompatibility complex (MHC) regions regulate the innate and adaptive arms of human immune response through antigen presentation, inflammation regulation and the complement system and the impact of this region in various immune-mediated conditions, including neurological diseases, has long been recognized.[4–9] The human *MHC* gene family maps to chromosome 6. With a size of nearly 5 Mbp it encodes approximately 165 protein-coding genes, many of them immune-related,[10] and comprises approximately 0·13% of the human genome.[9] After the first discovery of the mouse MHC in 1936[11] the human equivalent, the human leucocyte antigen (HLA), was subsequently mapped and extensively studied for both gene content and allelic variation. Thus, the *HLA* region became the most investigated region in vertebrate genomes. This region is considered the densest region of the human genome and with the effort of the *MHC* sequencing consortium the complete sequence and gene map of this region was first generated in 1999.[12]

The *HLA* region is characterized by an extreme level of polymorphism and extensive patterns of linkage disequilibrium (LD), which varies among populations. The genes of this region are divided into five subregions: (i) the extended class I, (ii) class I, (iii) class III, (iv) class II and (v) extended class II regions.[9] The extended MHC region comprises greater than 400 annotated genes and pseudogenes.[10] The *HLA* class I region consists of three classical loci, *HLA-A*, *HLA-B* and *HLA-C*, along with three non-classical loci: *HLA-G*, *HLA-E* and *HLA-F*. The non-classical HLA class I molecules are characterized by a more limited degree of polymorphism compared to the their classical counterparts.[9] HLA class I molecules are expressed on all nucleated cells and their main function is presentation of non-self antigens originated from intracellular sources to cytotoxic ($CD8^+$) T-cells for killing of the antigen-presenting cells (APCs).[13] Similarly, the class II region of *HLA* comprises three classical loci, *HLA-DP*, *HLA-DQ* and *HLA-DR*, along with two non-classical loci, *HLA-DO* and *HLA-DM*.[9] The genes of classical *HLA* class II loci are expressed on the surface of professional APCs, which generally present antigens of extracellular origin,[14] such as those derived from food (metabolites) or bacteria for the presentation to helper ($CD4^+$) T-cells. The *HLA* class III region consists of inflammatory regulatory genes,

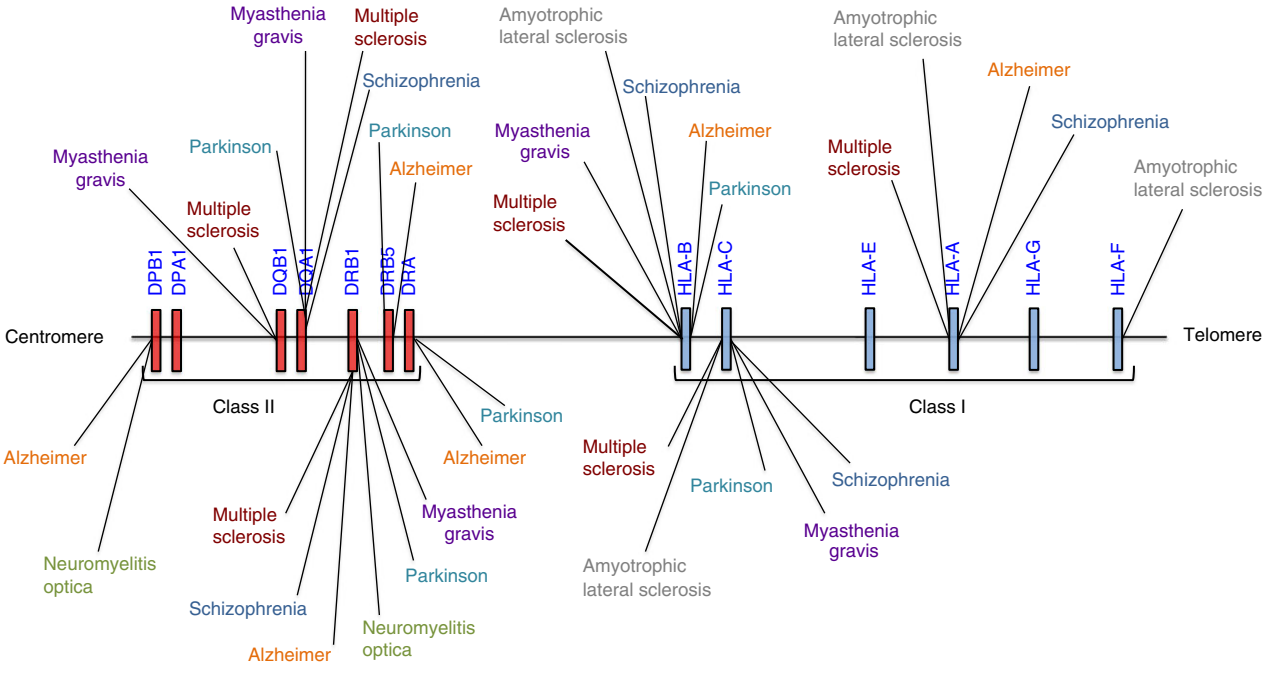

Figure 1. Genomic discovery in neurological disease mapped to the extended *MHC* region on chromosome 6.

such as complement (*C2*, *C4*, *CFB*), cytokine genes (e.g. *TNF, LTA, LTB)* and other genes with non-immune or unknown functions.[9]

The CNS is considered an immune privileged site, and it was long considered that typical neurons did not express *HLA* class I. However, this notion was rejected following the detection of *HLA* class I mRNA and/or protein expression in various neuronal populations, comprising motor nuclei, substantia nigra pars compacta,[15,16] dorsal root ganglia neurons,[17] dopaminergic nigral cells,[18] developing and adult hippocampal pyramidal cells,[19,20] sensory neurons of the vomeronasal organ,[21,22] brainstem,[15,18] and spinal,[15,23] motor neurons and cortical pyramidal cells.[16,20] More recently, a direct link has been established for *HLA* class I in functional and structural synapse pruning in the CNS.[24,25] Further, the capacity of microglia, the brain's resident macrophage, to present antigen through the class II MHC to T-cells permits these typically quiescent cells to perform an important role in determining the clinical outcome of various neurological diseases. The roles of microglia in several neurological diseases are well documented.[26–28]

Taken together, the *HLA* loci are vital for shaping cellular adaptive immune responsiveness, and their impact upon human health and disease has long been appreciated. During the course of four decades, the impact of variation in *HLA* has been studied with respect to neurological disease. A time-line of the crucial findings of *MHC* and *KIR* loci in relevance to neurological diseases are presented in Fig. 2. In the following sections, we discuss the role of *HLA* class I and II molecules in these diverse and often debilitating diseases (Table 1).

HLA and multiple sclerosis

The neurological disease most clearly and consistently associated with variation in the *HLA* region is multiple sclerosis (MS). The first evidence for the association of HLA class I antigens with MS was published in 1972,[29] with risk for MS initially reported to be associated with *HLA-A*03* and *HLA-B*07*[29,30] on the basis of their serological specificity.[29–32] It later became apparent that these class I alleles were part of an extended class I and class II haplotype, associated with the serological determinant *Dw2*,[33] later renamed *DR2*.[34] The advancement in *HLA* genotyping approaches and continuous investigation of this region in MS ultimately revealed that the *DR2* specificity has two distinctive molecular allotypes, *DR*15* and *DR*16*, and the correlation with MS was pinpointed to *DRB1*15:01*,[35] a subtype of *DRB1*15*.[36] In illustration of the strength and consistency of this association in individuals with European ancestry, a Human Genome Epidemiology (HuGE) report reviewing 72 published studies from 1993 to 2004 observed a significantly increased frequency of *DRB1*15:01* among MS patients in the vast majority.[37] Reports of non-association of *DRB1*15:01* with MS, in almost every instance, was performed in cohorts of non-European ancestry. Recently, GWAS performed in collaboration with the International Multiple Sclerosis Genetics Consortium (IMSGC) and the

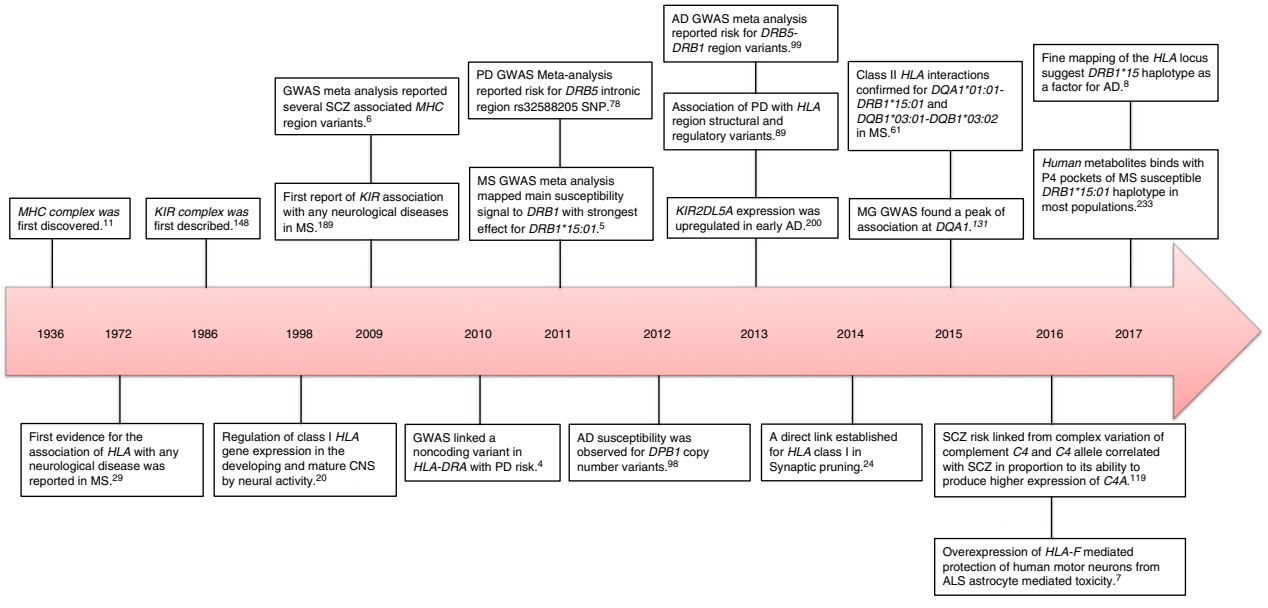

Figure 2. Time-line of the crucial findings in the immunogenetics of neurological disease. CNS, central nervous system; MS, multiple sclerosis; NMO, neuromyelitis optica; PD, Parkinson's disease; AD, Alzheimer's disease; SCZ, schizophrenia; MG, myasthenia gravis; and ALS, amyotrophic lateral sclerosis.

Table 1. Summary of *HLA* class I and II associated susceptible or protective alleles in neurological diseases

Neurological diseases	MHC class II		MHC class I		References
	Predisposing	Protective	Predisposing	Protective	
Multiple sclerosis	*DRB1*15:01, DRB1*15, DRB1*08:01, DRB1*04:05, DRB1*03:01; DRB1*13:03; DRB1*13 ~ DQA1*05:01 ~ DQB1*03:01*	*DRB1*14:01, DRB1*11, DRB1*13-DQB1*06:03, DQA1*01:01-DRB1*15:01, DQB1*03:01- DQB1*03:02*	*A*03, *0301; B*07*	*A*02:01; B*44:02, *44, *38:01, *55:01; C*07, *05*	5,29,30, 35–41, 50-55,57–64
Neuromyelitis optica	*DPB1*05:01, DPB1*03:01, DRB1*12, DRB1*16:02, DRB1*03*	*DRB1*09:01*	–	–	66–76
Parkinson	*DRA, DRB5, DRB1, DRB1*04, DRB1*04:03, DRB1*03, DRB1*03:01*	*DRB1*04:06, DRB1*04:04, DQA1*03:01*	*B*07:02, *17, *18; C*07:02*	*C*03:04*	4,77,78,84, 86,87,89
Alzheimer's	*DR1, DR2, DR3, DRB1*03, DPB1, DRB5-DRB1, DRA*	*DR4, DR6*	*A*02*	*B*07:02, A*03:01*	8,94–101,104
Schizophrenia	*DRB1*01:01, DRB1*03:01:01, DRB1*03:01:02, DQA1*	*DRB1*03:01, DRB1*04, DRB1*06*	*B*08:01, C*01:02*	*A*03, *011, *02; B*27, *51*	107,108,111, 114,117,118
Myasthenia gravis	*DQB1*05:02, DRB1*03, DRB1*04, DQB1*02, DQB1*03, DRB1*09, DRB1*15:01, DQB1*05:02, DRB1*16, DQA1*03:02/DQB1*03:03:02*	*DRB1*08, DRB1*13:01, DQA1*05:01*	*B*08, C*07:01*	–	63,121–125, 130,132, 133,138
Amyotrophic lateral sclerosis	–	–	*A*03, A*02, A*28; B*40, B*35, C*04*	*A*09, HLA-F*	7,140–142, 145,146

Wellcome Trust Case Control Consortium 2 (WTCCC2) project confirmed that the main susceptibility signal for MS maps to the *DRB1* in the class II region of the *MHC*, and describes up to 10·5% of the genetic variance underlying risk.[5] *DRB1*15:01* revealed the strongest effect with an average odds ratio (OR) of 3·08, and all additional *DRB1* associations emerge to describe less than 2% of the residual variance.[5]

Similar to other autoimmune diseases, *DRB1*15:01* in MS susceptibility adheres to an additive model in a dose-dependent manner with zero, one or two copies of the causal allele accounting for increased risk, respectively.[38,39] Along with the augmented risks for *DRB1*15:01* homozygous genotypes, an epistatic effect for MS risk has been reported for carriers of the *DRB1*15:01/*08:01* heterozygous genotype, with an augmented risk compared to other heterozygous *DRB1*15:01* genotypes,[40] while *DRB1*08:01* alone was not observed to be a risk allele. However, a report in an Ashkenazi Jewish cohort suggested an independent association of *DRB1*08:01* when considering clinical subgroups, with a weak significant signal observed only in primary progressive patients.[41] Moreover, *DRB1*15:01* is the most consistently reported MS susceptibility marker of disease severity. An effect of age and gender along with *DRB1*15:01* has also been reported, and it was suggested that female MS patients carrying the *DRB1*15:01* haplotype have an earlier age of disease onset.[42,43] In an attempt to correlate *DRB1*15:01* with disease progression or severity, this allele was associated with the existence of oligoclonal bands and increased immunoglobulin (Ig)G levels in the cerebrospinal fluid (CSF) of MS cases.[44,45] In contrast, there has been no consistent reporting of other MS predisposing *DRB1* alleles with respect to disease progression or severity.[38,46]

*DRB1*15:01* is most often observed in European populations as a segment of an extended haplotype with *DQA1*01:02* and *DQB1*06:02*, and therefore it has been considered challenging to discriminate the main casual allele or locus. Imputation of classical *HLA* alleles from single nucleotide polymorphism (SNP) data demonstrated *DRB1* as a primary risk locus in Europeans, and revealed that the majority of the effect attributed to *DQB1*06:02* can be elucidated primarily by association with *DRB1*15:01*.[47] As the *HLA* region displays varied patterns of linkage disequilibrium between populations, cross-population analysis can be explanatory in unravelling the predisposing locus from a multilocus association. Examination of the African American MS cohort indicated risk to be strongly attributable to *DRB1*15*.[48] In the same study, the evaluation of alternate *DQB1*06:02* haplotypes without *DRB1*15* suggested no difference between cases and controls, eliminating *DQB1*06:02* as the primary allele of the association signal.[48] This observation has been strengthened by a study in a population from Martinique with African ancestry.[49]

Non-European studies suggested a correlation of *DRB1*15* and *DRB1*04:05* with MS in Japanese[50] and Asian populations, respectively.[50,51] The same studies have reported the association of *DRB1*04:05* with a clinically

diverse disease course described by earlier onset age, decreased severity[50] and a lack of brain lesions.[51] Similarly, in Europeans the detection of a correlation of *DRB1*04:05* with MS in Sardinian,[52,53] Sicilian[53] and African American[54] populations provided a coherent model for *DR4* with MS aetiology. Additionally, the correlation of *DRB1*03:01* and *DRB1*13:03* was first detected in Sardinian[55] and Israeli Ashkenazi and non-Ashkenazi Jewish MS[41] patients, respectively, but this allele is extremely common throughout Europe, Africa and Asia. In contrast to *DRB1*03:01*, *DRB1*13:03* has been rarely found at population frequencies higher than 3% worldwide, but the correlation with MS shows effect sizes.[56] A study in Canadian multiplex MS families found overtransmission of the *DRB1*13~DQA1*05:01~DQB1*03:01* haplotype;[57] however, this study did not evaluate the *DRB1* locus at high resolution. This haplotype is almost constantly linked with the *DRB1*13:03* allele in Europeans, whereas the other common subtypes of *DRB1*13* allele, such as of *DRB1*13:01* and *DRB1*13:02*, are usually located on other *DQA1~DQB1* haplotypes; these additional *DR*13* haplotypes were not observed to be overtransmitted in the Canadian study.

Protective effects for *HLA* have also been observed in some studies. The protective effect of *HLA* class II alleles was seen for *DRB1*14:01* in the European MS cohort,[39,40] while *DRB1*11* was protective in both a Brazilian[58] and a Canadian MS cohort.[59] Similarly, the *DRB1*13~DQB1*06:03* haplotype was protective in Finnish[60] and Canadian MS families.[57] Another study confirmed interactions involving pairs of *HLA* class II alleles: *DQA1*01:01- DRB1*15:01* and *DQB1*03:01- DQB1*03:02*, with a protective effect in MS.[61] In the same study, *HLA* class I-mediated protection has also been observed for *HLA-A*02:01*, *HLA-B*44:02*, *HLA-B*38:01* and *HLA-B*55:01*.[61] More recently, *HLA-B*44*-mediated protection was also reported in MS.[62] Similarly, an imputation study revealed protection by the high-resolution *HLA-B*44:02* genotype in MS.[63] Finally, *HLA-B*44:02* was observed in LD with *HLA-C*05*, which independently demonstrated protection for MS in the absence of *DRB1* risk alleles;[64] thus, it is challenging to discriminate whether these observations reflect a single effect through strong LD.

HLA and neuromyelitis optica

Neuromyelitis optica (NMO) was initially considered a variant of MS, but the identification of antibodies for aquaporin 4 (AQP4) or NMO IgG considerably transformed clinical discernment of the disease as an independent entity.[65] This led investigators to evaluate the potential role of the *HLA* region in the aetiology of NMO. Numerous reports in Japanese populations, where the prevalence of NMO is higher than in European populations, suggested *DPB1*05:01* as a predisposing allele and *DRB1*09:01* with a protective effect.[66–68] These results were confirmed in a replication study on a southern Han Chinese NMO cohort.[69] Later, additional *HLA* class II alleles were found to be predisposing in NMO, including *DPB1*03:01*,[70] *DRB1*12*[71] and *DRB1*16:02*.[68,69] Meanwhile, in contrast to Asian populations,[69] *DPB1*05:01* revealed no association with NMO in a French population, but *DRB1*03* was shown to be a susceptibility marker.[66,67,72] Similarly, *DRB1*03* has been also observed with increased risks for NMO among Brazilian mulattos,[73] Afro-Caribbeans[74] and Mexican Mestizos,[75] but not in Muslim Arabs.[76] It is important to consider that as *DRB1*03* is comparatively less frequent and *DPB1*05:01* is more frequent in Asian population, there may be inadequate power to detect the risk for *DRB1*03* in Asian populations and *DPB1*05:01* in European populations, yielding these varied results.

HLA and Parkinson's disease

The association of *HLA* with Parkinson's disease (PD) was first reported more than 4 decades ago.[77] This study reported an increased risk for PD attributable to the *HLA-B*17* and *-B*18* antigens.[77] However, subsequent studies failed to replicate the association of *HLA* class I antigens with PD.[4,78] Genomewide association studies (GWAS) provided a new angle for investigating common complex traits such as PD.[4,78] Evaluation of more than a million SNPs in large sample sizes considerably enhanced the statistical power of the associations. Breakthrough discoveries made by two GWAS recognized SNPs in the *HLA-DR* region to be associated with PD, confirming the immune component in pathogenesis of PD.[4,78] Hamza *et al.*[4] suggested the association of rs3129882, a non-coding variant in *HLA-DRA* with PD in Americans of European ancestry, while a large-scale imputation-based approach applied in a meta-analysis of five GWAS with data generated from US and European cohorts identified chr6: rs32588205 A/G SNP located in the intronic region of *HLA-DRB5* locus with augmented risk for PD under an additive model.[78] Because the *HLA-DRA* locus is mostly monomorphic and less often identified in *HLA* disease association studies, attempts to replicate this observation have generated varied and conflicting results.[79–85] Similarly, the *HLA-DRB5* locus is in strong LD with *HLA-DRB1* and only present in approximately 20% of the population, and thus this association has also been challenging to decipher.

In an attempt to replicate the finding of a GWAS-reported association of rs3129882 in *HLA-DRA* locus, two studies in different populations used a candidate gene approach and confirmed the association of rs3129882 variants with increased risks of PD. The first was conducted in a small cohort of 284 Chinese Han cases and 258 controls from Mainland China,[79] and the second in 520 Iranian cases and 520 controls.[80] Meanwhile, a meta-

analysis of five case–control studies with a total of 2230 PD cases and 2262 controls from Mainland China, Taiwan, Singapore and Malaysia reported no association of *HLA-DRA* rs3129882 variants with PD.[85] Subsequently, a study performed in three different European-ancestry cases and controls from the United States, Ireland and Poland in a comparatively larger cohort of 1313 cases and 1305 controls observed no association of rs3129882 variants with PD under an additive or dominant model.[81] However, the same study found a protective effect of GG genotype in the Irish, Polish and combined cohorta under a recessive model.[81] Finally, no association with rs3129882 was reported in two GWAS: the first conducted in a relatively homogeneous Ashkenazi Jewish (AJ) population from New York comprised of 2050 cases and 1836 controls;[82] and the second in the largest single PD GWAS cohort of 3400 cases and 29 000 controls.[83]

A French case–control PD study revealed an association of rs660895 within the *HLA-DRB1* locus, which is significantly more polymorphic than *HLA-DRA* and, unlike *HLA-DRB5*, present in all individuals and is frequently associated with disease.[84]This study used an imputation approach to infer *HLA* alleles from SNP data, and suggested a protective effect for *DRB1*04.*[84] Another study reported an association of *DRB1*03* with increased risks to PD in individuals with European ancestry.[86] Subsequently, these results were confirmed in another study performed on 567 PD Han Chinese patients and 746 controls from Guangdong province of the China, and suggested the strongest association for PD causation with *DRB1*03:01*, the most common subtype of *DRB1*03* allele.[87] Meanwhile, the same study has also found a decreased frequency of *DRB1*04:06* in PD cases compared to controls, suggesting a protective effect.[87] Interestingly, the *DRB1*04:06* allele, a subtype of *DRB1*04*, is rare in European populations; however, it is common in Asian populations (http://www.allelefrequencies.net).[88] *DRB1*04:03*, another subtype of *DRB1*04,* has been reported to be more frequent among PD cases in Han Chinese.[87] Whether *DRB1*04:06* displays a susceptible effect in European ancestry populations still needs to be evaluated.

A more recent and large study implicated structural and regulatory variants in the *HLA* region.[89] This study suggested that rs3129882 located in intron-1 and the closely linked rs9268515 and rs2395163 SNPs positioned in intergenic region remained significant regardless of *HLA* alleles.[89] Further, this study used an imputation approach and suggested an increased risk for *B*07:02 ~ C*07:02 ~ DRB5*01 ~ DRB1*15:01 ~ DQA1*01:02 ~ DQB1*06:02* haplotype and a protective effect for *C*03:04*, *DRB1*04:04* and *DQA1*03:01* alleles.[89] However, when they conditioned on the associated SNPs, only *C*03:04* and *DRB1*04:04* alleles remained significant.[89] Finally, this study concluded that rs3129882 and rs2395163 SNPs are in expression quantitative trait loci (eQTLs) for *HLA-DR* and *HLA-DQ*, and suggested that *HLA* gene expression might impact PD.[89]

HLA and Alzheimer's disease

Like MS and PD, the first report of a role for *HLA* in Alzheimer's disease (AD) was published in the 1970s.[90] Since then, multiple studies have evaluated the role of *HLA* class I[91–94] and class II genes in *AD.*[95–99] The early findings of an association with *HLA-A*02* in AD were inconsistently replicated. While some studies confirmed a role for this antigen,[94,100] others failed to replicate any association.[91] Most of these studies suffered from small sample sizes, but two most well-powered studies failed to find any association of *HLA-A*02* with AD.[92,93] More recently, a trend for association of SNPs in the *HLA-A* locus with atrophy of brain structures has been reported, although the corrected *P*-values in this study would be considered marginal.[94]

The role of *HLA* class II antigens has also been investigated in the pathophysiology of AD. Curran *et al.*[95] showed that *DR1*, *DR2* and *DR3* antigens, in the absence of apolipoprotein E (APOE) risk alleles, are associated with an increased risk for developing late-onset AD, whereas *DR4* or *DR6* antigens appear to be associated with a decreased risk of AD. Aisen *et al.*[96] suggested that *DR4* might exert a protective influence in AD via modulation of glial activity. A later study also showed that risk for AD in older late-onset cases is associated with *DRB1*03* in *APOE4*-negative individuals.[97] However, as is the case for *HLA-A*02*, these studies have suffered from small sample sizes.

Large-scale GWAS have also provided evidence for the involvement of *HLA* class II in AD. Analysis of genome-wide copy number variation (CNV) suggested a susceptible association for *DPB1* in AD.[98] A subsequent GWAS meta-analysis in 17 008 late-onset cases and 37 154 controls with European ancestry identified a SNP from the *DRB5–DRB1* region to be associated with late-onset AD risk.[99] The association of this SNP was replicated in a Chinese cohort,[101] and further work showed that this SNP is associated with *cis*-gene expression levels of *DRB1* in the temporal cortex and cerebellum.[102] Nettiksimmons *et al.*[103] showed an association of the *DRB5–DRB1* clusters with cognitive decline at the gene-level, and more recently methylation of *DRB5* in the brain was associated with pathological AD, with another peak of association in *DRA.*[104] Yokoyama *et al.*[105] determined that variants associated with autoimmune disease are also associated with AD and found that a SNP close to *DRB5* is associated with AD and psoriasis. The authors also showed that although *DRB5* transcript expression is not altered in AD brains, there is an increase in transcript expression for *DRA* in AD brains compared to control brains.

Finally, an *HLA* imputation-based analysis of 5919 European-ancestry AD Caucasian patients and 5771 controls identified the extended haplotype *A*03:01~B*07:02~DRB1*15:01~DQA1*01:02~DQB1*06:02* as being associated with AD risk ($P = 9{\cdot}6 \times 10^{-4}$, OR = 1·21)[8] in individuals who are negative for APOE 4.[8] The authors also found an association of the class I haplotype *A*03:01~B*07:02*, with higher CSF amyloid levels and a dose-dependent association of the *DR15* haplotype with greater rates of cognitive decline and baseline levels of chemokine CC-4.[8]

HLA and schizophrenia

The first evidence for a probable role of *HLA* in schizophrenia (SCZ) was described in 1974.[106] Thereafter, multiple linkage studies provided some evidence for a susceptibility locus on the short arm of chromosome 6.[107,108] These studies correlated numerous class I and class II alleles with SCZ.[107,108] However, subsequent studies failed to replicate these initial findings.[107,108]

More recently, publication of the first GWAS and meta-analysis in SCZ made possible the study of the *HLA* region at higher resolution.[6] A meta-analysis of three GWAS identified several *MHC* region variants associated with SCZ in individuals with European ancestry.[6,108–110] Some of these were consistently replicated or found in other populations.[108,111–113] However, it is interesting to note that most of the significant variants correlated with SCZ in the meta-analysis were located in the extended *MHC* regions, near a cluster of histone genes comprising a position upstream of the class I region, along with a few additional immune genes such as ribonuclease P21 (*RPP21*) located in class I region and neurogenic locus notch homologue 4 (*NOTCH4)* located in the extended class II region.[109]

Subsequently, GWAS analysis performed in SCZ cases from Asia replicated the findings of the European GWAS, and additionally recognized a few novel variants in Chinese[112] and Japanese populations.[113] Similarly, the rs9272219 and rs9272535 variants in the *DQA1* gene revealed a moderate association with SCZ.[111] An *HLA* imputation study showed an association of the risk allele *HLA-C*01:02* in addition to trends for association of the protective alleles *DRB1*03:01* and *B*08:01*.[114] A GWAS in Ashkenazi Jews showed supportive evidence for association of the *HLA* region with SCZ in this population.[115] Finally, an eQTL study strengthened these results by providing evidence that the *TRIMP26*, *RNF5* and *DRB3* genes, located within the MHC region, are regulated by the top SNPs recognized by meta-analysis of GWAS data.[116] In addition to GWAS results, previous reports suggested an increased frequency of *DRB1*01:01* and a decreased frequency of *DRB1*04* among SCZ patients.[117,118] However, it is important to note that all *HLA* association studies performed in SCZ to date have either used low-resolution genotyping methods or GWAS/SNP imputation approaches. The lack of consistent findings suggest that high-resolution *HLA* genotyping approaches will be required to fully appreciate the role of *HLA* variants in SCZ.

More recently, a well-powered study associated SCZ risk with complex variation in complement component 4 (*C4*) genes, also located within the *MHC*.[119] This study found that *C4* alleles produced extensively varying levels of *C4A* and *C4B* expression in the brain, with each common *C4* allele correlating with SCZ in proportion to its ability to produce higher expression of *C4A*.[119] The findings of this study highlight the role of complement genes in pathophysiology of SCZ, and these observations open new frontiers for future investigations of genetic variation in complement genes with SCZ in other ethnic groups in the quest to find a coherent model for SCZ.

HLA and myasthenia gravis

The first report of an *HLA* association with myasthenia gravis (MG) was published in 1976.[120] Thereafter, several studies have reported evidence of association of *HLA* antigens/alleles with MG. An Italian study identified *DQB1*05:02* as being associated with MG,[121] while a Tunisian study identified the *DRB1*03*, *DRB1*04*, *DQB1*02* and *DQB1*03* alleles as possible predisposing factors for MG.[122] *DRB1*03* was then subsequently found to be associated with MG in a Portuguese study.[123] Meanwhile, in a northern Han Chinese population, *DRB1*09* was associated with risk of MG, while *DRB1*08* was protective.[124] A GWAS published in 2012 on North Europeans identified the class I SNP rs7750641 as the strongest signal in MG, and further imputation analysis identified *HLA-B*08* as being the major risk allele.[125] Similarly, an imputation study observed a risk association for *HLA-C*07:01* with MG.[63] There is strong LD between *HLA-C*07:01* and *HLA-B*08*, but the latter revealed a marginally weaker association than *HLA-C*07:01* in the same study.[63]

Examinations of age of onset effects of *HLA* in MG have yielded mixed results. Although multiple studies have reported the extended *HLA* haplotype, namely *A1-B8-DR3-DQ2*, as being associated specifically with early onset of MG (EOMG) in individuals with European ancestry, it is unclear whether the signal maps in class I or class II genes.[126–128] Interestingly, the A allele of the SNP rs1800629 at position 308 nucleotides upstream from the transcription initiation site of tumour necrosis factor-alpha (*TNF-α*) has been linked to higher expression level and higher serum levels of TNF-α in MG by several studies, and this SNP is known to be in LD with the *HLA A1-B8–DR3* haplotype.[129] Confounding interpretation of these results, *DRB1*13:01* was found to be

protective for EOMG in a Norwegian population,[130] while a GWAS performed in a European population by Renton *et al.*[131] found a peak of association for EOMG at *DQA1*.

The Norwegian study identified *DRB1*15:01* as being associated with the risk of late onset of MG (LOMG), while *DRB1*13:01* was also found to be protective in LOMG.[130] In an Italian cohort, *DQB1*05:02* and *DRB1*16* have been reported as being associated with LOMG.[132] Renton *et al.*[131] found a peak of association for LOMG at *HLA-DQA1*, which was distinct from that observed in the same GWAS in EOMG. Another GWAS showed three distinct and largely independent association peaks for LOMG corresponding to *MHC* class II, *HLA-A* and *MHC* class III SNPs, while imputation of *HLA* alleles showed a protective effect of *DQA1*05:01*.[133]

Additional studies have sought to elucidate an association of *HLA* with specific subtypes of MG. Four studies found an association of *DQ5* with the specific subgroup of muscle-specific kinase (MuSK) antibody-positive (Ab^+) MG patients.[134–137] A Turkish study also found that *DRB1*14* and *DRB1*16* were associated with this specific subgroup,[136] whereas in a Serbian cohort, *DRB1*13* seems to be completely absent in this specific patient population.[137] It has been hypothesized that childhood-onset ocular MG in southern Han Chinese may present a particular subgroup of distinct genetic background, correlating with the haplotype *DQA1*03:02/DQB1*03:03:02*.[138] Later, the haplotype *HLA-B*46:01-DRB1*09:01* was found to be associated with juvenile ocular MG in the same population.[139] However, it is important to note that all studies involved cohorts of, at most, a few hundred individuals, making it difficult to fully elucidate the role of *HLA* in MG.

HLA and amyotrophic lateral sclerosis

A very limited number of genetic association studies have evaluated the *HLA* region in amyotrophic lateral sclerosis (ALS). During the 1980s, a few studies with low-resolution genotyping sought to examine *HLA* in ALS.[140–142] Initial studies found no correlation between *HLA* antigens and ALS in patients from California[143] and Guam.[144] Later, a significantly increased frequency of *HLA-A*03* was reported in an ALS cohort from the greater Boston area[140] and Israel.[141] Similarly, *HLA-A*02* and *-A*28* have been shown to be more frequent in ALS cases recruited from Glasgow and Scotland,[145] while an increased frequency of *HLA-B*40* was found in an ALS cohort from Finland.[142] A study from the greater New York area observed *HLA-Bw35* and *-Cw4* more frequently in ALS cases, and a trend towards decreased frequency was also found for *HLA-A*09*.[146] These initial findings were marked by substantial inconsistency in identification of a link between a particular HLA antigen and ALS across study populations, suggesting perhaps that *HLA* determinants may not play a major role in susceptibility to this diseases.

Thereafter, almost three decades passed without *HLA* association studies conducted in ALS. However, a recent study demonstrating that overexpression of a single non-classical *HLA* class I molecule, *HLA-F*, resulted in protection of human motor neurons from ALS astrocyte-mediated toxicity, coupled with a role for the killer cell immunoglobulin-like receptor *KIR3DL2*,[7] clearly indicated an immune component in ALS pathogenesis. Finally, an association study published in 2017 in a Chinese Han population indicated a role for *HLA* class II in ALS.[147] While inconclusive, these more recent investigations suggest an immunogenetic component to ALS, warranting further study.

The killer-immunoglobulin-like receptor (KIR) complex: a new horizon in the immunogenetics of neurological disease

The *KIR* complex was first defined in 1986,[148] and was initially recognized as *KIR* inhibitory receptors. The family of the *KIR* proteins are mainly expressed on natural killer (NK) cells[149] and a small percentage of T-cells.[150] The *KIR* complex maps on the long arm of human chromosome 19q13·4, and is considered as a crucial component of innate and adaptive immunity. Although *KIR* and *HLA* are members of two different gene families, the interaction of *KIR* with their cognate *HLA* class I ligands serves as a functional bridge in the regulation of NK cell functions and maintenance of immune homeostasis. *KIR* are inhibitory and stimulatory surface receptors that regulate NK cell function and responsiveness.[151] All these receptors consist of either two (2D) or three (3D) extracellular immunoglobulin domains (D). The transmembrane and cytoplasmic domains govern the functional characteristics of these receptors. The inhibitory receptors consist of long (L) cytoplasmic tails comprising immunoreceptor tyrosine-based inhibitory motifs (ITIMs), whereas stimulating receptors possess short (S) cytoplasmic tails and link to the stimulating adaptor DAP12 through a charged residue in the transmembrane domain. However, *KIR2DL4* is an exception, and despite having a long cytoplasmic tail with an ITIM transmits a positive signal through its interaction with the stimulating adaptor Fc_eR1_γ.[152,153] Specific KIR molecules recognize one or more of four epitopes of HLA class I molecules. In contrast to the T-cell receptor, *KIR* bind to the upper face of the HLA class I molecule, creating contact with the N-terminal part of the α1 helix, the C-terminal part of the α1 helix, and the bound peptide.[154] Genetic variation in the class I α1 helix governs the three major epitopes perceived by *KIR*, *HLA-C1*, *-C2* and *-Bw4*. The inhibitory *KIR2DL1* and *KIR2DL2/3* and the stimulating *KIR2DS1*, *KIR2DS2* and *KIR2DS4* interact divergently

with the reciprocally unique *C1* or *C2* epitopes carried by all *HLA-C* allotypes and a small subset of HLA-B molecules.[155–157] *KIR3DL2*, *KIR2DS2* and *KIR2DS4* recognize a subset of *HLA-A* allotypes transmitting the *A*03/A*11* epitope (e.g. *A*11:01*).[56] Finally, *KIR3DL1/S1* binds subsets of *HLA-A* and *-B* allotypes that carry the *Bw4* epitope (e.g. *A*24:02*).[56] In contrast, *HLA-B* alleles with the *Bw6* epitope do not bind with any *KIRs*. Adding further complexity, these receptor interactions are further tuned by allelic variations of *KIR* and *HLA* class I and by the sequence of the bound peptide.[158–161]

The *KIR* gene complex exhibits extensive heterogeneity in gene content at both intra- and interpopulation levels. *KIR* haplotypes comprise from four to 14 genes and, based on their genomic structure, are divided into two groups, termed A and B.[162] The group A haplotype is characterized by a single configuration of seven genes that express predominantly inhibitory *KIR*, and all remaining configurations are termed B haplotypes. As an indication of probable functional differences between them, B haplotypes typically express more activating *KIR* than A haplotypes.[163–165] The haplotypes are formed from combinations of unique centromeric and telomeric gene-content motifs, which also belong to the A or B groups. Although a huge number of unique haplotypes are described, a few comparatively common haplotypes repeatedly account for greater than 90% of the *KIR* haplotypic variation detected within a specific population, and are observed throughout major ethnic groups.[166,167] Our recent work and that of others has shown that the prevalence of *KIR* haplotypes and specific combinations of cognate *KIR* and *HLA* allotypes are associated in autoimmune[162,168–170] and infectious diseases such as human immunodeficiency virus (HIV) and hepatitis C,[171–174] cancer,[175,176] and are critical to the success of solid organ and haematopoietic stem cell transplant (HCT)[177–180] and pregnancy.[181–185]

Although the correlation of *HLA* variation with neurological disease has been well documented, there is a paucity of studies aiming to evaluate the impact of NK cells or their receptors, including *KIR* in these diseases. As HLA class I molecules function as the primary ligand for several *KIRs*, it is possible that the class I association signals perceived for various diseases is, in fact, related to *KIR* function. In various neurological diseases, such as MS,[29,30,63,186] myasthenia gravis,[126–128] schizophrenia,[107,108,114] Parkinson's disease,[77,89] Alzheimer's disease[8,94,100] and amyotrophic lateral sclerosis,[140,141,145,146] the alleles of *HLA-A*, *-B* and *-C* that are recognized to function as cognate ligands for their respective *KIR* genes have been linked with disease (Table 2). Here, it is important to note that the majority of the identified *HLA* class I association with various neurological diseases described used an imputation approach from data obtained through GWAS rather than direct assay. Meanwhile, a direct link of *KIR* allele variations with neurological diseases has not been observed in GWAS, very possibly because of a limited number of markers in the *KIR* region on all common available GWAS platforms. An insufficiency of appropriate reference alignments has traditionally impeded incorporation of *KIR* exclusive SNPs on the available GWAS platforms, and the large diversification of gene-content in *KIR* haplotypes is characteristically discordant with standard quality thresholds. Finally, the Immunochip, which is exclusively enriched for markers in the *KIR* chromosomal region, predominantly recognizes non-coding variants on the common group A haplotype that mainly comprises inhibitory *KIRs*.[187] To date, therefore, the majority of described *KIR* correlations with immune diseases,[188] including multiple sclerosis[189–191] and schizophrenia,[192] used approaches which determine only *KIR* gene content variation. *KIR* genotyping approaches that determine gene content are usually impotent to discriminate copy number, but rather assess only presence/absence. As copy number has repercussions on the immune reactions,[193] this further hinders the capacity to detect any locus level associations with disease. Additionally, strong LD within gene content haplotypes[166,194] creates another hurdle in the determination of the causative locus.

A limited number of studies has examined the association of *KIR* gene content variation to date with neurological diseases, the majority of them in multiple sclerosis[189–191] and one in schizophrenia.[192] A study conducted on a relatively small sample size of 200 schizophrenia patients and 561 controls in European Polish populations have found no correlation of either *KIR* gene frequency or *KIR* gene ligands with disease.[192] There could be two probable reasons for the non-association of *KIR* variation with SCZ. First, the genotyping method for *KIR* varied considerably, and the differential accuracy of genotyping approaches due to the strong homology between *KIR* gene or possible amplification biases contingent upon sample quality makes it difficult to calculate *KIR* gene frequencies precisely. The second limitation is that this study genotyped only for epitopes *HLA-A*$^{Bw4+}$, *HLA-B Bw4*^{Ile}, *Bw4*^{Thr}, *HLA-C1* and *-C2* but did not genotype for particular *HLA-A*, *-B* and *-C* alleles, limiting the ability to analyse the interaction of *KIR* with specific *HLA* allotypes. Numerous reports of *KIR* gene content studies in MS from European populations have suggested a role for *KIR* loci in disease predisposition. Lack of the inhibitory *KIR2DL3* has been suggested in MS susceptibility,[195] implicating either *KIR2DL2* (which segregates as the alternate allele of the same locus) or the closely associated *KIR2DS2* in disease. Subsequently, a study has observed the increased incidence of *KIR2DL5* and *KIR3DS1* in MS cases compared to controls.[196] Finally, two other reports in Portuguese and Italian MS cohorts determined a diverse telomeric locus, *KIR2DS1*, as protective.[197,198]

Table 2. *HLA* class I associations and putative *KIR* receptor involvement in neurological diseases

Neurological disease	HLA class I associations	Potential KIR receptors	References
Multiple sclerosis	*HLA-B*07, *44, *44:02, *37:01, *38:01; HLA-C*07, *05; HLA-A*02:01, *03, *0301*	*KIR3DL1S1; KIR2DL1, KIR2DL2/3, KIR2DS1, KIR2DS2, KIR2DS4, KIR3DL2*	29,30,60–64
Parkinson's disease	*HLA-B *17, *07:02, HLA-C*07:02, *03:04*	*KIR3DL1S1, KIR2DL2/3, KIR2DS2, KIR2DS4, KIR3DL2*	77,89
Alzheimer's disease	*HLA-B*07:02, HLA-A*03:01, *02*	*KIR3DL2, KIR2DS4*	8,94,100
Schizophrenia	*HLA-B*27, *51; HLA-C*01:02, HLA-A*03, *011, *02*	*KIR3DL1S1; KIR2DL2/3, KIR2DS2, KIR2DS4; KIR3DL2*	107,108,114
Myasthenia gravis	*HLA-B*08; HLA-C*07:01*	*KIR2DL2/3, KIR2DS2, KIR2DS4*	63,125
Amyotrophic lateral sclerosis	*HLA-A*09, *02, *03, HLA-C*04, HLA-F*	*KIR3DL1S1, KIR2DL1, KIR2DS1, KIR2DS4, KIR3DL2*	7,140,141,145,146

Similarly, our study in an African American MS cohort revealed a strong protective effect for *KIR3DL1* in combination with *HLA-A* and *-B* alleles bearing the *Bw4* motif.[191] Finally, the up-regulated expression of *KIR2DL5A* was observed in early Alzheimer's disease.[199] Although these initial observations are encouraging, an extensive assessment of *KIR* allele-level variation in a set of established and well-characterized cohorts encompassing a wide range of neurological diseases in several different ethnicities, and their correlation with *KIR* expression, is needed to fully appreciate the role of these critical immune receptors in disease susceptibility and prognosis.

Notably, both immunoregulatory dysfunction and activated inflammatory mediator pathways have been suggested in the pathophysiology of neurological diseases, particularly PD,[200,201] MS[202] and MG,[203] as well as many other neurological diseases.[204] The reported disease association of *HLA* variations bolsters this notion. *KIR*, through the NK cell, regulates the production of cytokine and chemokines.[205] As cytokine and chemokines regulate neuroinflammation,[206] it remains a plausible hypothesis that *KIR* allelic variation may influence the course of various neurological diseases through neuroinflammatory pathways.

Accumulating evidence suggests a role for NK cells in various neurological diseases, such as MS,[207–209] NMO,[210] PD,[211,212] AD,[213] SCZ,[214] myasthenia gravis[215] and ALS,[216] strengthening the notion that *KIR* variation may be important in disease predisposition and/or development. NK cells are a key component of innate immunity and act as a first line of defence in resisting infections, but may also be involved in the induction of neurological diseases, and accumulate in specific neuronal cells or tissues in some diseases.[215–219] In the MS murine model, experimental autoimmune encephalomyelitis (EAE), studies suggested a role for NK cells in down-regulation of disease progression.[207–209] In the meantime, enhanced predisposition and disease severity in EAE has been linked with NK cells in concurrence with individual cytokines.[218,219] Studies in humans suggested an immunoregulatory role for NK cells in MS, causing an abatement of the inflammatory pathways.[220,221] In contrast, *in-vitro* studies demonstrated that NK cells can straightforwardly lyse neural tissue, and may consequently contribute to tissue injury in MS.[222,223] While the immunobiology of NK cells in certain neurological diseases such as MS has been explored, comparatively less is known about the specific role of NK cells in other neurological diseases, such as NMO, PD, AD, SCZ, MG and ALS. The results of NK cell studies in MS continue to be controversial, and fail to point to a coherent model. Thus, understanding the precise role of *KIR* variation in immunopathogenesis of neurological diseases may open new horizons for identification of biomarkers or could pave the way for new therapeutic approaches.

Consideration of *HLA* and *KIR* regulatory region variation in neurological disease

The emergence of next-generation sequencing enhanced our ability to determine the *HLA* and *KIR* sequences at a very high-resolution level. This provides the opportunity to determine the role of both coding and non-coding *HLA* and *KIR* region variations in a variety of neurological diseases, given that the non-coding regions of the human genome including *HLA* and *KIR* regions contain regulatory elements, such as promoters, enhancers and untranslated regions (UTRs); these are the strong candidate regions for pathogenic variation and participate directly in the determination of the abundance of expressed genes. In current laboratory practice almost all the reported *HLA* alleles, either in the disease association studies or in the databases, have used genotyping approaches that only sequenced through exons 2 (class I and class II) and 3 (class I), and this limits our ability to analyse *HLA* non-coding variations. *HLA* non-coding variations such as SNPs or small insertion/deletions (indels), as well as larger-scale copy number variants (CNV) present in regulatory regions, could impact the course of neurological diseases through alteration of gene expression. Non-coding variation in *HLA* has already been associated clearly with disease. For example, variation in the 3′UTR of *HLA-*

DPB1 is linked with spontaneous clearance of hepatitis B virus in both Japanese and US populations.[224,225] The proposed mechanism for enabling viral clearance might be linked to the rs9277534 A/G SNP, which describes *HLA-DP* cell-surface expression.[225] Similarly, rs2281389 is a non-coding region variant in *HLA-DP* linked with acute graft-versus-host disease (GVHD).[226] However, rs2281389 variants are not detectable through standard genotyping approaches. Finally, a promoter region SNP of *HLA-C* has been reported to be linked with control of HIV infection, and cell surface expression of the *HLA* molecule was identified to be in LD with a 3′UTR variant that regulates binding of micro-RNA, the putative source of the expression variation.[227] Distorted patterns of gene expression are a characteristic of many neurological diseases, such as MS, Alzheimer's disease and schizophrenia, and in various cases these altered gene expressions can be correlated straightforwardly to genomic/pathogenic variations.[228–230] These findings support the hypothesis of a robust association between anomalous gene expression and neurological diseases, suggesting that variants in non-coding regulatory elements are outstanding candidates for some of the observed missing heritability in neurological diseases. The identification of many null or expression variants of common *HLA* alleles will improve our understanding of their role in immune functions. Recently, a variant of the multiple sclerosis-linked allele *HLA-B*44:02* has been determined that produces only a soluble, rather than cell surface, molecule; a point mutation at the end of intron 4 alters the exon 5 splice site.[231] Meanwhile, this variant is not appreciable through standard genotyping approaches, and hence these alleles are usually genotyped as *B*44:02*; similarly, the actual population-level frequency of the marginal allele is not recognized. Moreover, if the non-surface-expressed variant of this allele is common, this might elucidate the link to disease. Taken together, these data recommend that the genotyping of regulatory regions variants may improve our understanding about the role of *HLA* and *KIR* in neurological disease.

Concluding remarks and future perspective

Taken together, the findings of *HLA* and *KIR* association studies are consistent with a polygenic model of inheritance in the heterogeneous and multifactorial nature of complex traits in various neurological diseases. The majority of the neurological diseases, such as MS, NMO, PD, AD, SCZ, MG and ALS, are considerably more common among individuals transmitting specific *HLA* alleles. This further strengthens the decades-long contention of a strong immune component in the determination of clinical outcomes of neurological diseases.

Looking to the future of immunogenetics in neurological diseases, we recommend focus upon high-resolution genotyping for both *HLA* and *KIR*. Investigating both coding and non-coding region variation in these immunogenetic loci using high throughput high-resolution technologies in groups with diverse ancestries will almost certainly be required to fully appreciate their role in neurological diseases. There are only limited examinations of *HLA* and *KIR* variations at transcriptomics and proteomics levels; therefore, the functional assessment of both allelic and regulatory regional variation is highly desirable. The impact of micro-RNA on diverse *HLA* and *KIR* alleles in regulatory regions also needs to be evaluated in neurological diseases in order to recognize the significance of epigenetic factors in disease pathophysiology. Finally, our recent observation, that certain human metabolites occupy the P4 pocket of MS-susceptible *DRB1*15:01* haplotype in most populations and could be implicated in autoimmunity,[232] suggest that similar investigations of both *HLA* class I and class II molecules in an allele-specific manner could be undertaken. This approach might be advantageous to weight or group together various *HLA* genes and alleles that are involved in predisposition across diseases. The functional assessment of binding of human metabolites with *HLA* class I and class II molecules, and investigation of their impact upon T-cell proliferation and responsiveness, could pave the way for designing novel therapies, leading to a step closer to reaching the goal of personalized medicine.

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None to declare.

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