Neuromyelitis optica spectrum disorders (NMOSD) comprise a variety of disorders being described by optic neuritis and myelitis. This disorder is mostly observed in sporadic form, yet 3% of cases are familial NMO. Different series of familial NMO cases have been reported up to now, with some of them being associated with certain HLA haplotypes. Assessment of HLA allele and haplotypes has also revealed association between some alleles within HLA-DRB1 or other loci and sporadic NMO. More recently, genome-wide SNP arrays have shown some susceptibility loci for NMO. In the current manuscript, we review available information about the role of genetic factors in NMO.

Keywords: genetics, HLA, association, neuromyelitis optica spectrum disorder, expression

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) comprise a variety of disorders being described by acute inflammatory responses in the optic nerve and spinal cord, i.e., optic neuritis and myelitis, respectively (1). NMO is mostly triggered by IgG autoantibodies against aquaporin 4 (AQP4) (2). AQP4 monomers comprise six transmembrane helical domains and two small helical parts around a thin aqueous pore (3). These monomers lump together to make corresponding tetramers with the ability of being aggregated in cell plasma membranes. The constructed supramolecular collections are named as orthogonal arrays of particles (OAPs) (3). AQP4 is the supreme ample water-channel protein in the central nervous system (CNS) (1). A number of NMO patients do not have AQP4-IgG, yet they have IgG antibodies against myelin oligodendrocyte glycoprotein, a glycoprotein in the outer myelin sheath of CNS neurons (4).

Following the discovery of AQP4-specific proliferative T cells in NMO patients, it has been recognized that AQP4-specific T cells exhibit Th17 features and display molecular mimicry with a peptide sequence encoded by the commensal bacterium Clostridium perfringens. Further studies have revealed distinct features of gut microbiota in NMO cases versus both multiple sclerosis (MS) cases and healthy subjects (5).
Although this disorder has some similarities with MS, it is important to distinguish between these two conditions, particularly at early stages of the disorder, since therapeutic modalities for these disorders are different (6). Most importantly, a number of prescribed agents for MS might be harmful for patients with NMO (7, 8). NMO and MS can be differentiated through assessment of NMO antibody. Although the existence of cerebral lesions has been formerly regarded as a criterion for differentiation between these two conditions, it is currently acknowledged that these lesions do not exclude NMO. In fact, with the advent of NMO antibody assessment techniques, some cases diagnosed as MS for a long time have been found to have NMO (9).

Typically, NMO manifests around the ages of 35 to 45 years, yet less than 20% of cases occur in children, and elderly account for 18% of cases. NMO is recognized as a condition with female predominance. Although 70% to 90% of total NMO patients are female, such sex bias is not seen in children (6, 10). In NMO-AQP4 cases, gender influences both age at disease onset and site of attack (11).

NMO is most probably a complex multifactorial disorder. Most cases of this disorder are sporadic, yet 3% of cases are familial (12). A previous meta-analysis of whole-genome association studies in NMO has shown association of AQP4-IgG positive NMO with two independent signals in the MHC region. Notably, one of these signals has been suggested to be related with structural variations in the complement component 4 region. Moreover, a significant causal effect has been found between AQP4-IgG positive NMO and recognized risk variant for systemic lupus erythematosus (SLE). Most notably, such causal link has not been observed with MS risk variants (13). A number of other studies have reported an association between genetic variants and gene expressions alterations and NMO. In the current manuscript, we review available information about the role of genetic factors in NMO.

FAMILY STUDIES

Familial and sporadic NMO are similar in terms of clinical manifestations, age onset of disease, gender-based effects, and proportion of AQP4-IgG positive cases (12). A pioneer study in this field has reported occurrence of NMO in identical twin sisters at the ages of 24 and 26, respectively (14). A subsequent study reported NMO manifestations such as sudden loss of vision and transverse myelopathy in two sisters at the age of 3. Notably, HLA haplotyping revealed a shared haplotype between these two sisters, yet an unaffected sib also had this haplotype (15). More recently, a group of researchers described a series of familial NMO cases including siblings, parent–child, and aunt–niece pairs, more than 80% of them being female. A number of reported cases had either maternal or paternal transmission. More than 75% of cases had AQP4-IgG. About half of cases had clinical manifestations or serologic markers of another immune-related condition. The observed familial transmission of NMO suggested a complex genetic etiology for this disorder (12).

A number of other studies also reported familial clustering of NMO cases, with some of them reported the presence of a shared haplotype among affected cases. Table 1 summarizes the results of family studies in NMO.

HLA STUDIES

An HLA genotyping study in seropositive Brazilian NMO patients has revealed some susceptibility loci for NMO, most importantly HLA-DRB1*04:05 and *16:02. A number of alleles within HLA class I showed association with NMO, yet this association did not remain significant after corrections for multiple comparisons (22). Another study in Afro-Caribbean NMO cases has shown higher frequency of HLA-DRB1*03 in NMO patients. On the other hand, HLA-DRB1*15, but not DRB1*03 allele has been recognized as a susceptibility locus for MS. In brief, distribution of HLA-DRB1 and DQB1 has been different among NMO and MS cases in this population (23). Another study in seropositive Brazilian NMO patients has shown overrepresentation of the HLA-DRB1*03 allele group in NMO cases compared with unaffected individuals. On the other hand, MS patients have shown higher frequency of the HLA-DRB1*15 allele group. DRB3 and DRB5 have had higher frequencies in NMO and MS cases, respectively (24). Another study has confirmed overrepresentation of HLA-DRB1*03 and HLA-DRB1*10 alleles in another group of Brazilian NMO patients compared with controls, in spite of no significant overrepresentation of MS-associated alleles (25). In addition, the DR3 and DR15 haplotypes have been found to be more common in NMO and MS, respectively. The association between HLA-DRB1*03:01 allele and NMO has not been dependent on seropositivity (26). In a study in Japanese patients, HLA-DRB1*08:02 and HLA-DRB1*16:02 have been found as risk loci, while HLA-DRB1*09:01 has been a protective allele (27).

Table 2 shows the results of HLA studies in NMO cases in different populations.

GENOMIC STUDIES

Whole-exome sequencing (WES) has facilitated identification of risk loci for NMO. Application of this method in addition to HLA sequencing in seropositive NMO cases of Chinese origin has shown significant association between HLA-DQB1*05:02 and NMO. Additionally, the frequency of “HLA-DQB1*05:02-DRB1*15:01” haplotype has been higher in the NMO group compared with controls. Besides, this study has shown higher frequency of loss-of-function mutations in NOP16 in these patients compared with healthy subjects. The G390R of IgG1, which decreases the threshold for BCR activation, has been another NMO-associated variant. Notably, most of the NMO-associated genetic factors have been enriched pathways related with nervous system and immune responses (43).

Another genome-wide study using an SNP array has identified the rs1964995 in the MHC region as a risk locus for
NMO. Notably, three MS-associated variants have also been found to be associated with NMO. A variant within KCNMA1 gene has been associated with disability score as well as presence of transverse myelitis (27).

The importance of copy number variations (CNVs) in conferring risk of NMO has been previously assessed using a genome-wide method. The majority of identified CNVs have been located at TCRγ and TCRα regions. These CNVs have been mostly deletions with sizes of 5 to 50 kb. Since they have been only in the peripheral blood T cells, it has been deduced that they are most probably somatically acquired CNVs. Moreover, it has been an association between the presence of CNVs in NMO cases and seronegativity for AQP4-IgG or low antibody titer (44).

Several SNPs within AQP4 gene have been genotyped in NMO cases to find possible risk loci for this condition in different ethnic groups. For instance, Matiello et al. have compared genotype frequencies of 8 SNPs within AQP4 gene in sporadic and familial NMO cases as well as healthy controls. One of these SNPs has been found to be associated with risk of NMO. Moreover, two missense mutations at Arg19 have been found in three NMO patients. The authors have reported that apart from one infrequent SNP, no other examined SNP or

**TABLE 1** Summary of the results of family studies in neuromyelitis optica [HLA, human leukocyte antigen, AQP4-Ab, aquaporin-4 antibody (NMO-IgG)].

| Cases | Population | Age at onset (years) | AQP4-Ab | HLA | Environmental factors | Year | Comments | Ref |
|-------|------------|----------------------|---------|-----|----------------------|------|----------|-----|
| Identical twin sisters | American | 24 and 26 | _ | _ | They had a history of bronchitis, measles and chickenpox. | 1936 | _ | (14) |
| 2 sisters | American | 3 (similar) | HLA-A1, 2 BW35, W40, BW622 | _ | _ | 1982 | Severity of the disease was different between cases. They had an unaffected sister until 3 years old, with a shared HLA haplotype. | (15) |
| 2 sisters | Japanese | 59 and 62 | HLA-A 2/33, B 39/44, Cw7/2, DR 4/6, DQ 1/3 | _ | _ | 2000 | One of the cases had rheumatoid arthritis since she was 30. | (16) |
| Mother and daughter | Unknown (published from USA) | 62 and 29 | Positive in mother (test was not performed in daughter) | _ | _ | 2007 | The daughter had a history of myasthenia gravis in childhood. | (17) |
| 2 sisters, Neice-aunt, Daughter-mother, Daughter-father, Brother-sister, Monozygotic twin sisters, Son-mother | Lao, African American, Mexican, Brazilian, Vietnamese, Korean, African Caribbean Japanese | Different | 76% of patients were NMO-IgG positive | _ | _ | 2010 | 48% of cases had clinical or serologic sign of another autoimmune disorder (thyroid disease, T1DM, Sjögren syndrome, CIDP and psoriasis). | (12) |
| 2 sisters | Unknown (report from USA) | 25 and 26 | Positive | HLA- A*31, B*61, *51, DRB1*0802, and DPB1*0501 | _ | 2011 | The same until first episode of disease | (18) |
| Mother and daughter | Unknown (published from USA) | 78 and 38 | positive | _ | Mother had history of recurrent urinary tract infections | 2015 | There was genetic anticipation in familial NMO. | (19) |
| 2 sisters | Unknown (report from USA) | 3 and 3.5 | positive | _ | _ | 2016 | NMO can have extended remission course but a persistent tendency to relapse. | (20) |
| Mother and daughter | Taiwanese | 39 and 22 | positive | HLA-DRB1*03 and HLA-DPB1*04 | _ | 2019 | _ | (21) |
### TABLE 2 | HLA studies in neuromyelitis optica (SSP-PCR, sequence-specific primers–polymerase chain reaction; PCR-SSO, polymerase chain reaction–sequence specific oligoprobes; SBT, sequencing-based typing; MOG-Ab, myelin oligodendrocyte glycoprotein antibody).

| HLA regions | Number of samples | Population | Source of sample/ assay methods | Associations | Year | Ref |
|-------------|-------------------|------------|-------------------------------|-------------|------|-----|
| HLA-A, B, C | 15 NMO patients and 806 healthy controls | Southern Brazilian | Peripheral blood/ Sanger sequencing | There was significant association between HLA-DRB1*16:02, *04:05, C*15:02 alleles and NMO susceptibility. There was significant association between HLA-DRB1*03 alleles and NMO disease. | 2019 | (22) |
| HLA-DRB1, DQB1, DPB1 | 42 NMO patients and 150 healthy controls | French Afro-Caribbean | Peripheral blood/ Sanger sequencing | | | |
| HLA-DRB1, DQB1, DPB1 | 27 NMOSD patients and 28 healthy controls | Mulatto Brazilian (Ribeira’s Preto) | Peripheral blood/ PCR-SSP | HLA-DRB1*03 and DPB1*10 alleles were overrepresented in NMOSD patients compared to controls. | 2009 | (24) |
| HLA-DRB1 | 35 NMO patients and 99 healthy controls | Brazilian (Mexico City) | Peripheral blood/ PCR-SSP | HLA-DRB1*03 and DPB1*10 alleles were more common in NMO cases compared to controls. | 2016 | (25) |
| HLA-DRB1, DQA1 and DPB1 | 65 NMO patients and 100 healthy controls | Brazilian (Rio de Janeiro) | Peripheral blood/ PCR-SSO and SSP | HLA-DRB1*01:02, 03:01, DQB1*02:01 and DQA1*01:05 alleles were more common in NMO cases compared to controls. | 2017 | (26) |
| HLA-DRB1 | 71 NMO patients and 97 healthy controls | Mexican | Peripheral blood/ SBT | Risk HLA alleles for NMO: DQB1*03:01, DRB1*08:02, DRB1*16:02, DRB1*14:06, DQB1*05:01 and DQA1*02:01, *05:01, DQB1*02:01 DRB1*03 alleles were significantly associated with NMO. There was no correlation between distribution of HLA alleles and IgG antibody subgroups. | 2020 | (28) |
| HLA-DRB1 | 39 NMO, 6 patients at risk of NMO, and 100 healthy controls | French Caucasian | Peripheral blood/ PCR-RFLP and PCR-SSP | There was significant association between HLA-DRB1*10 allele and IgG antibody subgroups. | 2009 | (29) |
| HLA-DRB1 | 22 NMO patients and 225 healthy controls | Spanish Caucasian | Peripheral blood | HLA-DRB1*10 allele was significantly associated with NMO disease. | 2011 | (30) |
| HLA-DRB1 | 31 NMOSD patients and 429 healthy controls | Japanese | Peripheral blood/ NGS-based HLA genotyping | HLA-DQA1*05:03 allele had the most association with NMOSD. | 2019 | (31) |
| HLA-DRB1 and DPB1 | 77 NMO, 39 NMOSD patients and 367 healthy controls | Japanese | Peripheral blood/ PCR-SSO | Higher occurrence of HLA-DRB1*1602, DQB1*0501 and lower occurrence of DRB1*0901 alleles were associated with anti-AQP4 antibody positive patients. | 2012 | (32) |
| HLA-DRB1 and DPB1 | 165 NMOSD patients | Japanese | Peripheral blood/ SSO (Luminex) | HLA-DRB1*08:02 and DPB1*05:01 alleles were associated with disease and DRB1*09:01 alleles was protective allele in NMOSD. | 2021 | (33) |
| HLA-DRB1 and DPB1 | 184 NMOSD patients and 317 healthy controls | Japanese | Peripheral blood/ PCR-SSO | HLA-DRB1*08:02, *16:02 alleles were associated to NMO whereas DRB1*09:01 allele was protective factor. | 2020 | (27) |
| HLA-DRB1 and DPB1 | 38 NMOSD AQP4-Ab+ patients and 125 healthy controls | Japanese | Peripheral blood/ PCR-SSO | HLA-DRB1*0501 allele was associated with NMOSD and reinforced presence of anti AQP4-Ab. | 2008 | (34) |
| HLA-DRB1 | 61 NMO and 32 NMOSD patients and 300 healthy controls | Indian | Peripheral blood/ PCR-SSP | HLA-DRB1*03 allele was significantly associated with disease and persisted associated with anti-AQP4 subtype. | 2015 | (35) |
| HLA-DP | 86 NMOSD patients and 29 healthy controls | Chinese | Peripheral blood/ flow cytometry and real-time PCR | HLA-DRB1*0501 allele was associated with NMOSD through affect transcription levels of HLA-DP gene in antigen presenting cells. | 2019 | (36) |
| HLA-DQA1, DQB1 and DRB1 | 41 NMO patients and 200 healthy controls | Caucasian (Danish) | Peripheral blood/ PCR-SSO | HLA-DQA1*0402 allele was significantly associated with NMO disease. There were no significant differences in HLA distributions between anti-AQP4 subtypes. | 2011 | (37) |
| HLA-DQ and DR | 8 NMOSD patients with AQP4-Ab, 10 with MOG-Ab and 14 healthy controls | Swiss | Peripheral blood/ PCR-SSO | HLA DQB1*02, DRB1*01 and DRB1*03 alleles were significantly associated with AQP4-Ab patients. | 2020 | (38) |
| HLA-A, B, C, DQA1, DQB1, DRB1 and DRB3/4/5 | 5 NMO patients | Southern Finnish | Peripheral blood/ NGS and SSP | HLA-DRB1*0501 allele was associated with AQP4-Ab+ NMO patient. | 2015 | (39) |
| HLA-A, B, C, DQA1, DQB1, DRB1 and DRB3/4/5 | 85 patients (including 43 MOG-IgG and 42 AQP4- | Dutch | Peripheral blood/ SSO (Luminex) and PCR-SSO | HLA-A*01, B*08, and DRB1*03 alleles were significantly associated with AQP4-IgG NMOSD. There was no association of MOG-IgG cases with HLA alleles. | 2020 | (40) |

(Continued)
TABLE 2 | Continued

| HLA regions | Number of samples | Population | Source of sample/assay methods | Associations | Year | Ref |
|-------------|------------------|------------|--------------------------------|--------------|------|-----|
| HLA-DRB1 and DQB1 | 35 NMO patients and 74 healthy controls | Israeli Muslim | Peripheral blood/PCR-SSO, Luminox technology and PCR-SSP | There was a significant positive association of HLA-DRB1*04:04 and DRB1*10:01 alleles and negative association of HLA-DRB1*07 and DQB1*02:02 alleles with NMO. | 2016 | (41) |
| HLA-DRB1 and DPB1 | 30 NMO patients and 93 controls | Southern Han Chinese | Peripheral blood/SBT | The frequency of HLA-DRB1*1602 and DPB1*0501 alleles was significantly higher in NMO AQP4-Ab-positive patients. DRB1*0901 allele had lower frequency in disease. | 2010 | (42) |

haplotype has been linked to NMO, possibly excluding the importance of AQP4 variants in conferring risk of NMO (45). Qiu et al. have also genotyped eight SNPs in AQP4 in a group of AQP4-IgG-positive NMO cases. They have shown associations between a number of SNPs and clinical manifestations of NMO such as extensive transverse myelitis, optic neuritis, or simultaneous systemic autoimmune disorders (46). Table 3 shows the results of genomic studies in NMO cases.

**EXPRESSION STUDIES**

Expressions of several immune-related genes have been assessed in NMO cases at transcript or protein levels. Moreover, a number of high-throughput sequencing strategies have been employed to assess expression of different subtypes of transcripts. For instance, lncRNA and mRNA profile has been assessed in these patients using microarray technique. Such type of analysis has led to the identification of more than 1,300 lncRNAs with differential expression between NMO cases and normal controls. Moreover, more than 700 mRNAs have been found to be differentially expressed between NMO cases and normal subjects. These genes have been functionally correlated with IL-23-related cascades, IFN-γ signaling, natural killer-κB pathway, and a number of other immune-related mechanisms (74). Another RNA expression profiling experiment has shown possible contribution of T-cell-related genes and the TNF/ NF-κB cascade in the pathogenesis of NMO. Notably, IL7Ra (CD127) has been found to be downregulated in the circulation of NMO patients compared with control subjects. Moreover, transcription factors located in the upstream of CD127 and survival pathways in its downstream have been considerably downregulated. These expression changes have been accompanied by decrease in the quantities of naïve T cells, reduction of BID-mediated T-cell survival signaling and activation of cell apoptosis. Taken together, these observations indicate the importance of IL7Ra signaling in the pathobiology of NMO (75). A high-throughput expression profiling in brain tissue samples obtained from an NMO patient as well as patients with Parkinson’s disease and amyotrophic lateral sclerosis has shown upregulation of more than 200 genes in brain lesions of NMO patients with the mostly upregulated ones being associated with immune response. Upregulation of IFI30, CD163, and SPP1 has also been confirmed by further RNA and protein-based techniques. Genes with high expression in NMO brain lesions has been functionally related with NF-κB and Blimp-1, indicating the importance macrophage-mediated inflammatory responses in the pathobiology of NMO brain lesions (76).

With the aim of finding effective markers for the assessment of response of NMO patients to therapeutic options, Vaknin-Dembinsky et al. have assessed miRNAs profile in the blood of NMO patients before and following treatment with rituximab. They have reported upregulation of 14 miRNAs and downregulation of 32 miRNAs in NMO patients after treatment with rituximab. Moreover, they have shown higher levels of 17 miRNAs and lower levels of 25 miRNAs in untreated cases compared with healthy controls. Notably, rituximab could normalize expression of a number of these miRNAs, among them have been brain-specific or brain-enriched miRNAs. Cumulatively, circulatory miRNA profile can be used as a biomarker for therapeutic response (77).

The pleiotropic cytokine IL-6 is also implicated in the pathogenesis of NMO through enhancement of survival of plasmablasts, induction of release of antibodies against AQP4, disruption of integrity of blood–brain barrier and its functionality, as well as increasing differentiation and activity of proinflammatory T cells (78). Expression of this cytokine has been reported to be elevated in CSF and blood samples of NMO patients (79). Table 4 shows the results of expression studies in NMO.

**IN VITRO STUDIES**

A number of in vitro studies have appraised the functional mechanisms of development of NMO. In an effort to find the impact humoral factors on astrocyte injury in NMO, Haruki et al. have conducted a series of experiments on immortalized human primary astrocytes. Moreover, they assessed the effect of TY09 human brain microvascular endothelial on the quantity and localization of AQP4 protein in astrocytes. Serum samples of NMO patients have been shown to induce toxic effects on AQP4-expressing astrocytes. Moreover, these serum samples could decrease AQP4 expression at both mRNA and protein levels, while increasing release of TNF-α and IL-6 from astrocytes. Experiments in an in vitro BBB model has shown...
**TABLE 3 | Genomic studies in neuromyelitis optica.**

| Genes                          | Number and type of samples | Population | Source of samples/ assay method | Associations                                                                 | Ref |
|-------------------------------|----------------------------|------------|--------------------------------|-------------------------------------------------------------------------------|-----|
| Exome sequence                | 228 AQP4+ NMOSD patients and 1,400 healthy controls | Chinese    | Peripheral blood/ whole exome sequencing | The result represented most variants related to immune and nervous system. Significant variation in HLA region specifically DQB1, DQA2, and DQA1 was shown and the most significant allele was HLA-DQB1*05:02. NOP16 mutation and g G1-G390 R variant were also more common in patients. - 46 SNPs were identified around the AQP4 gene - rs1964995 in the MHC region was the most associated SNP in NMO. - rs71186814 in chr 16 was associated SNP out of MHC region. - Three variants of MS risk were associated with NMO susceptibility. rs6677309 [CD58], rs1813375 [EDMES – CMCI], and rs694739 [PRDX5 – CCDC88F] - rs1516512 in the KCNMA1 was associated with EDSS and transverse myelitis. - 24 CNVs were significantly associated to NMO/NMOSD. They were mostly located on chr14. - A CNV deletion between 22,762,299 and 22,775,479 in TRA were prevalence in 13.27% of NMO. - Other CNVs were located on chr6 and 18. - Patients carrying CNVs tended to be AQP4-Ab⁺ | (43) |
| Genome wide SNPs             | 203 NMO patients and 1,782 healthy controls | Japanese   | Peripheral blood/ GWAS (HumanOmnExpress-12 BeadChip) | - On of [AQP4] SNPs (NC 18.8; chromosome pos. 22695167; T>A) was associated with disease. Two different allelic missense mutations, Arg19 (R191 and R19T) was specific to NMO. | (44) |
| Copy number variations       | Identification phase: 135 NMO/NMOSD patients and 288 healthy controls Confirmation phase: 76 NMO/NMOSD patients and 790 healthy controls | Japanese   | Peripheral blood/ GWAS (high density SNP microarray) and qPCR | - There were no substantial differences in frequency of alleles between NMO/ NMOSD and controls. | (45) |
| 8 SNPs in AQP4               | 177 sporadic NMO patients, 14 familial NMO patients, and 1,363 matched healthy controls | African American, Asian, and unknown | Peripheral blood/ TaqMan-based assay and sequencing | - rs1068424 (A/T) and rs3763043 (C/T) were correlated with LETM. - rs1068424 (A/T), rs335929(A/C), and rs151244(C/T) were correlated with optic neuritis. - rs6508459 and rs3763040 were associated with concurrent systemic autoimmune diseases. | (46) |
| 8 SNPs in AQP4               | 208 NMO patients (AQP4-Ab⁺) and 204 healthy controls | Chinese    | Peripheral blood | - rs1058424 (A/T) genotype of rs1058424 and C/T genotype of rs3763043 were more frequent in NMO. | (47) |
| 6 SNPs in AQP4               | 62 NMOSD patients and 109 healthy controls | Northern Han Chinese | Peripheral blood/ high-resolution melting PCR | - 6 SNPs sites in exons 2 and 5 were identified in NMO patients. - AQP4-Ab serum levels were significantly different between R108T/1110N, E280R/D281R, E317M variants and original cell line. | (48) |
| AQP4 exon 1,2,3,4,S          | 72 NMO patients | Chinese    | Peripheral blood/ sequencing | - 6 SNPs sites in exons 2 and 5 were identified in NMO patients. - AQP4-Ab serum levels were significantly different between R108T/1110N, E280R/D281R, E317M variants and original cell line. | (49) |
| AQP4 exon 1,2,3,4,S, AQP4 promoters | 64 NMO and 58 NMOSD for sequencing | Chinese    | Peripheral blood/ sequencing and PCR-LDR | - rs1516512 in the KCNMA1 was associated with EDSS and transverse myelitis. - OPC-2783724 (C/T) was associated with EDSS and transverse myelitis. - rs1086814 in chr16 was associated SNP out of MHC region. - Three variants of MS risk were associated with NMO susceptibility. rs6677309 [CD58], rs1813375 [EDMES – CMCI], and rs694739 [PRDX5 – CCDC88F] - rs1516512 in the KCNMA1 was associated with EDSS and transverse myelitis. - 24 CNVs were significantly associated to NMO/NMOSD. They were mostly located on chr14. - A CNV deletion between 22,762,299 and 22,775,479 in TRA were prevalence in 13.27% of NMO. - Other CNVs were located on chr6 and 18. - Patients carrying CNVs tended to be AQP4-Ab⁺ | (50) |
| AQP4 exons and 5 SNPs         | 27 NMO patients and 40 healthy controls | Han Chinese | Peripheral blood/ sequencing | rs72557968 in exon 2 was identified in one NMO-IgG⁺ patient. The mutated sequence correlated with higher AQP4-Ab expression. - Polymorphism at –1003 bp (A-G) position of promoter 0 was associated with AQP4-Ab presence. - Polymorphisms between –401 bp and –400 bp locations of promoter 1 were more frequent in NMO compared to controls. | (51) |
| AQP4 exons and 5 SNPs         | 16 AQP4-Ab⁺ NMO patients and 255 healthy controls | Japanese   | Peripheral blood/ sequencing and TaqMan assay | T allele of rs2075575 in promoter region was significantly more frequent in NMO and led to downregulation of AQP4 gene. | (52) |
| 35 non-MHC MS risk loci      | 110 NMO patients and 332 healthy controls | Southeastern China | Peripheral blood/ MALDI-TOF MS and multiple SNaPshot techniques | - Only rs1800693 in the TNFRSF17 locus tended to be associated with NMO. In SLC28A3 gene, rs10868138 and rs12378361 were correlated with higher and lower erythrocyte concentration of 6-TGNs, respectively. | (53) |
| Thiopurine nucleotides and SNPs in MTHFR T/PMP, SLC29A1, SLC28A1, ABCB1, SLC28A3, HLA, ABC04, SLC28A2 | 32 NMO patients | Chinese    | Peripheral blood/LC-MS/MS, MassARRAY and multiple SNaPshot techniques | | (54) |
| Genes         | Number and type of samples | Population | Source of samples/ assay method | Associations Ref |
|--------------|---------------------------|------------|---------------------------------|------------------|
| CYP27B1:     | 110 NMO patients and 294 healthy controls | Han Chinese | Peripheral blood/ MassARRAY system and sanger sequencing | rs703842 and rs10876994 were significantly associated with NMO compared to controls. (55) |
| rs12366853   |                           |            |                                 |                  |
| rs10876994   |                           |            |                                 |                  |
| rs118204009  |                           |            |                                 |                  |
| rs703842     |                           |            |                                 |                  |
| CYP24A1:     | 110 NMO patients and 294 healthy controls | Han Chinese | Peripheral blood/ Bead Express | - rs3808607 and rs1457043 were associated with NMO. -“G/G” genotype of rs3808607 had a higher protective effect on the risk of disease. (56) |
| rs2248359    |                           |            |                                 |                  |
| 11 SNPs in   | 90 NMO patients and 240 healthy controls | Korean     | Peripheral blood/ TaqMan assay  | rs2300747, rs1335532, rs12044852 and rs1016140 were associated with NMO. - rs1016140 led to T-cell hyperactivity that caused AQP4-Ab access to CNS. (59) |
| CYP7A1       |                           |            |                                 |                  |
| rs17426456   |                           |            |                                 |                  |
| rs2300747    |                           |            |                                 | - 4 SNPs (rs2300747, rs1335532, rs12044852, and rs1016140) and 2 haplotypes in the CD58 gene were significantly associated with NMO. (59) |
| rs1335532    |                           |            |                                 |                  |
| rs10802189   |                           |            |                                 |                  |
| rs56300466   |                           |            |                                 |                  |
| rs72291      |                           |            |                                 |                  |
| rs3789716    |                           |            |                                 |                  |
| rs1335531    |                           |            |                                 |                  |
| rs1335532    |                           |            |                                 |                  |
| rs2300747    |                           |            |                                 |                  |
| Promoter region of CYP7A1 | 89 NMO patients and 325 controls | Han Chinese | Peripheral blood/ sanger sequencing | −204A>C (rs3808607), −469T>C (rs3824260) and −208G>C were significantly associated with NMO. (57) |
| rs763361     |                           |            |                                 |                  |
| rs1294762    |                           |            |                                 |                  |
| rs17426456   |                           |            |                                 |                  |
| rs2300747    |                           |            |                                 |                  |
| rs1335532    |                           |            |                                 |                  |
| 230 NMO patients and 487 healthy controls | Han Chinese | Peripheral blood/ SNPscan Kit and PCR-LDR | - rs2300747, rs1335532, rs56302466, rs1016140, and rs12044852 were associated with NMOSD. - TAGCCCAA haplotype increased and TATTACGG haplotype reduced NMOSD risk. (60) |
| 9 SNPs in CD6: | 99 NMO patients and 237 healthy controls | Korean     | Peripheral blood/ TaqMan assay | rs12288280 in CD6 gene and rs767455, rs4149577, rs1800693, and ht2, ht3 haplotypes in TNFRSF5F1A were significantly associated with NMO. (61) |
| rs12288280   |                           |            |                                 |                  |
| 6 SNPs in FCRL3: | 150 NMO patients and 300 healthy controls | Chinese    | Peripheral blood/ MALDI-TOF-MS | G allele of -1901A>G and T allele of -668C>T polymorphism were significantly more frequent in patients Both allelic and homozygote model of s7528684, rs945635, rs3761959, and rs2282284 were significantly associated with NMO susceptibility. (63) |
| rs7528684    |                           |            |                                 |                  |
| rs11264799   |                           |            |                                 |                  |
| rs945635     |                           |            |                                 |                  |
| rs3761959    |                           |            |                                 |                  |
| rs2210913    |                           |            |                                 |                  |
| rs2282284    |                           |            |                                 |                  |
| rs2282283    |                           |            |                                 |                  |
| 7 SNPs in FCRL3: | 132 NMO patients and 264 healthy controls | Chinese    | Peripheral blood/ TaqMan assay and sequencing | rs1411751, rs9523762 and BL1_ht3 haplotype of GPC5 were significantly associated with NMO. (64) |
| rs1411751    |                           |            |                                 |                  |
| rs9523762    |                           |            |                                 |                  |
| 6 SNPs in GPC5: | 99 NMO patients and 237 healthy controls | Korean     | Peripheral blood/ TaqMan assay | rs1411751, rs9523762 and BL1_ht3 haplotype of GPC5 were significantly associated with NMO. (64) |
| rs10802189   |                           |            |                                 |                  |
| rs56300466   |                           |            |                                 |                  |
| rs72291      |                           |            |                                 |                  |
| rs3789716    |                           |            |                                 |                  |
| rs1335531    |                           |            |                                 |                  |
| rs1335532    |                           |            |                                 |                  |
| rs2300747    |                           |            |                                 |                  |
| rs1016140    |                           |            |                                 |                  |
| rs2300747    |                           |            |                                 |                  |
| rs1335532    |                           |            |                                 |                  |
| rs1335532    |                           |            |                                 |                  |
| rs2300747    |                           |            |                                 |                  |
| 5 SNPs in ATG5: | 109 NMO patients and 288 healthy controls | Southern Han Chinese | Peripheral blood/ MALDI-TOF-MS | CC/GC genotypes in polymorphism were correlated with higher EDSS. These genotypes were more frequent in patients with both optic neuritis and myelitis. MIF-173 in more associated with severity rather than susceptibility. CC genotype of rs548234 associated with NMO susceptibility while T allele of rs548234 and A allele of rs6937876 played a protective role in AQP4-Ab+ patients. (66) |
| rs2245214    |                           |            |                                 |                  |
| rs548234     |                           |            |                                 |                  |
| rs733775     |                           |            |                                 |                  |
| rs6660431    |                           |            |                                 |                  |
| rs6937876    |                           |            |                                 |                  |
| PD-1.3 and PTPN22 (1858 C/T) | 41 NMO patients and 200 healthy controls | Danish     | Peripheral blood/ sequencing and PCR-RFLP | -PD-1.3 A allele was associated with NMO. -There was no association between PTPN22 polymorphism and NMO. (37) |

(Continued)
TABLE 3 | Continued

| Genes | Number and type of samples | Population | Source of samples/ assay method | Associations | Ref |
|-------|---------------------------|------------|---------------------------------|-------------|-----|
| IL2RA: rs2104286, rs12722489, rs7090512 | 75 NMO/NMOSD and 238 healthy controls | Korean | Peripheral blood/ TaqMan assay | There was no significant association between IL2RA polymorphisms and NMO. | (67) |
| IL2RA: rs2104286, rs12722489, IL7RA: rs6897932 | 67 NMO patients and 133 healthy controls | Southern Han Chinese | Peripheral blood/ sequencing-based typing | G allele frequency of rs2104286 in IL2RA gene was significantly higher in NMO patients. | (68) |
| IL-7: rs1520333, rs1545298, rs4739140, rs6993386, rs7816065, rs2887502 | 167 NMO patients (57 AQP4-Ab+) and 479 healthy controls | Southeastern Han Chinese | Peripheral blood/ MassARRAY system and Sanger sequencing | rs6897932 in IL-7RA was significantly associated with NMO especially in AQP4-Ab+ patients. | (69) |
| 13 SNPs in IL7RA | 98 NMO patients and 238 healthy controls | Korean | Peripheral blood/ TaqMan assay | There was no significant association with NMO. | (70) |
| IL-17A: rs2275913 | 52 AQP4-Ab+ NMO patients and 131 healthy controls | Southern Han Chinese | Peripheral blood/ sequencing | T allele of rs763780 was significantly more frequent in NMO patients compared to controls. | (71) |
| IL-17F: rs763780 | 4 SNPs in IRF5 | Southeastern Han Chinese | Peripheral blood/ MALDI-TOF-MS | There was no association between IRF5 polymorphisms and NMO. | (72) |
| CH25H | 14 NMO patients and 882 healthy controls | Southeastern Han Chinese, European and Asian | Peripheral blood/ exome sequencing | | |

Localization of AQP4 protein at the astrocytic membrane following co-culture with TY09, in contact with these cells (132).

Sera samples of these patients or even NMO-IgG have also been shown to rapidly downregulate AQP4 levels on the surface of astrocytes. Astrocytes treated with NMO-IgG, IL-6/R, and NMO-IgG + IL-6/R have shown over-production of IL-6 transcripts. Moreover, NMO-IgG could elicit alterations in gene transcription via the JAK/STAT3 pathway. Cumulatively, NMO-IgG has been reported to induce the JAK1/2/STAT3 pathway in astrocytes, representing a crucial event in the pathobiology of NMO. Besides, suppression of JAK1/2 signaling might be a therapeutic modality for NMOSD (133).

Another in vitro study has shown similar magnitude of lymphoproliferation and cytokine profiles in peripheral blood mononuclear cells of NMO cases and healthy controls in response to *Staphylococcus aureus* and *Candida albicans*. However, NMO-originated *Escherichia coli*-induced cell cultures have exhibited higher proliferation of CD4+ T cells in association with higher production of IL-1β, IL-6, and IL-17. IL-10 release has been lower in NMO-derived cells compared with controls. Notably, the in vitro *E. coli*-stimulated expressions of IL-6 and IL-17 have been correlated with neurological deities. Overproduction of Th17-associated cytokines has been associated with the production of IL-23 and IL-6 by LPS-stimulated monocytes. Consistently, LPS levels have been higher in the plasma samples of NMO cases. Therefore, increase in Th17 type response to *E. coli* might contribute in the pathogenesis of NMO (134).

**DISCUSSION**

NMO comprises a group of immune-mediated conditions with complex etiology. While family studies have shown clustering of NMO cases in some families, the exact genetic background of this disorder has not been clarified yet. Since the first report of familial NMO cases in 1936 (14), several studies have attempted to find susceptibility loci for NMO. The first attempts have been focused on the HLA region, based on the importance of this region in the regulation of immune responses and their association with MS, a disorder that clinically resembles NMO. However, various studies have shown that HLA-related susceptibility loci for NMO is distinct from MS. The HLA-DRB1*03 allele has been the mostly appreciated risk locus for NMO. Several other HLA-DRB1, DQB1, and DPB1 alleles have been found to be associated with NMO. Yet, the results of these studies have not been validated in independent cohorts from different ethnic backgrounds.

Exome sequencing and genome-wide SNP arrays have also validated the significance of the HLA region in conferring risk of NMO. In addition, they have shown other risk loci within AQP4, CYP27B1, CYP7A1, CD226, CD58, CD6, FCRL3, GPC5, MIF, ATG5, PD-1.3, IL2RA, IL7RA, and IL17A. With the exception of AQP4 and CD58, almost other genes have been assessed in single studies, needing confirmation in independent cohorts. Moreover, a number of variants, particularly within SLC28A3 and SLC29A1, have been associated with clinical course or some immune markers in patients with NMO.
### TABLE 4 | Expression studies in neuromyelitis optica (NPSLE, neuropsychiatric systemic lupus erythematosus; OND, other non-inflammatory neurological disorders).

| Genes                  | Number and type of samples | Population                  | Source of samples/ assay method                                                                 | Associations                                                                 | Ref |
|------------------------|-----------------------------|-----------------------------|------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----|
| IncRNA and mRNA profiles | 16 NMO patients and 16 healthy controls | Chinese                     | Peripheral blood/ microarray and qRT-PCR                                                         | Results represented differential expression of 1310 IncRNAs and 743 mRNAs in NMO compared to the healthy group, which is related to IL-23-mediated signaling events, IFN-γ signaling, NF-κB signaling pathway, chemokine receptors, GRPR ligand binding, and metabolic disorders of biological oxidation enzyme pathways. | (74) |
| 526 immune-related genes | 65 NMO patients and 37 healthy controls | Israelis                    | Peripheral blood/ Nano String n Counter technology, RT-PCR, ELISA and Flow cytometry             | Two main clusters were differentially expressed in NMO, namely, T-cell associated genes and NF-κB signaling genes. IL-7RA was the most differentiated gene in the T-cell cluster that downregulated in patients. Furthermore, sIL7Ra and miL7Ra isoforms were also lower in NMO especially AQP4+ samples. | (75) |
| mRNAs profile           | 1 NMO patient, 1 Parkinson patient and 1 ALS patient | —                           | Post mortem Brain tissues/microarray, Real-time PCR, northern blot and Western blot                  | 200 genes were significantly upregulated in NMO brain tissue which mostly related to immune regulation involved NF-kB and Blimp-1. | (76) |
| microRNAs profile       | 9 rituximab-responsive NMO patients, 16 non-treated AQP4+ NMO patients and 15 healthy controls | Israelis                    | Peripheral blood/ RNA-seq and real-time PCR                                                      | miRNA expression signatures were different in patients compared to healthy controls, also between rituximab responders and non-responders (e.g., miR-125). Rituximab changed the expression patterns similar to healthy controls (miR-7 and miR-124). | (77) |
| QKI-V5                  | 23 NMO patients and 8 healthy controls | Israelis                    | Peripheral blood/ qPCR and Western blot                                                         | QKI-V5 was significantly downregulated in patients.                          | (83) |
| QKI-V6                  | 215 NMOSD patients (adult and pediatric patients) | Japanese and Brazilian      | Serum/cell-based assay (CBA)                                                                     | 64.7% of patients were AQP4-Ab positive and 7.4% were MOG-Ab positive. No one had both antibodies. MOG-Ab+ patients had better prognosis. | (81) |
| QKI-V7                  | 29 NMOSD patients | Iranian                     | Serum/ chemiluminescence immunoassay (LIAISON® and immunofluorescence assay)                     | 25(OH)D3 serum levels were significantly lower in AQP4-Ab+ patients than patients with negative AQP4-Ab. | (82) |
| MOG and AQP4 antibodies | 51 AQP4-Ab positive NMOSD patients and 204 healthy controls | Korean                      | Peripheral blood/LC-MS/MS                                                                         | 25(OH)D3 levels were significantly lower in NMOSD patients compared to controls and its levels negatively correlated with EDSS scores. | (83) |
| AQP4-Ab|25(OH)D3 | 19 NMO patients and 33 healthy controls | Indonesian                  | Serum/ chemiluminescence immunoassay                                                             | There were no significant differences in 25(OH)D3 serum levels between NMO patients and healthy controls, and its levels were lower in patients who received corticosteroid treatments. | (84) |
| AQP4-Ab|25(OH)D3 | 76 NMO/NMOSD patients and 54 patients with demyelination events | Thais                        | Peripheral blood/ Elecsys®                                                                        | There was no significant difference in 25(OH)D3 levels among patients with demyelinating disease | (85) |
| ANA                     | 6 NMO patients with SLE diagnosis history (during relapse and remission) and 11 healthy controls | Hungarian                   | Serum/flowcytometry, ELISA and MSD Human V-Plex kit                                              | AQP4-IgG1 was presented years before NMO diagnosis in SLE patients and correlated with the concentration of IFN-γ, CXCL10/IP-10, and COL17/TARC. AQP4-IgG1, ANA, anti-dsDNA, and anti-nucleosome antibodies were increased during relapse. Autoantibody responses in NMO/SLE followed by Th1 responses. | (86) |
| Anti-dsDNA, anti-nucleosome, AQP4 and MOG antibodies | 22 AQP4+ NMO patients and 32 NPSLE patients as a control group | Japanese                    | CSF/multiplex cytokine bead- based assay                                                          | IL-17, IL-2, FGF-basic, IL-5, IL-15, IL-9, IFN-gamma, IL-12, IL-10, IL-7, IL-13, TNF-a, and EOTAXIN levels were significantly lower in NMO compared to NPSLE. | (87) |
| Cytokines and chemokines | 20 NMO/NMOSD patients and 18 OND patients as a control group | Japanese                    | CSF/Multiplexed fluorescent bead-based immunoassay                                               | Upregulation in a group of Th17- and Th1-related proinflammatory cytokines/ chemokines was represented in NMO. IL-8 and CXCL8 levels were significantly correlated with CSF protein concentration, cell count, neutrophil count, and EDSS. | (88) |
| Th17 cell- cytokines/ chemokines | 31 NMO patients and 18 OND patients as a control group | Japanese                    | CSF and serum/                                                                                    | The CSF levels of IL-1 receptor antagonist, IL-6, IL-8, IL-13, IL-10, g-csf, and IP-10 were significantly higher in NMO, while only IL-6 level in serum has upregulation. CSF IL-6 level correlated with CSF cells and glial fibrillary acidic protein. | (89) |

(Continued)
TABLE 4 | Continued

| Genes               | Number and type of samples | Population | Source of samples/assay method | Associations                                                                                                                  | Ref |
|---------------------|----------------------------|------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----|
| Th1, Th2, and Th17 cytokines | 34 NMO patients (20 with IFN treatment) and 30 healthy controls | Taiwanese | Serum/cytometric bead array (CBA) | IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ levels were significantly higher in patients who received IFN-γ treatment than higher IL-2 level. | (99) |
| Soluble CD27        | 31 NMO patients and 22 controls with noninflammatory neurological diseases | Chinese   | CSF/ELISA                      | CD27 concentration was higher in NMO patients, especially in AQP4-IgG positive cases compared to the control group. Its higher level correlated with CSF total protein and worse disease disability. | (100) |
| Soluble Syndecan-1 (sSDC-1) | 23 NMO patients and 16 healthy controls | Chinese   | CSF and serum/ELISA            | sSDC-1 concentration was higher in NMO patients. It had a positive correlation with disease severity and CSF levels of IL-6, IL-8, and IL-17. | (101) |
| B-cell subsets and T-cell subsets | 22 AQP4+ NMOSD patients and 13 healthy controls | South Korean | PBMC/flow cytometry | Breg cells as IL-10-producing B (B10) cells were elevated in patients and correlated with AQP4-Aβ. In addition, IL-17+Treg cells were higher in remission phase of disease. | (102) |
| IL-4                | 45 NMO patients and 45 healthy controls | Iranian   | Serum/ELISA                    | IL-4 serum levels were increased in patients compared to healthy controls. Furthermore, gender (female) and AQP4-Aβ were associated with IL-4 levels. | (103) |
| IL-4                | 28 NMO patients and 28 healthy controls | Afro-Brazilians | Plasma/ELISA                  | IL-4 higher levels in NMO represented of its crucial role in Th2 regulatory cell activation. | (104) |
| IFN-gamma           | 17 NMO patients at relapse time and 21 OND patients | Japanese | CSF/FACS                       | Significantly higher levels of IL-6 identified in NMO patients. | (105) |
| IL-6                | 23 NMO patients and 19 healthy controls | Turkish   | Serum and CSF/ELISA            | Higher level of IL-6 was identified in sera and SCF samples of patients, particularly in seropositive AQP4-ab than negative type. CSF IL-6 level also correlated with disease severity and AQP4-ab levels. | (106) |
| IL-6                | 95 NMO patients (59 acute and 36 chronic phase) and 333 OND patients | Japanese | SCF/CLEIA                      | NMO patients had higher IL-6 levels of CSF. IL-6 represented high sensitivity and specificity for NMO diagnosis. Its concentration correlated with spinal cord lesion length and AQP4-Ab. | (107) |
| IL-6                | 22 NMO patients and 14 healthy controls | Chinese   | CSF/ELISA                      | IL-6 and sIL-6R levels were significantly higher in NMO. sIL-6R level also correlated with EDSS. | (108) |
| IL-6                | 13 NMO patients and 20 ONNOD and 24 idopathic CNS inflammatory patients as a control group | Japanese | CSF/CLEIA                      | CSF concentration of IL-6 and GFAP was significantly higher during initial NMOSD attacks. They could diagnosis early stage of NMO with high sensitivity. | (109) |
| IL-6                | 9 definite NMO patients and 8 limited forms of NMO with myelitis | Japanese | SCF/ELISA                      | Higher levels of IL-6 and IL-1B were shown in definite NMO patients compared to limited form. | (110) |
| IL-6                | 8 NMO and 16 healthy controls | Argentines | SCF/ELISA and radioimmunoassay | Higher levels of IL-5, IL-6, MOG-ab, and eosinophil-related factors were identified in NMO patients. | (111) |
| IL-12               | MOG-Ab |          |                               |                                                                                                                             |     |
| IL-6                | 56 NMOSD patients and 100 healthy controls | Iranian   | Serum/ELISA                    | IL-6 and IL-17A serum levels were higher in patients. There was significant association between lower insulin sensitivity and higher level of IL-6. | (112) |
| IL-17A               | Inulin sensitivity |          |                               | All parameters were significantly higher in NMO patients. HMGB1 level correlated with TNF-α, IFN-γ, and IL-17 levels. HMGB1 could diagnose and differentiate NMO with high sensitivity and specificity. | (113) |
| HMGB1               | TNF-α |          |                               | HMGB1 was higher in CSF of NMO patients and correlated with IL-6 and IL-17 levels. | (114) |
| IFN-γ               | IL-17 |          |                               | HMGB1 CSF levels were significantly elevated in NMOSD. its concentration correlated with other CSF parameters such as IL-6 level, cell counts, protein levels, glial fibrillary acidic protein levels, and CSF/serum albumin ratio. | (115) |
| IL-6                | HMGB1 |          |                               |                                                                                                                             |     |
| GFAP                |          |          |                               |                                                                                                                             |     |

(Continued)
| Genes | Number and type of samples | Population | Source of samples/ assay method | Associations | Ref |
|-------|-----------------------------|------------|---------------------------------|-------------|-----|
| IL-6  | 31 NMO patients and 39 healthy controls | Iranian    | Serum/ELISA                     | IL-6 serum level was lower than controls whereas IL-17 level was higher in NMO patients. | (106) |
| IL-17A| 20 NMO patients and 20 healthy controls | Brazilian  | PBMC/flow cytometry and ELISA   | IL-6, IL-17, and IL-21 were highly secreted from CD4+ T cells in patients. Disability scale in patients correlated with IL-6 and IL-21 levels. Furthermore, anti-IL-6R had potential to decreased Th17 cytokines. | (107) |
| IL-6  | 26 NMO patients and 22 healthy controls | Chinese    | Serum/ELISA                     | IL-32x serum level was higher in patients and correlated with EDSS, IL-6, and IL-17A levels. | (108) |
| IL-17A| 35 NMO patients and 20 healthy controls | Brazilian  | PBMC/flow cytometry and ELISA   | IL-21, IL-6, and IL-17 concentrations were significantly higher in NMO while IL-10 was lower in patients. Th17 cells were higher in relapsing course and correlated with disease activity. Th17 cells were decreased under Methylprednisolone treatment. | (109) |
| peripheral memory Th17 | 14 NMO patients and 16 healthy controls | Peripheral blood/Flow cytometry and ELISA | Th17 cells and IL-17-secreting CD8(+) T cells were significantly higher in NMO. Serum IL-17, IL-21 and IL-23 were significantly higher in NMO samples. | (110) |
| IL-17A| 16 NMO patients and 16 healthy controls | Chinese    | Peripheral blood/flow cytometry and ELISA | All the parameters were significantly higher in NMO and correlated with disease duration and relapse. Furthermore, intravenous methylprednisolone therapy could decrease IL-23 levels in patients. | (111) |
| IL-23 | 21 NMO patients and 16 healthy controls | Chinese    | CSF/ELISA                       | CSF IL-21 level was significantly higher in NMO and correlated with humoral immune activity. | (112) |
| Th22  | 21 NMO patients and 12 healthy controls | Chinese    | Peripheral blood/flow cytometry and ELISA | Proportions of Th22 and Th17 were significantly higher in patients. IL-21, IL-22, and FN-γ concentration were increased in NMO. | (113) |
| Th17  | CD4+IL-22+IL-17A+ T cells IL-21, IL-6, IL-21, IL-23 and TGF-β | Peripheral blood/flow cytometry and ELISA | Th17 responses were deregulated in patients. Serum IL-9 levels were higher in AQP4+ patients compared to negative serotype. | (114) |
| IL-4, IL-10, IL-9, IL-12, IFN-γ, IL-17, IL-23, and TGF-β | 18 relapsing NMO (11 AQP4+ and 7 AQP4-) and 30 healthy controls | Turkish | Serum/ELISA | IL-37 levels were significantly increased in patients and correlated with EDSS and disease duration. | (115) |
| IL-37 | 31 NMO patients and 49 healthy controls | Iranian    | Plasma/ELISA                    | NF-κB, Bcl-2 and MAP3K7 gene expression was upregulated in NMO. IL-1β and TNF-α levels were elevated and led to MAP3K7 induction, which promoted NF-κB expression related to survival of CD4+ T cells. | (116) |
| IL-1β | TNF-α, NF-κB, Bcl-2, PD3K/Akt MAP3K7 in CD4+ T cells | Peripheral blood/ cytokine multiplex assay | Specific subsets were increased in NMO patients along with total monocytes and they could be decreased via glucocorticoids therapy. In addition, IL-1β and TNF-α expression levels were significantly upregulated in NMO. | (117) |
| IL-17A| 15 NMO patients and 9 OND and 15 healthy individuals as controls | Chinese    | Peripheral blood, CSF/Flow cytometry, qRT-PCR, ELISA | Specific subsets were increased in NMO patients along with total monocytes and they could be decreased via glucocorticoids therapy. In addition, IL-1β and TNF-α expression levels were significantly upregulated in NMO. | (117) |
| IL-1β | TNF-α, ENA 78 | 25 NMO patients and 20 healthy controls | Chinese    | Plasma/MILLIPLEX® map | IL-1β, TNF-α, and ENA 78 plasma levels were significantly increased in NMO. There was significant correlation between ENA 78 expression and EDSS in patients. Tfh cell percentage and IL-21 were significantly increased in patients. Some subsets were correlated with AQP4-ab and WBC count in CSF. Corticosteroid therapy suppressed subtypes and IL-21 levels. | (118) |
| IL-21 and AQP4-Ab in memory T follicular helper (Th) cells | 25 NMO/NMOSD patients (before and after treatment) and 17 healthy controls | Chinese    | Peripheral blood and CSF/flow cytometry and ELISA | 4 epitopes of AQP4 were showed in NMO and their specificity changed during disease course cell responses to these epitopes represented more IL-17 and IL-10 secretions. | (119) |
| Cytokine and chemokine induced by specific AQP4 | 14 NMO patients and 7 Israelis | PBMC/cytometric bead array and flow cytometry | (Continued) | (Continued) | (Continued) |
Deletion-type CNVs can also be regarded as predisposing factors for NMO. Notably, these CNVs have been found to occur as somatic changes.

In addition to several cytokines that are altered in the course of NMO development, expressions of numerous mRNAs, lncRNAs, and miRNAs have been found to be deregulated in the peripheral blood or brain lesions of NMO patients. Not surprisingly, these genes are mostly enriched in pathways related to functions of the immune system.

Finally, in vitro studies have shown the effects of NMO sera on deregulation of function of astrocytes, suggesting the impact of humoral responses on pathophysiology of this condition. Moreover, these circulatory markers could negatively affect permeability of the blood–brain barrier.

Taken together, NMO has a complex genetic background with prominent roles of immune-related genes, particularly cytokine coding genes and those coding cytokine receptors. Future genome-wide studies in NMO patients from different ethnic background would facilitate identification of risk loci for this condition. Finally, systematic review and meta-analysis studies are recommended to produce quantitative results without any bias along with an overview of genetic aspects of
disease. Also, further studies should assess treatment responses in association with distinct genetic backgrounds. Finally, a limitation of studies conducted in this field is that the expression profiles of genes and cytokines have not been assessed in association with different treatment options.

TABLE 5 | In vitro studies (BMECs, brain microvascular endothelial cells).

| Genes and cells | Number and type of samples | Population | Source of samples/assay method | Results | Ref |
|-----------------|-----------------------------|------------|--------------------------------|---------|-----|
| AQP4IL-6 T-cell functions | 5 AQP4+ NMO patients and 5 healthy controls | Japanese | Astrocyte cells (hAST-AQP4) exposure to human sera/anti-AQP4, Western blot and Immunocytochemistry | NMO sera had a cytotoxic and harmful effect on astrocyte cells. Also decreased AQP4 mRNA and protein levels while increased IL-6 and TNF-α in astrocytes. | (132) |
| AQP4IL-6 | 10 NMOSD patients and 10 healthy controls | Chinese | Astrocyte cells exposed to human sera/Western blot, qRT-PCR, and ELISA | NMO sera downregulated AQP4 levels on the astrocyte surface and induced JAK1/2/STAT3-dependent inflammatory response through IL-6 expression. | (133) |
| Immune responsiveness to Escherichia coli (EC), Staphylococcus aureus (SA) and Candida albicans (CA) | 20 NMO patients and 20 healthy controls | Brazilian | PBMC exposed to EC, SA, and CA/flowcytometry and ELISA | Upregulation of IL-1β, IL-6, IL-17, and CD4+ T-cell proliferation, which correlated with neurological disability and downregulation of IL-10 represented in NMO-derived EC-stimulated cell cultures. Increase in LPS levels was reported in plasma of NMO patients. | (134) |
| MMP-2/MMP-9/cellubrevin/Claudin-5/VCAM-1 | 14 NMOSD patients and 10 healthy controls | Japanese | BMECs, astrocytes, and FH-BNBs cells treated with human sera in presence of MMPs inhibitor/ELISA | MMP-2/9 and VCAM-1 secretion was increased in BMECs after exposure to NMOSD sera that led to increased BBB permability. | (135) |
| AQP4/GFAP/myelin immunoreactivity | AQP4+ NMOSD patients | — | Spinal cord slice cultures of null AQP4 mice treated with NMOSD SCF and serum | AQP4-IgG bound to astrocytes in spinal cord slice cultures and led to a decrease in AQP4, GFAP, and myelin. NMO lesion was more severe according to increase in specific immune cells and cytokines. | (136) |
| Eosinophil | NMO patients | — | Eosinophils cultured from mouse bone marrow exposed to NMO sera | Eosinophils induced antibody-dependent cell-mediated cytotoxicity in AQP4-expressed cells and through complement-dependent cell-mediated cytotoxicity led to killing cells. | (137) |
| 27 cytokines/chemokines | 20 NMOSD patients and 10 healthy controls | Japanese | BMECs treated with human sera/multiplexed fluorescent bead-based immunoassay system and ELISA | IL-6, MCP-1, and IP-10 were significantly upregulated in BMECs treated with NMOSD acute phase sera. IP-10 levels were correlated with CSF/serum albumin ratio. | (138) |
| T-cell functions | 20 NMO patients and 20 healthy controls | Brazilians | PBMC, CD4-free PBMC, and purified CD4+ T cells cultured and exposed to glucocorticoid inhibitor/flow cytometry and ELISA | T-cell proliferation and Th1 cytokine production were significantly lower in NMO cell cultured, while Th17-like phenotype, IL-6, and IL-23 production were increased. IL-6, IL-21, and IL-23 secretion were less sensitive to glucocorticoid inhibitor. | (139) |

AUTHOR CONTRIBUTIONS

MT and SG-F wrote the draft and revised it. TA collected the tables and data. All authors contributed to the article and approved the submitted version.

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