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The origins and immunopathogenesis of autoimmune central nervous system disorders

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Abbreviations

AGS Aicardi Goutières Syndrome, AMPAR alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, APC antigen presenting cell, AQP4 aquaporin-4, CASPR2 contactin-associated protein like 2, CNS central nervous system, CSF cerebrospinal fluid, CTLA4 cytotoxic T-lymphocyte-associated protein 4, D2R dopamine 2 receptor, dCLN deep cervical lymph nodes, DNA deoxyribonucleic acid, EBV Epstein-Barr virus, $GABA_{A/B}R$ gamma aminobutyric $acid_{A/B}$ receptor, GFAP glial fibrillary acidic protein, GBS Guillian-Barre Syndrome, EWAS epigenome-wide association study, HHV-6 human herpes virus 6, HLA human leucocyte antigen, HSV herpes simplex virus, HSVE herpes simplex virus encephalitis, ICI immune checkpoint inhibitor, Ig immunoglobulin, IL interleukin, GWAS genome-wide association study, LGI1 leucine rich glioma inactivated 1, mAbs monoclonal antibodies, MHC major histocompatibility complex, MS multiple sclerosis, nIRAE

neurological immune related adverse event, NMDAR N-methyl-D-aspartate receptor, NMOSD neuromyelitis optica spectrum disorder, NPSLE neuropsychiatric systemic lupus erythematosus, OMAS opsoclonus myoclonus ataxia syndrome, OR odds ratio, PD1 programmed cell death protein 1, PDL1 PD1 ligand, PNS peripheral nervous system, RNA ribonucleic acid, SLE systemic lupus erythematosus, SNP single nucleotide polymorphism, Th T helper cell, TLR toll like receptor, TNF tumour necrosis factor, Treg regulatory T cell, VGCC voltage gated calcium channel

Abstract

The field of autoimmune neurology has rapidly evolved and recent discoveries have advanced our understanding of disease aetiologies. In this article, we review key pathogenic mechanisms underlying the development of central nervous system (CNS) autoimmunity. Firstly, we review non-modifiable risk factors such as age, gender, and ethnicity; and focus on important advances in genetic risk, including monogenic disorders, common variants in vulnerability genes, and emerging human leucocyte antigen associations. Secondly, we highlight how the interaction between environmental factors and epigenetics can modify disease onset and severity. Thirdly, we review possible disease mechanisms underlying triggers that are associated with loss of immune tolerance, such as infections, tumours, and the administration of immune checkpoint inhibitor therapy. Finally, we outline how understanding the anatomy of lymphatic drainage and neuroimmune interfaces challenge long-held notions of central nervous system immune privilege, with direct relevance to these diseases; and how disruption of B and T cell tolerance and passage of immune cells between the periphal and intrathecal compartments play key roles in initiating disease activity. In this review we synthesise advances in our understanding of recently identified genetic, environmental, and cellular influences on the underlying immunobiology of autoimmune CNS disorders, and reflect on novel therapeutic approaches.

Introduction

The field of autoimmune neurology has rapidly expanded over the last two decades. However, we still lack a comprehensive understanding of the precise origins of neurological autoimmunity. Recent advances explaining pathogenic mechanisms underpinning the development of disease have become increasingly vital to develop precision therapeutics[1,2]. Autoimmune neurological disorders of the CNS span many clinically distinct and overlapping syndromes, as summarised in Box 1. A recently recognised group of disorders are diagnosed based on the presence of serum and/or cerebrospinal fluid (CSF) autoantibodies targeting neuroglial cell-surface antigens, and will be the focus of this review. Antibodies which target intracellular antigens may also be biomarkers of autoimmune neurological disorders, particularly those associated with tumours. More prevalent autoimmune neurological conditions, such as multiple sclerosis (MS), are not currently associated with specific autoantibodies, but have enabled highly powered studies confirming the influence of genetics and infection on disease immunobiology, and hence provide insights into potential similar contributors in autoantibody-mediated CNS disorders. This review will refer to this spectrum of neurological conditions (Box 1) to illustrate factors which may contribute to the underlying immunopathogenesis of autoimmune CNS disorders (Figure 1), and summarise likely pathogenic pathways in these conditions.

We initially evaluate our current understanding of non-modifiable risk factors of age, sex, ethnicity, and genetics; and the interaction of environmental and epigentic factors which can modify disease onset and severity. We will then detail recent advances in the contributions of infectious, malignant, and iatrogenic triggers for the loss of immune tolerance. Finally, we provide an overview and highlight recent updates related to the generation of autoreactive B and T cells, and interactions at the neuroimmune interface which initiate disease activity.

Non-modifiable risk factors in CNS autoimmunity

Age, gender, and ethnicity

Age, gender, and ethnicity are important contributors to the risk of developing specific autoantibody-mediated neurological disorders (Figure 2). Age appears to play a significant role in the manifestations of a number of autoantibody-mediated neurological disorders. Some conditions present primarily in young adults. For example MS has a median age of onset in the 20s and 30s[3], and N-methyl-D-aspartate receptor (NMDAR)-antibody encephalitis in the early 20s[4], with both disorders also having a proportion of patients presenting in childhood. Age of onset may influence clinical associations, such as children with NMDAR-antibody encephalitis less frequently presenting with ovarian teratomas compared to adults[5]. In contrast, other autoimmune neurological disorders such as leucine rich glioma inactivated 1(LGI1)-antibody encephalitis or contactin associated protein like 2 (CASPR2)-antibody encephalitis typically present in patients over the age of 60[6], and are extremely rare in children[7]. The few children described with LGI1-antibody encephalitis rarely present with faciobrachial dystonic seizures, a clinical manifestation which is pathognomonic of this disorder in adults. In myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), the clinical presentations vary in children versus adults[8]. Acute disseminated encephalomyelitis occurs almost exclusively in children with MOGAD, while this is rare in adolescents and adults who frequently present with recurrent optic neuritis and transverse myelitis[8]. Across these syndromes, potential reasons for the variation of age of onset and clinical presentations may include the expression of the target antigen through development, and the relative expression of the antigen in tumours, when these are present. For example, in opsoclonus myoclonus ataxia syndrome, neuroblastomas are more common in children, while lung cancers are more common in the elderly. Development of the immune

system in young children and the immunological challenges they face in the first years of life may play a role in altering immune tolerance, in addition to genetic contributors of immune dysregulation being more pertinent in young children. Likewise, with age, the loss of immune tolerance due to the cumulative exposure to environmental factors and immune senescence may contribute to developing autoimmunity[9].

Gender influences are well established contributors to systemic autoimmunity with females having a higher rate of numerous autoimmune conditions such as thyroid disease, lupus, and rheumatoid arthritis[10]. This phenomenon is also observed in some autoimmune neurological disorders: ~3:1 female:male ratio in MS[11], ~4:1 in NMDAR-antibody encephalitis[12], and up to ~8:1 in AQP4-antibody neuromyelitis optical spectrum disorder (NMOSD) (Figure 2)[13] Sex hormones are involved in regulating the innate and adaptive immune systems, and have been hypothesised to play a role in this autoimmune sex divergence. This phenomenon is perhaps most clearly observed by the reduction in relapses of MS during pregnancy versus the increased risk of postpartum MS relapses[14]. Other explanations may include the incomplete inactivation of X-linked genes, as has been demonstrated with toll-like receptor 7 (TLR7) expression, and an increased risk of developing lupus[15]. While female dominance is more common, female to male equivalence occurs in conditions such as glial fibrillary acidic protein (GFAP)-antibody associated disorders[16] and MOGAD[8,17,18]. In contrast, patients with LGI1- and CASPR2-antibody encephalitis are most frequently male, with striking female to male ratios of up to 1:5 and 1:9 respectively[19,20,21].

Finally, ethnicity appears to correlate with clinical manifestations and outcomes for some autoimmune neurological disorders. The presentation of ‘typical’ MS is historically identified as being most prevalent in Caucasians[22], although is increasingly recognised in subcontinental

and African individuals. The strong Afro-Caribbean association in AQP4-antibody NMOSD[23], and increased prevalence of NMDAR-antibody encephalitis in children with Pacific Islander, Maori, and Asian backgrounds[24], and relative absence of Afro-Caribbean patients in LGI1-antibody encephalitis all point towards underlying genetic contributions. Some of these associations are described later in the review in association with HLA risk profiles, but most remain unknown.

The relative contributions of these non-modifiable risk factors, their interaction with environmental factors, and the subsequent triggers of infections or malignancies, may partially explain the onset of neurological autoimmunity in a predisposed individual who has encountered 'multiple hits' to break immune tolerance, as highlighted in Figure 1.

Genetic contributors to neurological autoimmunity

Monogenic causes of neurological autoimmunity

Highly penetrant monogenic genetic variation in DNA that causes autoimmunity can provide insights into the origins of autoimmunity. Table 1 presents monogenic causes of autoimmunity associated with CNS autoimmunity, and highlights the close association between autoimmunity, immunodeficiency syndromes, and lymphoproliferative disease.

Early components of the complement classical pathway include C1q, C1r, C1s, C4, and C2. Genetic defects in these factors may result in failure to clear apoptotic material, with secondary inflammation and autoimmunity[25,26]. C1q deficiency has the strongest association with neurological autoimmunity, particularly neuropsychiatric systemic lupus erythematosus (NPSLE); and, interestingly, C4 deficiency has also been associated with NMDAR-antibody encephalitis[26].

The FAS pathway is the apoptosis 'death signal' and includes FAS receptor, FAS ligand and other FAS associated genes (Fas-opathies). These, and other genes central to apoptosis, can result in autoimmunity in up to 70% of patients, typically presenting as a combination of lymphoproliferation (adenopathy, hepatosplenomegaly), autoimmunity, and malignancy (lymphoma); with neurological autoimmunity including cerebellar ataxia and transverse myelitis described in some patients[27].

Abnormalities of protein and nucleic acid degradation can also lead to autoimmunity and inflammation. Aicardi Goutières Syndrome (AGS) encompasses early-onset brain inflammation, encephalopathy and other systemic inflammatory disease. The genes associated with AGS (including TREX1, RNASEH2A, RNASEH2B, and RNASEH2C) are predominantly involved in nuclease function, and clearance or sensing of cellular DNA and/or RNA, leading to a downstream activation of the interferon pathway. Some patients develop systemic autoimmunity (typically SLE), and a small number of patients have been reported to develop specific autoimmune neurological syndromes such as ospsoclonus myoclonus ataxia syndrome and AQP4-antibody NMOSD, although pathogenic cell surface autoantibodies are only rarely reported (Table 1)[28,29]. In addition to the nucleic acid enzyme genes, other highly penetrant mutations in interferon pathway genes (as demonstrated by the Type 1 and Type 2 interferon pathways in Figure 1), can cause brain inflammation, often with cerebral vasculopathy or intracranial pathology[30-32].

Variations in genes involved in the regulation of immune signaling may also be associated with CNS autoimmunity, with examples including STAT3 mutations and the development of AQP4-antibody NMOSD[33]; or TLR3[34] or IRAK4[35] mutations in patients who develop autoimmune encephalitis (Table 1).

Despite these illustrative examples, most people with autoimmune brain diseases do not harbour highly penetrant monogenic variants; and conversely, most monogenic immune disorders do not manifest with CNS autoimmunity. Therefore, the majority of genetic risk in autoimmune brain diseases is likely secondary to more common gene variations with lower penetrance, and the impact of gene-environment interactions.

Common variants and polymorphisms in 'vulnerability' genes

Some risk-modifying low penetrant variants have been identified using genome wide association studies (GWAS) or whole genome studies. The most common autoimmune neurological disease, MS, has demonstrated the power of GWAS studies, and identified over 200 genes, which are almost exclusively immune genes[36,37]. Outside of HLA genes, those implicated in MS include the interleukin-2 receptor (IL2RA), interleukin-7 receptor (IL7RA) (Figure 1), CD226 (glycoprotein on T cells and NK cells) and NFKB1 (regulator of NFKb transcription factor central to cytokine regulation), amongst others[38,39].

In AQP4-antibody NMOSD, studies have associated HLA and non-HLA gene variants with NMOSD risk in patients from the US[40], China [41,42] and Japan[43]. These included non-HLA genes within major histocompatibility complex (MHC) regions, including the complement 4 gene cluster[40]; as well as other less consistently replicated non-HLA genes[39-43]. In narcolepsy, a disease with a very strong HLA association, two non-HLA genes, both involved in T cell responses, CTSH (Cathepsin H) and TNFSF4/OX40L (tumour necrosis superfamily 4) [44], have been implicated.

It should be noted that the GWAS and whole genome studies in the MS studies were highly powered (tens of thousands of subjects), compared to narcolepsy studies (thousands of

subjects) and AQP4-antibody NMOSD (hundreds of subjects) studies. GWAS studies have also shown the strongest associations are in regulatory rather than coding gene regions[38]. These vulnerability gene studies have not been performed in rarer autoimmune CNS disorders, but the work undertaken in MS sets the scene for larger genetic studies in these disorders.

HLA associations

B cell activation by T cells is critically dependent on T cell receptor recognition of peptide antigens presented by HLA class II molecules (Figure 1). HLA associations in diseases likely imply restriction of certain peptides, specific to the binding groove of the HLA molecule, in disease immunopathogenesis. While this has been mostly studied in MS, stronger associations have been recently identified in a number of other autoantibody-mediated CNS disorders (Table 2).

Robust studies have reproducibly identified HLA-DRB1 associations as the main susceptibility locus for MS, with HLA DRB1*15:01 having the strongest effect (odds ratio (OR)>3). This gene shows a dose-response effect, with a higher risk in homozygous subjects[45,46]. The overrepresentation of HLA DRB1*15:01 is present in those of Caucasian background, but has also been reported in those of Japanese, and Middle Eastern ethnicity[45]. Other identified HLA vulnerability alleles vary by ethnicity with DRB1*15:03 in African-American[47] and DRB1*04:05 in Asian populations[48]. DRB1*14 and DRB1*07 have been identified as potentially protective alleles in MS[46]. The recent identification that two HLA-DR15 allomorphs can present foreign peptides and autoantigens to autoreactive CD4+ T cells in patients with MS may have implications for viral pathogens, like Epstein-Barr Virus (EBV) in the pathogenesis of MS[49].

Narcolepsy is a sleep disorder with the strongest HLA-disease association among neurological disorders, as almost all patients across all ethnic groups carry HLA-DQB1*06:02, with a dominance of the HLA-DQA1*01:02-DQB1*06:02 haplotype[50-53]. Carriers of certain alleles (DQB1*06:02 / 06:01, DQB1*06:02 /05:01, or DQB1*06:02 /06:03) have a decreased risk, suggesting a protective effect[51,52]. Hence, HLA combinations, which translate to antigen presenting molecules with often highly-tuned peptide specificities, may be key determinants of either causative or protective CNS autoimmune responses.

Recent studies of patients with LGI1-antibody encephalitis have identified HLA associations almost as strong as in narcolepsy, with HLA-DRB1*07:01 in ~90% of patients, compared to 26% of healthy controls (OR 27.6, 95% CI 12.9-72.2)[54-56]. Non-carriers of the risk HLA may have atypical features with a younger age of onset, female gender, and fewer psychiatric and frontal symptoms[56]. A recent study identified an additional association of DRB1*04:02 with a younger age at LGI1-antibody disease onset[57]. There was no clear evidence of a difference in HLA alleles in tumour vs non-tumour patients, suggesting even in paraneoplastic cases, the antigen exposures may be similar[55,56]. Patients with CASPR2-antibody disease demonstrated an over-representation of HLA-DRB1*11:01, in around 50% of patients, compared to 9% of healthy controls (OR 9.4, 95% CI 4.6-19.3)[55]. The increasingly recognised divergent clinical and prognostic characteristics of LGI1 and CASPR2-antibody diseases[58], are further supported by the dichotomous HLA profiles of these two disorders. To further refine the clinical-genetic associations, it was reported that HLA-DRB1*11:01 was present in 93% of CASPR2-antibody positive patients with CNS involvement manifesting as limbic encephalitis; while patients with dominant peripheral nerve hyperexcitability had similar HLA-DRB11*:01 frequencies to healthy controls[59]. This divergence is less striking in other

cohorts[55] but provides a compelling hypothesis for the influence of immunogenetics on diverse clinical manifestations.

Patients with IgLON5 antibodies usually do not present with a characteristic subacute autoimmune encephalitis, but instead develop a chronic or progressive syndrome with disordered sleep and ventilation, brainstem, gait dysfunction, cognitive abnormalities and movement disorders[60]. While patients may have a poor outcome with disease progression, there are increasing reports suggesting immunotherapy can lead to stabilisation or improvement[61-63]. The HLA-DRB1*10:01-DQB1*05:01 haplotype has been observed in ~90% of IgLON5 antibody-positive patients compared to 27% of controls[64,65]. The DRB1*10:01 allele was 36 times more prevalent in patients than than in the general population, while DQB1*05:01 was 3.5 times more frequent[64]. In IgLON5-disease, patients with DRB1*10:01 alleles more frequently manifested sleep or bulbar dysfunction compared to those patients with other HLA alleles[65].

In contrast to these disorders with strong HLA associations which typically have IgG4 subclass autoantibodies, the identification of at risk HLA haplotypes has been less successful with NMDAR-antibody encephalitis[54] and AQP4-antibody NMOSD, which are characterised by predominant immunoglobulin G1 (IgG1) isotype antigen-specific autoantibodies. This observation suggests a role for HLA Class II molecules in aberrant priming of autoreactive T-cells to skew the response towards the generation of IgG4 subclass autoantibodies[66].

Environmental and epigenetic influences

The role of environmental factors in disease susceptibility is best exemplified by the literature in MS, and has been recently comprehensively reviewed[67]. In summary, smoking is

an established as a risk factor for developing MS[68]. Latitudinal variations in the incidence of MS have associated increased ultraviolet radiation exposure and a reduced risk of MS[69]. Increased vitamin D levels and sun exposure in youth are associated with a decreased risk of MS later in life,[70,71] and low sun exposure in mothers during the first trimester of pregnancy is associated with a higher risk of MS in the offspring[72]. An increased body mass index in adolescence, particularly in females, also appears to be associated with an increased risk of developing MS[73], with proposed pathophysiological mechanisms postulated including low grade inflammation, increased levels of the pro-inflammatory leptin, and decreased bioavailability of vitamin D[67]. There is a rapidly emerging literature regarding the role of the gut microbiome in promoting an excess of a T helper (Th17) response or a deficiency of a regulatory T cells, thereby increasing the propensity to autoimmunity.[74] The collective gut microbiome encodes over a million genes, and it is hypothesised that particular bacterial gene products with sufficient homology to human proteins could trigger autoimmunity through a process of molecular mimicry, or alternatively, perpetuate a state of chronic immune activation of the innate immune system[74]; this paradigm has been specifically interrogated in AQP4-antibody NMOSD and Clostridium species as detailed below.

Autoimmune disease concordance in monozygotic disease is on average 20-30%, suggesting that the nucleotide sequence alone is often not sufficient for disease development[75]. This implicates more nuanced and complex interactions between genetic vulnerability and environmental factors. The environmental factors most commonly incriminated in autoimmunity in general include infections, gut microbiota (related to diet), smoking, pollution and stress. Global data supports the concept that autoimmune diseases are increasing in prevalence, and environmental factors may explain how increasing prevalence may occur over a few decades, a timescale insufficient to explain variation in genomic (DNA) sequences[76].

Epigenetic modification refers to how environmental factors can affect gene expression without altering DNA nucleotide sequences, and typically occurs via three main mechanisms. The first is DNA methylation, where methyl groups attach predominantly to CpG-rich sites and generally results in reduced gene expression (Figure 1). Epigenome-wide association studies (EWAS) in MS have shown differentially methylated CpG sites, including the HLA-DRB1 locus[77]. A recent methylation study of monozygotic twins discordant for MS, found a high degree of similarity in methylomes between twins, with significant differential methylation between the discordant twins of MS in two genes: TMEM232, an immunological associated gene, and ZBTB16, a transcription factor upregulated after glucocorticoid exposure[78]. A single EWAS study in narcolepsy found the most differentially methylated pathways were involved in hormone secretion, and that 95% of the most differentially methylated positions were hypomethylated in narcolepsy patients[79].

A second epigenetic mechanism is histone acetylation and other histone modifications. Chromatin wraps around histone proteins, and acetylation (and other) modifications result in unwinding of chromatin, which increases opportunities for gene transcription. However, evidence for histone modification in autoimmune brain disease is minimal to date[39].

A third epigenetic mechanism involves microRNA - small non-coding RNAs which fine tune gene expression by degrading messenger RNA or repressing mRNA translation (Figure 1). Specific microRNAs are involved in positive and negative regulation of innate and adaptive immune responses[80]. In MS, it has been reported that 165 different miRNA were differentially expressed, and many of these are involved in fine tuning Th17 differentiation, and blood brain barrier permeability[39,81,82]. A small number of papers in AQP4-antibody

NMOSD show that microRNA expression differs in NMOSD compared to MS[83], and some of the microRNA changes normalise after rituximab therapy[84].

All three of these epigenetic mechanisms can be modified by environmental factors such as stress and infection, and are evolved processes to maintain cellular homeostasis and avoid 'over' or 'under' responsiveness. Epigenetic factors therefore represent a hypothetically appealing model of how the environment can modify autoimmunity risk. While the literature in autoimmune neurology is in its infancy to date, a recent study integrating genetic and epigenetic data found that 90% of causal variants identified in GWAS studies of 21 autoimmune diseases localise to non-coding DNA, and 60% map to immune cell enhancers[85].

Loss of immune tolerance

Triggers of loss of immune tolerance

Infection, tumours, and iatrogenic mechanisms such as the administration of immune checkpoint inhibitor therapy, have all been identified as serving as potential triggers for the loss of immune tolerance.

Infection

Specific infectious triggers of neurological autoimmunity are well established. As depicted in Figure 1, immunological cross-reactivity between host and foreign antigens (shared amino acid sequences, peptides, carbohydrates, protein structures, or DNA) forms the basis of the molecular mimicry hypothesis, where a viral or bacterial infection results in a targeted host autoimmune attack on self-antigen. In this section we review the evidence of infection as a precipitating trigger for autoimmune neurological disorders of the CNS.

While the classic infection associated autoimmune neurological condition consistent with molecular mimicry is Campylobacter jejuni induced Guillain Barre Syndrome associated with ganglioside antibodies[86-89], one of the earliest parallel hypotheses in CNS autoimmunity comes from monoclonal antibodies and serum IgG derived from Sydenham chorea patients. These antibodies can show specific binding to mammalian lysoganglioside and the group A streptococcal carbohydrate epitope N-acetyl-beta-D-glucosamine, and can bind to the surface of human neuronal cell with passive transfer of IgG replicating disease in animal models[90-92,].

Narcoplepsy is a hypersomniac disorder thought to be triggered by the loss of hypocretin (orexin) producing neurons in the lateral hypothalamus[93]. Following the novel H1N1 influenza A virus (H1N1pdm09) global pandemic in 2009, numerous epidemiological studies demonstrated that the AS03 adjuvanted Pandemrix vaccine was associated with an increased incidence of narcolepsy in children and adolescents[93-95], and to a lesser degree in adults[96]. One study identified that narcolepsy onset was increased by 3-fold during the pandemic in a largely unvaccinated population, suggesting H1N1 infection itself may also be associated with this phenomenon[97]. The majority of data however associates with the Pandremix vaccine, with an increased risk of narcolepsy in the order of 5-14 fold in children and 2-7 fold in adults, compared to unvaccinated individuals[94,98]. These findings implicate the AS03 adjuvant or the H1N1 viral protein may act as a trigger in patients, perhaps in those with a vulnerable genetic predisposition and HLA profile. Further support for this concept of immune cross-reactivity between a vaccine antigen and a neuronal self-antigen comes from animal models where adoptively transferred orexin-specific T cells can induce loss of orexinergic neurons after Pandremix vaccination[99]. However such models do not account for the marked HLA-restriction observed in patients nor the low risk of developing disease in this

clinical context. This disease may well be predominantly T cell-mediated as hypocretin-specific CD8+ T cells, have been identified in patients with narcolepsy[100].

There are numerous systematic reviews and meta-analyses of infectious risk factors in MS, with the most consistent associations between IgG seropositivity to EBV nuclear antigen (EBNA) (OR 4.46), and infectious mononucleosis disease (OR 2.17)[101,102]. In fact, in a prospective study evaluating 10 million young adults of whom 955 developed MS, all serologically converted to EBNA-IgG positivity, at the latest in the few weeks prior to developing MS; such that prior infection with EBV increased the risk of developing MS by 32 fold[103]. Inversely, based on a recent study of over 900 patients, the authors highlight that negative EBV serology in patients with demyelination is so rare that this should alert clinicians to strongly consider differential diagnoses other than MS[104]. Hence, the necessity of preceding EBV infection in the development of MS appears very strong; however, given the ~90% prevalence of EBV IgG in the general population, it is clear that EBV infection does not act in isolation. A recent meta-analysis identified that there was an additive risk with various combinations of environmental factors; including EBV antibody titre and HLA genotype, prior infectious mononucleosis in HLA-DRB1*1501 positive individuals, and smoking in patients with high anti-EBV antibodies[105]. While a history of either EBV infection or obesity alone increases the risk of MS twofold, a combination of the two risk factors increases the risk by 14 fold, irrespective of the HLA-DRB1*15:01 risk allele status[106]. Due to the case-control and cohort level studies, the association of EBV with the development of MS reaches Level IV evidence. Emerging studies postulating molecular mimicry between EBNA1 and the CNS protein GlialCAM, and EBNA1 specific CSF B cells in MS patients, suggests a mechanistic link underling the pathogenesis between the EBV

association with MS, and raises the potential for EBV vaccination as a novel therapeutic approach in MS[107].

It has been recognised for some decades that patients with acute herpes simplex virus (HSV) encephalitis (HSVE), who are treated with antiviral therapy and improve, may subsequently develop a neurological relapse characterised by choreoathetosis and cognitive deterioration[108,109]. Recent prospective cohorts have identified that NMDAR-autoantibodies are negative during the primary infectious event, but that 27% of patients develop a secondary autoimmune encephalitis around 8 weeks after HSVE, with serum and/or CSF autoantibodies specifically targeting most commonly NMDAR, but also other neuronal surface antigens[108,110-112]. The high frequency of this association and its widespread reporting from multiple groups worldwide suggests a strong relationship for HSVE serving as a trigger for subsequent autoimmune encephalitis, and reaches Level V evidence. As the NMDAR antibodies identified in these patients are IgG, rather than the less mature IgM, they are likely to be as pathogenic as the antibodies from patients with 'primary' NMDAR-antibody encephalitis: a hypothesis which could be tested in experimental animals. Indeed, two thirds of mice inoculated intranasally with HSV-1 were found to develop serum NMDAR antibodies between 1-2 months post-inoculation[113]. A recent paper identified a potential further form of infection triggered autoimmunity: around 20% of children with Japanese viral encephalitis went on to develop autoimmune encephalitis[114]. 2/5 showed NMDAR antibodies in the serum and CSF, and one developed gamma-amino butyric $acid_B$ receptor ($GABA_BR$) antibodies in the CSF. The patients with autoantibodies had more severe outcomes and elevated levels of cytokines, including the chemotractant CXCL13, in the serum and CSF.

This viral heterogeneity suggests the underlying pathogenesis for pathogen-induced autoimmune neurology is likely to be more than just molecular mimicry and, indeed, no sequence homology has yet been reported between proteins in HSV or Japanese encephalitis virus and the NMDAR. An alternate explanation is that viral destruction of infected neurons may result in extensive inflammatory sequelae which may be the trigger for the subsequent immune response to hitherto concealed antigens[109,115]. This pathway may well implicate cervical lymph nodes as key sites of antigen drainage and immune response initiation as we discuss further below[116].

An excellent example of a infection-disease association which may be mediated via T cell mimicry is illustrated by AQP4-antibody NMOSD, where AQP4-specific proliferative T cells have been shown to recognise a dominant AQP4 T-cell epitope (p63-76), have a T helper 17 (Th17) phenotype, and cross-react with a homologous peptide sequence of the protein adenosine triphosphate-binding cassette transporter permease of Clostridium perfringens, a commensal gut bacterium in humans[117]. More widespread gut microbiome investigations identified the overrepresentation of Clostridium perfringens in AQP4-antibody NMOSD patients compared to MS patients or healthy controls[118]. Similar associations have been identified with an increased prevalence of Clostridium bolteae in Indian AQP4-antibody NMOSD patients compared to controls[119].

Tumours

The strong association between cancer and neurological autoimmunity has been well established for decades, wherein patients with a systemic malignancy that expressed the key autoantigen can manifest a paraneoplastic neurological syndrome associated with an anti-tumour autoantigen-specific response[120]. One group of such patients are characterised by the

detection of antibodies targeting intracellular antigens, exhibiting a dominantly T cell mediated pathogenesis, with 'high risk' autoantibodies for a paraneoplastic process (Table 3)[121,122]. Examples include Hu (small cell), Ri (small cell or breast adenocarcinoma), or Yo (breast or gynaecologic adenocarcinomas) antibodies. These antibodies are considered diagnostic biomarkers but not demonstrated to be pathogenic as they cannot access their target antigens *in vivo*. Most patients have a progressive disease course driven by their underlying malignancy, and are largely less responsive to immunotherapy[123]; although a subgroup have more recently been shown to respond to immunotherapy, most notably with GFAP[16], KLHL11[124] and amphiphysin antibodies[125]. A second group of patients have paraneoplastic neurological syndromes characterised by pathogenic autoantibodies targeting neuroglial cell surface antigens (Table 3)[123]. These patients are characteristically immunotherapy responsive, with disease pathogenesis thought to be dominantly B cell-mediated.

A key advancement with recently proposed paraneoplastic neurological syndrome criteria is that the cognate antigen is shared with the tumour[122]. This is exemplified by reports of the identification of Yo antigen in gastric adenocarcinomas[126], $GABA_AR$ and LGI1 in thymomas[127], and NMDARs in ovarian teratomas[128]. The identification of B and T cell infiltrates and tertiary lymphoid architecture reminiscent of germinal centres in teratomas, and the demonstration that teratoma explants in patients with NMDAR-antibody encephalitis can produce NMDAR specific autoantibodies from *in vitro* cultures, suggests intratumoural B cells have the capacity to secrete pathogenic autoantibodies and induce disease[116,128]. In conjunction with the clinical response to oophorectomy observed in these patients, these findings suggest that the initiation of paraneoplastic neurological syndromes may occur outside the CNS with intratumoural autoantibody synthesis in teratomas, and subsequent

passage of antigen-specific B cells and autoantibodies to the circulation and intrathecally. This hypothesis aligns with the consistently higher levels of autoantibodies in serum compared to CSF in these conditions[2,21], although is contraindicated by the observation that some patients – including those with teratomas – may not have detectable serum NMDAR-antibodies despite the presence of CSF antibodies[129]. While this observation may imply a CNS-initiated and isolated response in a subset of patients, it may also be related to the limited sensitivity of detecting lower NMDAR-antibody levels in serum. Alternatively, a very recently reported concept – of the rodent skull bone marrow containing CNS-autoantigen reactive B cells which may be rapidly tolerised upon exposure to their autoantigen – may explain the phenomenon of 'CSF-exclusive' autoantibodies[130]. If this concept extends to humans, it is possible that failure to appropriately tolerise these cells leads to their escape and may account for a CNS-initiated autoantibody-mediated process.

Finally, an important question that remains to be answered is why some tumours and some antigens incite a T cell mediated paraneoplastic process, while others incite a dominantly B cell mediated disorder; and whether this is influenced by whether the initiating immune response is against an extracellular or intracellular peptide.

Iatrogenic disruption of immune checkpoints

The use of immune checkpoint inhibitor (ICI) therapy to block regulatory molecules, such as programmed cell death protein 1 (PD1), PD1 ligand (PDL1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) (Figure 1) has revolutionised the treatment of cancer with significantly increased survival in selected advanced or metastatic malignancies[131]. While the rationale for their effect is the expansion of anti-tumour effector T cells, these treatments can simultaneously result in the release of autoreactive T and B cells, disruption in immune

tolerance, and the consequent development of systemic immune related adverse events (IRAEs) in many patients. Neurological IRAEs (nIRAEs) occur in 1-10% of patients treated with ICIs, with higher rates in patients on combination CTLA4 and PD1/PDL1 therapy[132]. nIRAEs usually occur within the first three months of ICI treatment[132,133], and can result in morbidity, interruptions to cancer therapy, and death due to the autoimmune complication itself, or the malignancy. While peripheral nervous system manifestations including myasthenic syndromes, myositis, and neuropathies, account for 75% of nIRAEs, CNS manifestations account for 25% (Table 4) [134], and may have a severe disease course and associated mortality[132,133]. While non small cell lung cancers are more frequent in patients with CNS nIRAEs, melanomas are more common in patients with PNS nIRAEs[133].

A number of hypotheses may explain some of the underlying immunobiology related to nIRAEs. Hypophysitis following CTLA4 blockade therapy can be present in up to 4% of treated patients[135]. Pituitary gland tissue has been shown to express CTLA-4, dominantly in prolactin and thyrotropin secreting cells, with evidence of CTLA-4 blockade resulting in lymphocytic infiltration, and subsequent complement activation and deposition. ICIs may alternatively trigger more specific nIRAEs when the tumour tissue expresses the relevant antigen. This was elegantly demonstrated in an animal model of a paraneoplastic neurologic disorder where a haemaglutinin (HA) antigen was expressed both in Purkinje neurons and implanted breast tumour cells[136]. Co-injection of CTLA4-blocking monoclonal antibody together with CD4 and CD8 T cells resulted in antigen-specific T cell migration into the cerebellum, and progressive neurologic impairment despite tumour resolution. This occurred only in experimental conditions including both CTLA4 blockade and antigenic expression in the CNS as well as the tumour cells, but not in control groups including only one of these conditions in isolation[136]. Other hypotheses for the development of nIRAEs include a

paraneoplastic neurological syndrome associated with their malignancy, or pre-existing serum autoantibodies which are not associated with clinical manifestations until ICIs act as a second or third hit to unmask clinical disease. In a case series of patients with thymomas under treatment with avelumab, a PDL1 antibody, only the four patients with pre-existing muscle AChR antibodies went on to develop myositis[137]. Similarly, Ma2 antibodies were retrospectively identified in serum prior to ICI therapy in patients who progressed to develop Ma2 antibody associated limbic encephalitis[138]. A recent publication identified a higher prevalence of the HLA-B*27:05 genotype in patients treated with a PD-L1 inhibitor who went on to develop autoimmune encephalitis (60%), compared to the general population (2.5%)[139], suggesting some patients may have a pre-existing propensity to develop autoimmune complications. Finally, ICIs may exacerbate pre-existing autoimmune disease, as demonstrated in patients with radiologically isolated syndrome who receive ICI for their malignancy and develop overt manifestations of clinically definite MS[140].

There is growing literature that the presence of IRAEs , at least in the case of PD-1 and PDL1 blockade, may predict a more robust anti-tumour effect and increased progression-free survival compared to patients who do not experience IRAEs[141]. This mirrors prior observations in paraneoplastic neurological syndromes, on the increased survival of patients with small cell lung cancer (SCLC) who have Lambert-Eaton myasthenic syndrome accompanied by P/Q type voltage gated calcium channel (VGCC) antibodies, compared to patients with SCLC alone[142,143]. Similarly, in the case of opsoclonus myoclonus ataxia syndrome (OMAS) associated with neuroblastomas - children with neuroblastomas and OMAS had a higher chance of non-metastatic disease and improved 3-year survival compared to children with neuroblastomas who did not develop OMAS[144], albeit at the expense of neurological sequelae. Potential reasons contributing to better survival rates may

include more tumour-cell destruction in patients with antibody-mediated syndromes, lead time bias where the diagnosis of a paraneoplastic syndrome predating tumour detection resulted in increased vigilance and paraneoplastic screening and therefore an earlier diagnosis and treatment of the malignancy; or the possibility of the earlier age of onset of SCLC in patients with VGCC antibody-associated LEMS acting as a confounder with respect to better outcomes.

Mechanisms involved in the loss of immune tolerance

Relative roles of the periphery and the CNS

In autoantibody-mediated neurological disorders, the 'trigger' for the break in immune tolerance appears to occur in the periphery[115]. Yet, the relative timing by which systemic versus intrathecal autoantibodies are generated remains a critical question for targeting therapeutics to the appropriate compartments. One way to address this is the evaluation of serum and CSF autoantibody titres. In patients with a wide range of autoantibody-mediated neurological encephalitic and demyelination syndromes, this ratio demonstrates a recurrent theme: there are higher concentrations of autoantibodies in the serum compared to the CSF, suggesting the initial generation of autoantibodies is consistently peripheral[21]. This hypothesis is borne out by the therapeutic response to agents such as rituximab or plasmapheresis, which targets the peripheral B-cell compartment or circulating soluble IgG respectively, and likely have a limited direct action on the CNS and intrathecal compartment. However, alongside this, the presence of intrathecal autoantigen-specific B cells in patients with NMDAR- and LGI1-antibody encephalitis[145,146], and intrathecal AQP4-reactive B cell clones in AQP4-NMOSD patients experiencing a relapse[147], draw attention to a clear role of the

intrathecal compartment which should also be considered, particularly in treatment-resistant patients. The marked concentration of autoantigen-specific B cells and plasma cells observed in the intrathecal compartment, alongside histopathological studies showing both cell types are found in the CNS of patient autopsies and biopsies, suggests that these cells home to the CNS and are thereafter retained in this compartment[148]. This may occur after encountering their cognate autoantigen, and hence ongoing germinal centre reactions may perpetuate in the CNS akin to the tertiary lymphoid follicles seen in patients with MS. If so, the ongoing proliferative and chemotactic activity of germinal centres could be prime therapeutic targets to terminate disease progression.

But how could the periphery drive the CNS in cases where brain infection precipitates CNS autoimmunity, such as HSVE? One explanation is that autoantigens released by neuronal destruction due to viral invasion may be delivered to regional cervical lymph nodes, which are now known to drain the CNS meninges[115]. These antigens, upon encountering naïve B cells and CD4+ T helper cells in cervical lymph nodes, may incite differentiation of autoantigen-reactive B cells into autoantibody-producing memory and plasma cells, and hence initiate or perpetuate autoantibody-mediated neurological disease.

Indeed, early results from the first two studies sampling deep cervical lymph nodes (dCLNs) from patients with autoantibody-mediated neurological syndromes (NMDAR-antibody encephalitis and AQP4-antibody NMOSD), were able to detect NMDAR- and AQP4-antibody reactive B cells from some of the dCLNs sampled[116,149]. In patients with NMDAR-antibodies, this was especially observed in patients with higher serum NMDAR-antibody levels and more elevated dCLN CXCL13 levels, suggesting these autoantigen-specific dCLN measures reflect ongoing germinal centre, and hence disease, activity. This is of particular interest given ~80% of patients with NMDAR-antibody encephalitis do not have an ovarian

teratoma[150], suggesting the dCLNs as a potentially alterative site of immune activity. In patients with AQP4-antibody NMOSD, the dCLNs also contained AQP4-IgGs and, both this and the AQP4 B cell reactivities, were no longer detectable after administration of rituximab to the patients[149]. Hence, the dCLNs may be sites of initiation and perpetuation across autoantibody-mediated diseases, and also provide valuable measures of immunological activity to help guide choices of therapeutics and better understand their mechanisms of action. Evaluation of other lymph node groups outside of the dCLNs, is of interest. Recent advances in our understanding of the trafficking of immune cells between the brain, the CSF, and the peripheral circulation are outlined in Box 2.

B cell tolerance checkpoints

If the disease process is peripherally initated, it follows that autoantigen-specific B cells should be identified in the circulation of patients with certain autoantibody-mediated neurological syndromes. Indeed, this has been observed in patients with AQP4-, LGI1-, MOG- and NMDAR- antibody-mediated diseases[128,151-153]. However, to permit accurate therapeutic targetting of autoantigen-specific B cells, it is important to understand at what B cell developmental stage this autoreactivity first emerges. This, in turn, can identify whether central or peripheral tolerance checkpoints are impaired, and how the circulating pool of antigen-specific autoantibodies may be generated. For example, a proportion of the most recent bone marrow emigrant B cells may express B cell receptors which react with autoantigen(s). If so, the reactivity is present after a central tolerance checkpoint. Alternatively, if the autoantigen reactivity is only acquired by B cells later in their development, (ref the Kotzomi paper and the old Lanzevecchia pemphigus / GM-CSF papers) this may be generated in cells which have traversed a peripheral B cell checkpoint and have

694 been, inadvertently, retained in the B cell repertoire. Hence, this developmental mapping
695 offers targeted insights into deletion of pathogenic B cells.
696
697 Thereafter, in terms of autoantibody perpetuation a series of possibilities exist, and have been
698 explored in a recent review in this journal[2]. In brief, one model proposes that these
699 autoreactive B cells could undergo short extrafollicular reactions and generate pathogenic
700 IgMs. While studies of antigen-specific IgMs have yielded very different results, with only
701 some suggesting pathogenic potential (perhaps due to the use of monoclonals versus serum
702 derived antibodies[145,154]), serum IgMs against autoantigens are clearly present in these patients
703 and may represent an underlying extrafollicular reaction[128,149,155,156]. Alternatively, these B
704 cells may have the potential to initiate 'follicular' germinal centre reactions and mature to
705 higher affinity memory antibodies, via two dominant pathways. B cells typically undergo
706 active germinal centre reactions after repeated antigen encounter and help from cognate
707 CD4+ T helper cells in secondary lymphoid organs. This may perpetuate the maturation of
708 memory B cells which exit the germinal centre, and develop into plasmablasts and long-lived
709 plasma cells, with the subsequent continual production of antigen specific IgM and IgG, as
710 has been demonstrated in the case of NMDAR-antibody encephalitis[128]. In another model,
711 after germinal centre activation of B cells, selected affinity-matured long-lived plasma cells
712 may sequester in bone marrow niches and remain responsible for autonomously secreting the
713 majority of the antigen-specific autoantibodies – this model does not require continuous
714 antigen exposure[2], and could go some way towards explaining treatment resistant patients
715 who may not successfully respond to B cell depletion which largely targets circulating B cells
716 rather than autoantibody-producing plasma cells. A recent trial of 12 patients with AQP4-
717 NMOSD who underwent autologous haematopoietic stem cell transplantation developed
718 persistent AQP4 seronegativity which is uncommon in this disorder when treated with other

forms of immunosuppression, and may support the pathogenic potential of long-lived plasma cells in tissue reservoirs such as the bone marrow, which are generally resistant to conventional immunotherapy[157]. It is likely that a combination of these models operates in individual patients, and should be simultaneously considered when therapeutic options are approached.

Therapeutic implications of understanding disease immunopathogenesis and future directions

Understanding disease pathogenesis from an immunobiological perspective is critical as it allows refinement of the therapeutic algorithm. While steroids are largely successful in rapidly reducing symptoms across a range of autoimmune neurological disorders, their widespread systemic sequelae are unacceptable in the long-term. Autoantibodies do not act in isolation, and CSF and serum autoantibodies can be present even during disease recovery and clinical remission, suggesting the inflammatory milieu of cytokines, chemokines, complement, and innate immunity have critical influences on T and B cell mediated autoimmunity[158-160], and therefore provide important therapeutic targets (Figure 1). The role of targeted therapy can be demonstrated in the utility of anti-CD20 therapies in cell surface autoantibody syndromes[161-163]; eculizumab in complement mediated disorders such as AQP4-antibody NMOSD[164,165]; monoclonal antibodies targeting type 1 interferon receptors in lupus; anti-interleukin-6 therapy in new onset refractory status epilepticus[166]; janus kinase inhibition in Aicardi-Goutieres syndrome[167]; and anti-interleukin-6 therapies like satralizumab and tocilizumab[168] currently undergoing clinical trials in autoantibody-mediated encephalitis and demyelination. Investigating epigenetic mechanisms may further open novel therapeutic opportunities such as inhibition of DNA methyltransferases, histone deacetylase inhibitors, or small-interfering and other RNA drugs[169]. The role of EBV vaccination in MS prevention,

given the recent definitive evidence regarding the role of EBV in MS pathogenesis, is compelling.

It remains unknown why some patients with autoimmune neurological disorders have a monophasic disease course and why others relapse. The relapse rate in the natural history of these disorders varies – in NMDAR-antibody encephalitis relapses occur in ~20%[21], in MOGAD ~50%[170], and in AQP4-antibody NMOSD >80%. A key factor that remains to be determined is whether early therapeutic management can change the relapse rate and natural history. The well-established literature on the early use of high efficacy therapy in MS such as natalizumab and alemtuzumab suggests this may alter the natural history of the disease[171]. Rituximab, a monoclonal antibody targeting CD20+ B cells, reduces relapse rates in AQP4-antibody NMOSD[161,172] and NMDAR-antibody encephalitis[163]. Repeated treatment with rituximab results in increasingly longer intervals to B cell repopulation, and the potential for less frequent redosing[173], although the question remains whether rituximab can permanently alter B cell dynamics. A recent study demonstrated that AQP4-antibody NMOSD patients have both impaired numbers and function of regulatory B cells, both of which are restored following B cell depletion therapy, suggesting a more pervasive influence of treatment on disease immunopathogenesis[174].

Autoimmune neurology is a dynamic field, and while patients may be significantly impaired with seizures, cognitive impairment, blindness, or paralysis; early recognition and appropriate immunotherapy allows for the reversibility of disability in many cases, and is a compelling reason to optimise our understanding of underlying disease mechanisms in order to elevate our management of these disorders to a more precision medicine approach.

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Key Points

1. The immunopathogenesis of autoimmune neurological disorders highlights the complex interplay between a number of contributing factors

2. Firstly, non-modifiable risks including age, gender, ethnicity, and genetic predispositions (inclusive of monogenic disorders, common variants and polymorphisms in vulnerability genes, and HLA associations) may help determine an individual's predisposition to neurological autoimmunity
3. Secondly, the interaction of epigenetic and environmental factors can modify disease onset and severity.
4. Thirdly, identified 'triggers' for the loss of immune tolerance, such as infections, neoplasms, and iatrogenic drugs such as immune checkpoint inhibitors, may precipitate neurological autoimmunity.
5. Finally, the disruption of B and T cell tolerance, and the passage of immune cells from the peripheral circulation to the central nervous system, play a key role in initiating disease activity.

Table 1: Monogenic disorders and their associated CNS autoimmune neurological sequelae

Immune pathway	Gene (protein)	Inher.	Protein function	Mutation effect on function	Typical immune associations	CNS disease	CNS autoimmunity	Associated neuronal antibody
Complement	C1q (C1a A, B, C)	AR	Opsonisation, inflammation, phagocytosis	LoF causes impaired clearance of apoptotic material	SLE, recurrent infection	+	NPSLE, CNS vasculitis[25]	-
	C4 (C4 A, B)	AR			SLE, GN, recurrent infection	+	Anti-NMDAR encephalitis[26]	NMDAR antibody
Apoptosis	TNFRSF6 (FAS)	AD, AR	Cell surface death receptor	LoF causes defective apoptosis and impaired lymphocytic tolerance	Autoimmune Lymphoproliferative syndrome (ALPS), autoimmune cytopenia	+/-	Cerebellar ataxia, transverse myelitis[27]	-
	PRKCD (PKC delta)	AR	Protein kinase involved in deletion of autoreactive B cells (apoptosis)	Loss-of-function causes defective apoptosis and proliferation and expansion of autoreactive B cells	SLE, CVID, lymphoproliferative disease	+	NPSLE, CNS vasculitis[175]	-
Protein degradation	TPP2 (TPP2)	AR	Removal of misfolded protein, proteosome degradation	Loss-of-function causes defective protein degradation	Immune deficiency, systemic autoimmunity	++	NPSLE, MS-like syndromes, intracranial calcification[176]	-
Nucleic acid	TREX1	AR	DNA 3'-repair			++	Neuropsychiatric	-

species removal and sensing, interferonopathy	(TREX1)		exonuclease	LoF causes failure of degradation of endogenous nucleic acids, activation of interferon pathway	Interferonopathy (Aicardi Goutières syndrome), SLE		SLE, Opsoclonus myoclonus ataxia syndrome[28]	
	RNASEH2B (RNase H2B)	AR	Ribonuclease H2			++	Opsoclonus myoclonus ataxia syndrome[28]	-
	IFIH1 (MDA5)	AD	Cytoplasmic viral RNA receptor	Gain-of-function activates interferon signalling		++	Neuromyelitis optica spectrum disorder[29]	Aquaporin-4 antibody
Interferonopathy	ACP5 (TRAP)	AR	Negative regulator of interferon-alpha, via osteopontin	LoF causes loss of negative regulation of interferon production	Spondyloenchondrodysplasia (SPENCD), autoimmune cytopenia, SLE, recurrent infection	+	Spastic paraparesis, developmental delay, intracranial calcification[177]	-
	ISG15 (ISG15)	AR	Type 1 interferon inducible ubiquitin-like protein	LoF results in loss of negative regulation of type 1 interferon production	Susceptibility to mycobacterial disease	+	Intracranial calcification[30]	-
	TMEM173 (STING)	AD	Stimulator of interferon genes	GoF and activation of STING-interferon pathway	STING associated vasculopathy in infancy (SAVI)	+	Cerebral vasculopathy, and strokes[31,32]	-
Regulation of immune signalling	STAT1 (STAT1)	AD	Signal transducer and activator of transcription	GoF or LoF causes abnormal JAK-STAT and NFKB signalling	Chronic mucocutaneous candidiasis, immune deficiency, autoimmune disease	+/-	Cerebral vasculitis, multiple sclerosis-like[178]	-
	STAT3	AD	Signal	GoF causes	Early-onset	+/-	Neuromyelitis optica	Aquaporin-

	(STAT3)		transducer and activator of transcription	abnormal JAK-STAT and NFKB signalling	multiorgan autoimmune and lymphoproliferative disease		spectrum disorder[33]	4 antibody
	TLR3 (TLR3)	AD	Innate immune infection and danger signal receptor	Abnormal innate immune signalling and deficient NFKB immune signalling	Herpes simplex encephalitis	+	Autoimmune encephalitis post HSE[34]	-
	NLRP3 (NLRP3)	AD	Intracellular receptor, sensor of infection and danger signal	GoF causes NLRP3 inflammasome activation and interleukin-1B secretion	Cryopyrin associated periodic syndromes including CINCA	+	Multiple sclerosis like CNS demyelination[179]	-
	TNF1AP 3 (A20)	AD	TNF alpha induced protein 3 restricts and terminates NFKB signalling	LoF causes loss of negative-feedback of NFKB activation, with consequent increased immune gene expression	Autoinflammation, Behcets-like syndrome, SLE	+	Neuropsychiatric SLE, CNS vasculitis[180,181]	Anti-Sm antibody
	IRAK4 (IRAK4)	AR	Interleukin-1 receptor-associated kinase	LoF impairs IL-1 receptor and TLR signaling	Immune deficiency, bacterial infection	+/-	Anti-NMDAR encephalitis (and HHV6 reactivation)[35]	NMDAR antibody
Loss of tolerance	FOXP3 (FOXP3)	X-linked	Transcription factor of T regulatory cells	LoF impairs T cell regulation and loss of tolerance	IPEX syndrome: immune dysregulation (autoimmune cytopenias), polyendocrinopathy	+/-	Neuromyotonia[182]	LGI1 and CASPR2 antibody

					and diabetes, enteropathy			
	CTLA4 (CTLA4)	AD	T cell regulation, checkpoint inhibitor	LoF causes loss of CTLA inhibitory function and subsequent T cell hyperactivity	Immune deficiency, autoimmune disease, lymphoproliferative disorder	+	Neuroinflammatory encephalomyelitis (32% of patients)[183]	-
	AIRE (AIRE)	AR or AD	Thymic transcription factor involved in eliminating self-reactive T cells	LoF causes failure to eliminate self-reactive T cells	Autoimmune disease (AD), Autoimmune polyendocrinopathy syndromes (APS1 and APECED usually AR)	+/-	Autoimmune encephalitis[184]	GAD autoantibody

LEGEND

Monogenic genes associated with neurological autoimmunity. Only genes with reports of neurological autoimmunity (multi-system autoimmunity with clear reports of NP involvement, or selective neurological autoimmunity. Relative proportion of patients with monogenic variants who have neurological involvement is presented as: ++=>50%, +=<50%, +/-= occasional reports

Table 2: HLA associations in autoimmune CNS disorders

Autoimmune neurological disorder	Dominant autoantibody subclass	HLA haplotype	Clinical association	Level of evidence
Multiple sclerosis	Not applicable	HLA DRB1*15:01 in Caucasians and other ethnic groups[45,46]	Risk allele OR>3	Robust genome wide association studies and meta-analyses for HLA DRB*15:01
		HLA DRB1*15:03	Risk allele in African-American populations[47]	
		HLA DRB1*04:05	Risk allele in Asian populations[48]	
		HLA DRB1*14 HLA DRB1*07[46]	Protective alleles	
Narcolepsy	Not applicable	HLA-DQB1*06:02 HLA DQA1*01:02	Risk allele in 98% of patients DQB1*0301, DQA1*06, DRB1*04, DRB1*08, DRB1*11, and DRB1*12 DQB1*0602 association highest in cases with hypocretin deficiency[52]	Large cohort studies and genome wide association studies of over 500 individuals[50,51]
		DQB1*06:02 / 06:01 DQB1*06:02 /05:01 DQB1*06:02 /06:03	Protective alleles[51]	
LGI1-antibody autoimmune encephalitis	IgG4	HLA-DRB1*07:01	Risk allele present in over 90% of LGI1 autoimmune encephalitis patients[54-56,185] Non-carriers more likely to be younger and/or female[56]	Cohort studies from Korea, the UK, Netherlands, and France
		HLA-DRB1*04:02	Younger age of onset[57]	

CASPR2-antibody autoimmune encephalitis	IgG4	HLA-DRB1*11:01	Present in 60-93% of patients[55,56] Strongly associated with limbic encephalitis phenotypes but not peripheral nerve hyperexcitability phenotypes[56]	Cohort studies from the UK and France
IgLON5-antibody autoimmune encephalitis	IgG4	HLA-DRB1*10:01 -	Present in up to 80% of patients. HLA-DRB1*10:01-DQB1*05:01 haplotype in 57% of patients compared to 2.4% of controls[64,65]. 93% of patients also had DQA1*01 and DQB1*05 chains compared to 27% of controls[65]. More frequently manifested sleep or bulbar dysfunction[65]	Cohort studies Two IgLON5 peptides showed strong binding to HLA-DRB1*10:01[65].
		DRB*10:01 negative patients	Trend to better immunotherapy response[65]	
KLHL11		HLA-DQB1*02:01 HLA-DRB1*03:01	Risk alleles[124]	

Table 3: Malignancies and associated B and T cell mediated autoimmune neurological disorders

Autoantibody Risk profile	Antigenic profile		Frequency of malignancy associated with antibody	Associated malignancy	Neurological manifestations
	Antigen	**Localisation of antigen**			
High risk (>70% associated with malignancy)	SOX1[186]	Intracellular	>90%	SCLC	LEMS, paraneoplastic cerebellar degeneration
	Yo/PCA-1[187-189]	Intracellular	>90%	Ovarian cancer, breast cancer, uterine cancer	Paraneoplastic cerebellar degeneration, polyneuropathy
	Tr/DNER[190]	Intracellular	>85%	Hodgkin lymphoma	Paraneoplastic cerebellar degeneration
	Hu/ANNA-1[189]	Intracellular	85%	SCLC, NSCLC, neuroendocrine tumours, neuroblastoma, prostate cancer, ovarian cancer	Sensory neuronopathy, gastrointestinal pseudo-obstruction, limbic encephalitis, encephalomyelitis, paraneoplastic cerebellar degeneration, motor neurone involvement
	CRMP5/CV2[191]	Intracellular	>80%	SCLC, thymoma (particularly in patients with MG), gastrointestinal stromal tumour	Encephalomyelitis, myelopathy, sensory neuronopathy, axonal polyradiculoneuropathy, gastrointestinal pseudo-obstruction, optic neuritis
	PCA2/MAP1B[192]	Intracellular	80%	SCLC, NSCLC, breast cancer, squamous cell cancer, renal cell carcinoma	Polyradiculoneuropathy, sensory neuronopathy, sensorimotor neuropathy, autonomic neuropathy, paraneoplastic cerebellar degeneration, encephalomyelitis, Lambert Eaton myasthenic syndrome, brainstem involvement
	Amphiphysin[125,193]	Intracellular	80%	Breast cancer, SCLC	Polyradiculoneuropathy, sensory neuronopathy, facial neuropathy with

					gastroparesis, myelopathy, stiff person syndrome, encephalomyelitis, cochleovestibulopathy
	KLHL11[124,193,194]	Intracellular	80%	Testicular germ cell tumours dominantly, lung adenocarcinoma, chronic lymphocytic leukaemia	Brainstem syndrome, cerebellar ataxia, cochleovestibulopathy (sensorineural deafness)
	TRIM46[195]	Intracellular	>80%	SCLC, neuroendocrine tumours of the pancreas/ oesophagus/endometrium, adenocarcinoma (lung, breast, ovarian, endometrial), sarcoma	Cerebellar syndrome dominantly, encephopathy and seizures, limbic encephalitis, brainstem encephalitis, myelopathy, parkinsonism/dystonia,
	Ma/Ma2[196]	Intracellular	>75%	Testicular cancer, NSCLC, cervical cancer	Brainstem encephalitis, diencephalitis, limbic encephalitis
	Ri/ANNA-2[197]	Intracellular	>70%	Breast cancer, SCLC, NSCLC	Brainstem syndrome, cerebellar syndrome, opsoclonus myoclonus ataxia syndrome, jaw dystonia, myoclonus, tremor, parkinsonism
	ZIC4	Intracellular	TBC	SCLC dominantly, diffuse large B cell lymphoma	Paraneoplastic cerebellar degeneration
Intermediate risk (30-70% associated with malignancy)	AMPAR[121,198]	Cell surface	>50%	SCLC, malignant thymoma, breast cancer, ovarian cancer, rare - Ewing sarcoma, thyroid cancer	Autoimmune encephalitis
	$GABA_BR$[199]	Cell surface	>50%	SCLC in half the patients, neuroendocrine tumours, thymoma, melanoma, carcinoid tumour	Autoimmune encephalitis
	mGluR5[200]	Cell surface	50%	Hodgkin lymphoma dominantly, SCLC	Autoimmune encephalitis
	VGCC	Cell surface	50%	SCLC dominantly, breast	LEMS dominantly, cerebellar ataxia,

	(P/Q or N)[201]			adenocarcinoma, pelvic malignancy, neuroendocrine tumours, lymphoma	encephalomyelitis, sensory neuropathy, autonomic ganglionopathy
	NMDAR[202]	Cell surface	20-30% (rare in children)	Ovarian teratomas dominantly, extraovarian teratomas, other varied tumours rare and mostly in elderly (SCLC, uterine/prostate adenocarcinoma, Hodgkin lymphoma, neuroendocrine tumours, neuroblastoma)	Autoimmune encephalitis
Low risk (<30% associated malignancy)	mGluR1[203]	Cell surface	30%	Hodgkin lymphoma, non Hodgkin lymphoma, acute lymphocytic leukaemia prostate adenocarcinoma, cutaneous T cell lymphoma, testicular seminoma	Cerebellar ataxia, cognitive dysfunction
	$GABA_AR$[204,205]	Cell surface	25%	Malignant thymoma, less commonly with non Hodgkin lymphoma, SCLC, rectal cancer	Autoimmune encephalitis
	CASPR2[59,206]	Cell surface	20% (up to 50% in Morvan syndrome)	Malignant thymoma dominantly, also SCLC, endometrial adenocarcinoma	Autoimmune encephalitis, neuromytonia, sleep dysfunction, Morvan syndrome
	GFAP[207]	Intracellular	20%	Ovarian teratomas, adenocarcinomas	Meningoencephalitis, myelitis
	GAD65[208]	Intracellular	10%	SCLC, malignant thymoma, neuroendocrine tumours, thyroid cancer, breast cancer	Limbic encephalitis, stiff person syndrome, cerebellar ataxia, seizures
	LGI1[55,209]	Cell surface	<10%	Malignant thymoma dominantly, neuroendocrine	Autoimmune encephalitis

				tumours and other varied tumours rare (basal cell carcinoma, bladder, breast, prostate, pancreatic cancer, mesothelioma)	
	DPPX[210]	Cell surface	<10%	B cell neoplasms including gastrointestinal follicular lymphoma, chronic lymphocytic leukaemia	Autoimmune encephalitis, PERM
	GlyR[211]	Cell surface	<10%	Malignant thymoma, Hodgkin lymphoma, breast cancer	Autoimmune encephalitis, PERM, opsoclonus myoclonus
	AQP4[212]	Cell surface	<5%	Adenocarcinoma of the lung, breast	AQP4-NMOSD
	MOG[213]	Cell surface	<1%	Ovarian teratoma	MOGAD
	IgLON5[64]	Cell surface	Not reported		Autoimmune encephalitis with neurodegenerative features (movement disorders, sleep dysfunction, apnoea)
	Neurexin-3α[214]	Cell surface	Not reported		Autoimmune encephalitis
	D2R[215]	Cell surface	Not reported		Autoimmune/basal ganglia encephalitis

This table used the same stratification as the recently proposed PNS diagnostic criteria[122] and adapated and updated Tables 1-3 from this publication to reflect the current literature.

Table 4: CNS immune related adverse events in patients treated with checkpoint inhibitor therapy

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Neurological manifestations	Clinical characterisation	Autoantibodies identified in seropositive cases	Immunotherapy response and outcomes
Hypophysitis[132,134]	In up to 4% of ICI treated patients Headache, cognitive dysfunction, anterior pituitary hormone deficiency, central diabetes insipidus, particularly after CTLA4 blockade	Not reported	Corticosteroids, may require long term hormone replacement therapy
Meningitis, meningoencephalitis[132,133]	Altered mental state, headache, fever	GFAP	Corticosteroid responsive, partial or full recovery in most cases
Encephalitis[132-134]	Limbic encephalitis, encephalopathy, neuropsychiatric manifestations, seizures, movement disorders, cognitive dysfunction Ma2 most common, can present with diencephalitis (weight gain, sexual dysfunction, narcolepsy-cataplexy)	Ma2 most commonly NMDAR CASPR2 GAD65 Hu Ri SOX1 CRMP5 Amphiphysin VGCC	Can be immunotherapy responsive (corticosteroids in most, other treatments include IVIg, PLEX, rituximab) 20% mortality (dominantly described in Ma2 positive cases)
Cerebellar ataxia[132,133]	Isolated ataxia in most, some with concurrent opsoclonus myoclonus	Hu VGCC Amphiphysin CRMP5	Immunotherapy responsive in seronegative cases, modest response to IVIg in Hu antibody positive case
Myelopathy[132,134]	Myelitis	CRMP5 AQP4	Partial/full recovery in up to 70%
Exacerbation of CNS	Patient with radiologically isolated syndrome	Not identified in	Partial/full recovery in 75%

demyelination [140] or new onset demyelination[134]	developing clinically definite MS New onset demyelination	patients without myelitis	
Inflammatory ophthalmological presentations[132]	Optic neuropathy Retinopathy – bilateral diffuse uveal melanocytic proliferation (BDUMP), melanoma associated retinopathy Vogt-Koyanagi-Harada Syndrome Tolosa Hunt Syndrome	CRMP5 Hu	Retinopathy improved with steroids, IVIg, plasmapheresis in BDUMP patient, and with IVIg and bevacizumab in melanoma associated retinopathy patient
Sarcodosis/ CNS granulomatosis[216]	Bihilar lymphadenopathy and neurosarcoidosis	Not present	Successfully treated with corticosteroids
CNS vasculitis[134]		Not present	

Figure Legend

Figure 1: Immunopathogenic mechanisms contributing to CNS autoimmunity

This figure highlights some of the potential environmental, genetic, and cellular interactions whereby immune tolerance may be compromised, and outlines opportunities for targeted therapeutic approaches. T lymphocytes interact with B lymphocytes (as represented by an antibody secreting cell in this figure) and antigen presenting cells. . Non-modifiable risk factors include age, gender, ethnicity, and genetic factors. The importance of human leucocyte antigen (HLA) Class II presentation of peptides between T lymphocytes and other immune cells is critical, and illustrates the strong association of specific HLA risk alleles in some autoimmune neurological disorders. Less commonly, monogenic disorders may be associated with autoimmune neurological sequelae. For example, interferons (IFN) are proteins which play a major role in innate immunity, activate the JAK/STAT pathway. Interferonopathies (including Aicardi Goutieres Syndrome), may arise from monogenic disorders involving IFN, and may be targeted with Janus kinase inhibition. Underlying cellular processes may contribute to an individual's predisposition to immune dysregulation and may include variation in DNA code, and epigenetic modification such as methylation (M), histone modification, and micro RNA expression. Transcription from DNA to mRNA, and translation to cytoplasmic proteins, are key in cellular homeostasis. Environmental influences, including latitude, smoking, body mass index, and the gut microbiome interact with non-modifiable risk factors, and play a role in modifying disease onset and severity. Triggers for loss of immune tolerance include infections (as illustrated by a viral infection), tumours, and iatrogenic treatment such as checkpoint inhibitor therapy. The use of immune checkpoint inhibitor therapy to block regulatory immune checkpoints such as PD1, PDL-1, and CTLA4, has revolutionised the treatment of cancer, but is associated with an increased risk of neurological and systemic autoimmunity. In antibody-mediated neurological disorders, the critical role of B cells and therapeutic methods of action targeting removal of CD20+ B cells, or secreted IgG is well-established. Additional targets of cytokines and cytokine receptors such as CXCL13 and IL-6R continue to be under investigation in managing treatment resistant patients.

BCR B cell receptor, CD cluster of differentiation, CTLA4 cytotoxic T-lymphocyte-associated protein 4, DNA deoxyribonucleic acid, HLA Class II human leucocyte antigen II, IgG immunoglobulin G, IFN interferon, IgM immunoglobulin M, IL-6 R interleukin 6 receptor, IL-7 interleukin-7, IL-7R interleukin-7 receptor, JAK janus kinase, mRNA messenger RNA, PD1 programmed cell death protein 1, PDL1 PD1 ligand, RNA ribonucleic acid, STAT signal transducer and activation of transcription,TCR T cell receptor, TYK tyrosine kinase. Some components of the figure are adapted and modified from motifolio.com.

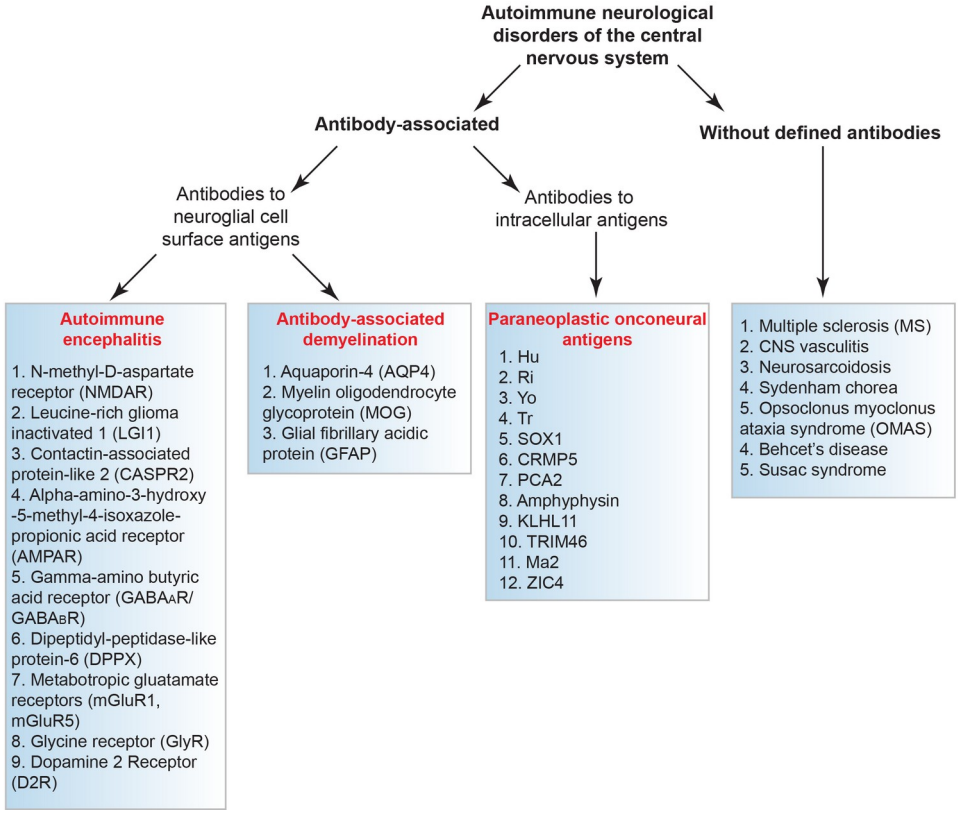
Figure 2: Demographic associations in autoimmune central nervous system disorders.

This figure summarises the age at disease onset, the gender preponderance, and known ethnic associations for a number of autoimmune neurological conditions. The data for this figure was collated from a number of case series, cohort studies, reviews, and systematic reviews in each of these disorders including MS[3,11,22], AQP4-NMOSD[13,23,217,218], NMDAR-antibody encephalitis[4,5,12,24,115,163], LGI1- and CASPR2-antibody encephalitis[6,7,19-21,58,206,209,219,220], and MOGAD[8,18,221,222]. It is noted that the evidence for some of these associations such as disease incidence and ethnic predisposition in the rarer disorders is less well established.

AQP4-NMOSD – aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder; CASRP2-Ab+ AE – contactin associated protein like 2 antibody-associated autoimmune encephalitis; LGI1-Ab+ AE – leucine rich glioma inactived 1 antibody-associated autoimmune encephalitis; MOGAD - myelin oligodendrocyte glycoprotein antibody-associated disease; MS - multipe sclerosis; NMDAR-Ab+ AE – N-methyl-D-asparatate receptor antibody-associated autoimmune encephalitis

Box 1 The spectrum of autoimmune neurological disorders of the central nervous system

Some autoimmune neurological disorders may be associated with the detection of specific autoantibodies in serum and/or cerebrospinal fluid. In some patients who present with encephalitis or demyelination, these autoantibodies target neuroglial surface antigens, have a dominantly B cell mediated pathophysiology, are increasingly identified to be pathogenic in *in vitro* and *in vivo* models, and may be immunotherapy responsive[121]. Another group of patients have autoantibodies targeting intracellular antigens, often in the context of systemic malignancy, have a dominantly T cell driven pathology, and are less responsive to immunotherapy. These patients may present with rapidly progressive neurological presentations such as cerebellar ataxia or limbic encephalitis, and the autoantibodies are though to be biomarkers of inflammation rather than pathogenic. Other autoimmune neurological disorders such as multiple sclerosis may have a more multifactorial aetiology with presumed genetic, environmental and infectious contributions, and no clearly defined antibody biomarker. Some syndromes such as Sydenham chorea or opsoclonus myoclonus ataxia syndrome (OMAS) either have an as yet unidentified antigenic target, or an alternative immunopathogenesis.



Box 2 CNS, intrathecal, and peripheral compartments: the blood-brain barrier and immune privilege

The CNS has been deemed to be a site of 'immune privilege' for close to a century[223], due to the perceived integrity of the blood brain barrier and the lack of brain parenchymal lymphatics - this phenomenon is now understood to be more nuanced, with the opportunity for immune cells to traverse between the brain (parenchymal), CSF (intrathecal), and blood (peripheral) compartments through afferent and efferent mechanisms. Indeed, the leptomeningeal and perivascular compartments of the CNS harbour antigen presenting cells (APCs) including dendritic cells and macrophages, which may activate T cell responses in the CNS[224]. Live cell imaging additionally demonstrates that the leptomeninges present a checkpoint whereby activated T cells enter the CNS parenchyma and non-activated T cells may be released into the CSF, from where they can reach areas of accessible antigen and tissue damage[225]. Thereby, the concept of 'immune privilege' does not extend to the leptomeninges and CSF, and a broader concept of 'immunosurveillance' involving the CNS is at play. The first major advancement is understanding how immune cells from the brain traverse into the circulation. Recent literature has shown that CSF drains via nasal and dural sinsuses and cranial nerve roots into the nasal lymphatics and cervical lymph node chain, and from the spinal nerve roots and lumbar subarchnoid space to the lumbar lymph nodes; and is the only afferent route for APCs to drain to regional lymph nodes[226]. In contrast, interstitial fluid from the parenchyma of the CNS, drains via narrow (100-150 nm) intramural basement membrane pathways of cerebral capillaries, arterioles, and arteries to the lymphatic system, only allows for the passage of fluid and solutes, and does not permit trafficking of antigen presenting cells which are too large to traverse by this mechanism[227]. A second advancement in our understanding is how peripherally generated immune cells may in turn breach the blood brain barrier and enter the CNS through a two step process involving traversing the outer layer of the blood-brain or blood-CSF barrier, and the inner layer of the glia limitans. Lymphocytes targeting the CNS may bypass the post capillary vascular endothelium by receptor-mediated crossing, and enzyme-mediated penetration of the glia limitans covering the CNS[224]. Once through the blood brain barrier, B cells may produce antigen-specific autoantibodies which may result in neuronal dysfunction through a variety of mechanisms. Examples of this end-target effect include selective and reversible internalisation of cell surface NMDA[228] and AMPA[229] receptors, or prevention of LGI1 binding to pre and post-synaptic domains ADAM22 and 23[151,230].