Identification of genetic risk loci associated with aquaporin 4-positive neuromyelitis optica spectrum disorder: a genome-wide association study

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Summary

Background Little is known about the causes of serum aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (AQP4-positive NMOSD) or how its pathophysiology differs from other demyelinating autoimmune diseases, which limits therapeutic and preventative opportunities despite available diagnostic biomarkers. By performing a pan-ancestry genome-wide association study (GWAS), we aimed to deepen our understanding of the genetic architecture of AQP4-positive NMOSD and to explore shared heritability with other autoimmune diseases.

Methods We performed a pan-ancestry GWAS in 2833 individuals, including 1573 AQP4-positive NMOSD cases and 1260 controls (comprising non-affected relatives, healthy non-relatives, and those with other autoimmune diseases). Samples were collected from the International NMOSD Genetics Consortium, comprising 36 hospitals and research facilities across the world. All individuals with AQP4-positive NMOSD fulfilled the 2015 international consensus diagnostic criteria for NMOSD, including positive AQP4-IgG status. We also performed a second GWAS with only the 1857 samples of European ancestry (803 cases and 1054 controls). We then compared our GWAS findings to those from other autoimmune diseases.

Findings We found three independent associations with AQP4-positive NMOSD that reached genome-wide significance: two within the MHC and a third within an intron of the *STAT4* gene. In the pan-ancestry study, we identified a complement C4A-associatied variant, rs1150753 (chr6:32092090:A>G, p=$1{\cdot}61\times10^{-29}$, odds ratio [OR] 2·95, 95% CI 2·44–3·56), rs607929 (chr6:32619221:C>G, p=$2{\cdot}87\times10^{-24}$, OR 1·93, 95% CI 1·70–2·20), and a STAT4-associated variant, rs35593987 (chr2:191051800:AC>A, p=$8{\cdot}49\times10^{-14}$, OR 1·75, 95% CI 1·51–2·03). In Europeans, we identified variants that were either in linkage disequilibrium with or the same as those from the pan-ancestry study: rs1270942 (chr6:31951083:A>G, p=$2{\cdot}52\times10^{-28}$, OR 3·01, 95% CI 2·47–3·66), rs607929 (p=$1{\cdot}12\times10^{-20}$, OR 1·99, 95% CI 1·72–2·30), and rs3821236 (chr2:191038032:G>A, p=$1{\cdot}20\times10^{-10}$, OR 1·74, 95% CI 1·47–2·06). rs1270942 is in linkage disequilibrium with rs1150753 (r^2=0·96) as well as two AQP4-positive NMOSD-associated HLA alleles, *HLA-DRB1*03:01* (p=$2{\cdot}80\times10^{-26}$, OR 2·79, 95% CI 2·30–3·37) and *HLA-B*08:01* (p=$1{\cdot}02\times10^{-24}$, OR 2·68, 95% CI 2·22–3·24). A priori testing of the P1104A variant (rs34536443, chr19:10352442:G>C) within the *TYK2* gene, which acts upstream in the STAT4 pathway, found it to be protective (p=0·0008, OR 0·52, 95% CI 0·35–0·76 in the pan-ancestry study). Genetic sharing was observed with several comorbid autoimmune diseases for both the complement C4A-associated and STAT4-associated variants, including Sjögren's syndrome and systemic lupus erythematosus.

Interpretation AQP4-positive NMOSD is more genetically similar to systemic autoimmune diseases than to multiple sclerosis, despite sharing overlapping clinical phenotypes. Specifically, a polymorphism associated with reduced complement C4 was identified as the biggest disease genetic risk factor, which has been shown to facilitate the development of autoantibody-producing B cells. Our findings also support a pathogenic role of HLA-restricted $CD4^+$ T cells, owing to both a genome-wide significant association of *HLA-DRB1*03:01* as well as heritable risk within the TYK2-STAT4 signalling pathway. Having already been shown to be a successful target for treating psoriatic arthritis and, potentially, systemic lupus erythematosus, we propose the TYK2-STAT4 pathway as a possible therapeutic target in AQP4-positive NMOSD.

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Research in context

Evidence before this study

We searched all original research articles on PubMed written in English from database inception to Nov 16, 2025, using the term "neuromyelitis optica spectrum disorder" in combination with one of the following terms: "genome-wide association study", "whole genome sequencing", "genetic association", or "HLA association". To date, a small GWAS including 132 individuals with aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD) has been done, which included both genotyping and whole-genome sequencing analysis. To try and overcome the limitations of small datasets, subsequent studies have also performed secondary analyses using the same patient cohort and summary statistics to compare against other autoimmune diseases with larger sample sizes, as well as alternative analytical models to identify associations. Alternatively, direct testing for specific single nucleotide polymorphism (SNP) frequencies and HLA typing has been used to identify shared heritability between other diseases and NMOSD. Collectively, measuring the genome-wide heritable risk of AQP4-positive NMOSD has been limited by the number of patients studied.

Added value of this study

The International NMOSD Genetics Consortium was established in 2013, with the aim to generate the largest resource of DNA samples in which to interrogate and compare the genomes of patients across ancestries. This endeavour amassed a total of 3592 samples. We confirm that the strongest risk signal for AQP4-positive NMOSD is located within the MHC class II region and is colocalised with a signal associated with the expression of complement factor C4. Additionally, outside the MHC region, we identify a risk signal associated with the expression of the *STAT4* gene. This SNP was associated with disease risk in a previous NMOSD study that specifically tested for *STAT4* SNPs, having already been identified as a risk factor in several other autoimmune diseases. Our European analysis confirms previous reports that the most associated HLA risk allele for AQP4-positive NMOSD is *HLA-DRB1*03:01*, and we provide further statistical resolution of the region, which indicates a pivotal role in antigen presentation as driving this risk. A meta-analysis of our study and that of the previous GWAS by Estrada and colleagues did not result in additional findings.

Implications of all the available evidence

Taking our findings in the context of existing knowledge, we propose that genetic risk for AQP4-positive NMOSD is associated with successive failure of central and peripheral tolerance mechanisms that rely on: (1) complement C4-mediated clearance of apoptotic cells or direct killing of autoreactive B cells (or both), (2) *HLA-DRB1*03:01*-restricted antigen presentation to autoreactive CD4+ T cells, and (3) altered TYK2-STAT4 signalling, which promotes CD4+ T cell-mediated expansion and maturation of AQP4-specific B cells. Having also observed a shared genetic association with AQP4-positive NMOSD and several other autoimmune diseases for which TYK2 inhibitors already show efficacy, we consider the TYK2-STAT4 pathway to be a promising new target for future treatments.

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease of the CNS that affects approximately 1–10 per 100 000 and more than 250 000 people worldwide. More than 70% of people with NMOSD have serum antibodies directed against the astrocyte aquaporin 4 (AQP4) water channel, classified as AQP4-positive NMOSD.[1] Although AQP4-positive NMOSD is observed globally, increased prevalence is reported in individuals of east Asian and Black or African American ancestries, suggesting that ancestry affects heritable disease risk.[2]

At onset, individuals with AQP4-positive NMOSD have clinical phenotypes such as optic neuritis and transverse myelitis, which can overlap with other demyelinating CNS diseases, in particular multiple sclerosis and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Diagnostic accuracy is dependent on tests for disease-specific antibodies against AQP4-IgG and on MRI findings.[3] Patients with AQP4-positive NMOSD are predominantly female (9:1 female to male ratio)[4] and often have other comorbid autoimmune diseases, such as Sjögren's syndrome and systemic lupus erythematosus, as well as organ-specific autoimmune disorders like autoimmune thyroid disease and myasthenia gravis.[5–7] These comorbid autoimmune diseases add to the complexity of disease management for patients with AQP4-positive NMOSD,[8] and suggest the possibility that shared heritability and pathological processes exist between them. In contrast to multiple sclerosis, genetic studies that aim to better understand the genetic architecture of AQP4-positive NMOSD have been scarce because of low disease frequency and low accessibility to diagnostic tests globally. To date, the largest genome-wide association study (GWAS), which included 132 patients, identified two independently associated signals within the MHC: one within the MHC class II gene region and another that might be associated with the complement component 4 genes, *C4A* and *C4B*, within the MHC class III region.[9] The small sample size of this previous study is in stark contrast with the 47 000 cases included in the most recent GWAS of multiple sclerosis, which identified 233 independent associations: 32 within the MHC, one within chromosome X, and the remaining 200 across the rest of the genome, located within or in close proximity to immune-related genes.[10] The findings highlighted a prominent role of genetically calibrated

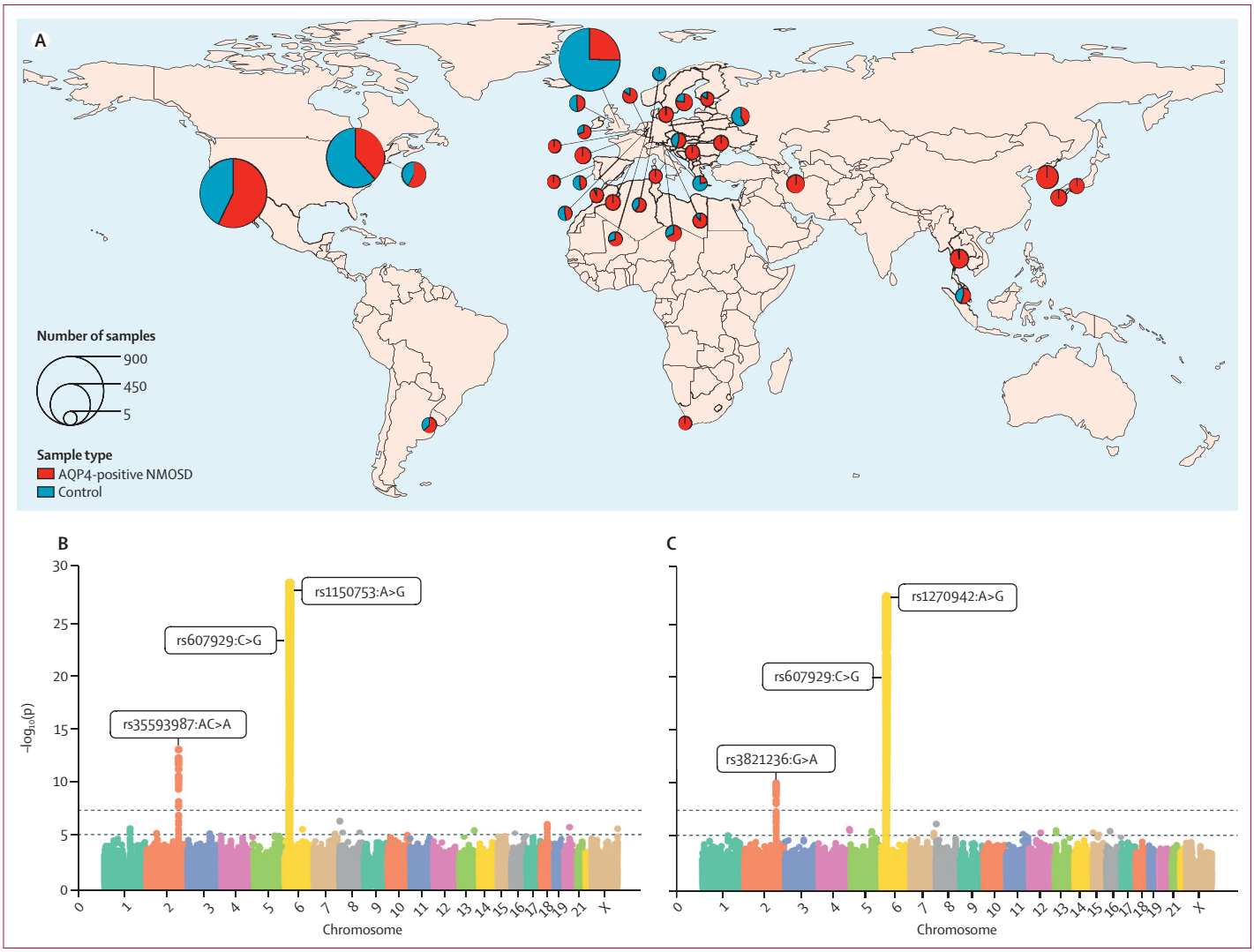

Figure 1: **Pan-ancestry and European genome-wide association studies of AQP4-positive NMOSD**
(A) Map of samples. (B) Manhattan plot for the pan-ancestry study. (C) Manhattan plot for the European study. Horizontal lines correspond to the 10^{-5} and 5×10^{-8} (genome-wide) significance levels. Independently associated variants that reached genome-wide significance are labelled. AQP4=aquaporin 4. NMOSD=neuromyelitis optica spectrum disorder.

immune responses to environmental exposures, including roles for both innate and adaptive immune cells.

We established the International NMOSD Genetics Consortium, bringing together neurologists and immunologists from across the world. We aimed to provide the first pan-ancestry GWAS of individuals with clinically confirmed AQP4-positive NMOSD, and to explore the hypothesis of shared heritability of AQP4-positive NMOSD with other autoimmune diseases, some of which are common comorbidities.

See Online for appendix 1

Methods

Study design and sample processing

3592 DNA samples from individuals with AQP4-positive NMOSD (fulfilling the 2015 NMOSD criteria for inclusion,[2] including AQP4-IgG status) or controls (comprising non-affected relatives, healthy non-relatives, and those with other autoimmune diseases) were curated from 36 hospitals and research centres across the world and then genotyped (figure 1A; appendix 1 pp 4, 7, 17). After quality control (appendix 1 pp 18–20), samples from 1573 individuals with AQP4-positive NMOSD (1377 female and 196 male) and 1260 controls (764 female and 496 male) remained. 627 (40%) of 1573 individuals with AQP4-positive NMOSD had a reported comorbid autoimmune disease (table). Genome-wide imputation[11–13] was performed to infer single nucleotide polymorphisms (SNPs) and insertion–deletions (indels) not assessed by the genotyping array, and HLA imputation[12] was done to infer HLA SNPs as well as classical HLA alleles, HLA amino acids (including combinations) and amino acid indels, and HLA intragenic SNPs and indels, which we

refer to collectively as extended HLA variants (appendix 1 p 20). SNPs and nucleotide indels from both imputations were merged to create a genome-wide dataset (appendix 1 p 20). Additionally, SNPs and nucleotide indels in chromosome 6 were merged with the remaining variants from the HLA imputation to create an extended chromosome 6 dataset (appendix 1 pp 20–21), which was used to analyse all types of variants in the extended MHC (xMHC) region.

Association analysis

To include all ancestries in our sample cohort, while also mitigating any potential ancestry bias, we aimed to perform both pan-ancestry and ancestry-specific association analyses. A pan-ancestry association analysis was first performed with all samples for the 6 264 966 variants with minor allele frequency of at least 0·05 among the samples (ie, with the less frequent allele present in ≥5% of the samples) conditioning on 12 principal components (computed by PC-AiR[14]), sex, and kinship coefficients (computed by PC-Relate[15]) using GENESIS[16] (appendix 1 pp 5, 11, 21). After assigning ancestry to the samples using the 1000 Genomes Project dataset (appendix 1 p 21),[17] we proceeded with ancestry-specific analyses when at least 200 cases and 200 controls were available. This requirement was only met for European participants, for which we had 803 cases (684 female and 119 male) and 1054 controls (629 female and 425 male). An association analysis was therefore performed with the European samples for the 6 007 187 variants with minor allele frequency of at least 0·05 among those samples, using four principal components computed from those samples (appendix 1 pp 4, 12, 20). Independent associations ($p \leq 10^{-5}$) were identified by an adaptation of the Max-Min Parents and Children algorithm[18] (appendix 1 pp 21–22) and were matched across the two studies either directly (ie, the same variant was involved) or indirectly (ie, the variants were in linkage disequilibrium; appendix 1 p 22). Independent associations were also matched to those of studies in any trait in the GWAS Catalog (r2024-02-11).[19] Finally, for each independently associated variant, molecular trait associations of the variant with $p \leq 10^{-5}$ were identified in the eQTL Catalogue.[20]

To identify additional associations in Europeans, we performed a meta-analysis of our European AQP4-positive NMOSD data with that of the previous study by Estrada and colleagues (appendix 1 p 22).[9]

Bayesian fine-mapping and colocalisation of signals

Bayesian fine-mapping was performed using SuSiE[21,22] for each region around independently associated variants to estimate the probability of each variant in the region being causal (posterior inclusion probability) and to generate 95% credible sets, each corresponding to an independent signal (appendix 1 pp 22–23). Bayesian colocalisation analysis between our fine-mapped regions in Europeans and the fine-mapped regions around expression quantitative trait loci (eQTLs) in the European datasets of the eQTL Catalogue was then performed using coloc[23] (appendix 1 p 23) to identify GWAS and QTL signals with a high posterior probability of sharing the same causal variant.

	AQP4-positive NMOSD (n=1573)	Control (n=1260)
Age at onset, years	39 (28–51)	..
Sex		
Female	1377 (87·5%)	764 (60·6%)
Male	196 (12·5%)	496 (39·4%)
Other autoimmune disease	627 (39·9%)	909 (72·8%)
Ethnic background		
American Indian or Alaska native	7 (0·4%)	5 (0·4%)
Asian	355 (22·6%)	50 (4·0%)
Black or African American	181 (11·5%)	44 (3·5%)
Greater Middle Eastern	60 (3·8%)	0
Hispanic or Latino	82 (5·2%)	65 (5·2%)
Native Hawaiian or Pacific Islander	1 (0·1%)	1 (0·1%)
White	726 (46·2%)	964 (76·5%)
Mixed	36 (2·3%)	26 (2·1%)
Other	5 (0·3%)	7 (0·6%)
Unknown	120 (7·6%)	98 (7·8%)

Data are median (IQR) or n (%). AQP4=aquaporin 4. NMOSD=neuromyelitis optica spectrum disorder.

Table: **Demographic characteristics of the study cohort**

Cell type and tissue enrichment

We sought to identify cell types and tissues that were enriched in disease heritability and thereby provide further insight as to where these variants could be acting in disease (appendix 1 p 23). However, after false discovery rate correction, there were no significant findings.

Comprehensive xMHC analysis

Having previously tested SNPs and indels for association with AQP4-positive NMOSD, including those within the xMHC, we then considered all types of HLA variation with minor allele frequency of at least 0·05. Independent chromosome 6 associations were identified using the extended chromosome 6 dataset, and those within the xMHC were extracted (appendix 1 pp 23–24). Because the results comprised the same MHC SNPs as in the genome-wide analyses, we sought to identify disease-associated HLA variation that is tagged by those SNPs. For each such SNP in the European analysis, we identified extended HLA variants (excluding HLA amino acid combinations) that were also disease-associated in the analysis ($p \leq 10^{-5}$) and were proxies for the SNP ($r^2 \geq 0·7$) in Europeans.

Genetic risk sharing with other autoimmune diseases

To quantify the genetic risk shared among AQP4-positive NMOSD and other autoimmune diseases, we focused on autoimmune diseases for which European studies in the GWAS Catalog had matches with our European study (appendix 1 p 23). After adding multiple sclerosis (represented by the most recent study in Europeans,[10] with which there was no match; appendix 1 p 24) and AQP4-positive NMOSD (represented by our European study) to those diseases, we computed and plotted the matching coefficient (ranging from 0 to 1; see appendix 1 p 23 for definition) between the diseases. As an alternative method to measure genetic sharing, we used linkage disequilibrium score regression[24] to test for genetic correlation (r_g) between each pair of diseases with available summary statistics (appendix 1 p 23). Finally, we performed a literature review to evaluate the efficacy of currently available non-steroidal treatments for a selection of autoimmune diseases (appendix 1 p 23).

STREGA reporting guidelines were followed in this study.[25]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In the pan-ancestry GWAS, including samples from 1573 individuals with AQP4-positive NMOSD and 1260 controls, we identified 17 independent associations with $p \leq 10^{-5}$, three of which reached genome-wide significance ($p \leq 5 \times 10^{-8}$). Two of these were within the MHC: rs1150753 (chr6:32092090:A>G, $p=1 \cdot 61 \times 10^{-29}$, odds ratio [OR] 2·95, 95% CI 2·44–3·56) and rs607929 (chr6:32619221:C>G, $p=2 \cdot 87 \times 10^{-24}$, OR 1·93, 95% CI 1·7–2·20). The third association was on chromosome 2: rs35593987 (chr2:191051800:AC>A, $p=8 \cdot 49 \times 10^{-14}$, OR 1·75, 95% CI 1·51–2·03; figure 1B; appendix 2 p 1).

See Online for appendix 2

Bayesian fine-mapping generated two credible sets for the xMHC (appendix 2 p 2). One comprised 100 variants, including our top variant, rs1150753, which was ranked joint second (posterior inclusion probability 0·03), the first being rs389884 (chr6:31973120:A>G, $p=5 \cdot 57 \times 10^{-29}$, OR 2·90, 95% CI 2·40–3·50, posterior inclusion probability 0·04). The other credible set comprised 28 variants, with rs9270663 ranked first (chr6:32598324:A>G, $p=9 \cdot 82 \times 10^{-26}$, OR 1·99, 95% CI 1·75–2·27, posterior inclusion probability 0·06). Neither set included our second variant, rs607929. The low posterior inclusion probability of the xMHC variants, which did not allow us to confidently pinpoint candidate causal variants, highlights the difficulty of fine-mapping signals in that region. By contrast, fine-mapping for the region around rs35593987, our third genome-wide significant variant, in chromosome 2, generated a single credible set of nine variants (appendix 2 p 2), with rs35593987 ranking first (posterior inclusion probability 0·51).

In the eQTL Catalogue, rs1150753 is a QTL for multiple genes within the MHC (appendix 2 p 3). Most significantly, it is a protein QTL (pQTL) for MHC class I polypeptide-related sequence B (MICB) in plasma ($p=1 \cdot 20 \times 10^{-88}$), as well as an eQTL for *MICB* in the brain ($p=1 \cdot 45 \times 10^{-18}$). It is also an eQTL and pQTL for complement *C4A* ($p=7 \cdot 98 \times 10^{-77}$ and $p=9 \cdot 51 \times 10^{-34}$, respectively). The second independently associated variant, rs607929, is a QTL for several genes, including an eQTL in B cells for *HLA-DRB1* ($p=2 \cdot 59 \times 10^{-73}$) and a pQTL for C4A and C4B in plasma ($p=7 \cdot 05 \times 10^{-13}$; appendix 2 p 3). Outside the MHC, rs35593987 is a deletion of a cytosine located within intron 14 of the *STAT4* gene on chromosome 2. This variant is significantly associated with increased expression of *STAT4* across multiple RNA studies and tissue types (appendix 2 p 3).

In the European GWAS, including samples from 803 individuals with AQP4-positive NMOSD and 1054 controls, we identified 16 independent associations with $p \leq 10^{-5}$, three of which reached genome-wide significance ($p \leq 5 \times 10^{-8}$; figure 1C; appendix 2 p 4). Overall, five independent associations were matched between the pan-ancestry and European studies (appendix 2 pp 5–6), including the three that reached genome-wide significance. The top independently associated SNP, rs1270942 (chr6:31951083:A>G, $p=2 \cdot 52 \times 10^{-28}$, OR 3·01, 95% CI 2·47–3·66), is a proxy for rs1150753 ($r^2=0 \cdot 96$). The second SNP, rs607929 (chr6:32619221:C>G, $p=1 \cdot 12 \times 10^{-20}$, OR 1·99, 95% CI 1·72–2·30), was also identified in the pan-ancestry study. The third, rs3821236 (chr2:191038032:G>A, $p=1 \cdot 20 \times 10^{-10}$, OR 1·74, 95% CI 1·47–2·06), is a proxy for rs35593987 ($r^2=0 \cdot 97$).

Meta-analysis with the study by Estrada and colleagues[9] did not result in additional discoveries. 14 lead associations were identified (appendix 2 p 7), two of which had matches in the pan-ancestry study (appendix 2 pp 8–9) and five of which had matches in the European study (appendix 2 pp 10–11). Two SNPs reached genome-wide significance: rs1150753, the previously discovered top SNP in the pan-ancestry analysis ($p=7 \cdot 29 \times 10^{-37}$; appendix 2 p 8), and rs3024886 (chr2:191035723:G>A, $p=2 \cdot 17 \times 10^{-12}$), which is in complete linkage disequilibrium with the pan-ancestry SNP, rs3821236 (appendix 2 p 9), and is a proxy for rs35593987 in Europeans (appendix 2 p 11).

Bayesian fine-mapping resulted in two 95% credible sets for the xMHC and one for the region around rs3821236 (appendix 2 p 12). One xMHC set included rs1270942 as its top variant (posterior inclusion probability 0·06) and the other had rs7454108 (chr6:32713706:T>C) and rs3957146 (chr6:32713753:T>C) jointly at the top ($p=2 \cdot 80 \times 10^{-9}$, OR 0·47, 95% CI 0·36–0·60, posterior inclusion probability 0·02).

rs607929 was, again, not included in either set. As per our pan-ancestry results, the complex heritable structure of the xMHC prevented us from identifying a variant with a posterior inclusion probability greater than 0·5 (all variants had posterior inclusion probability <0·06) and therefore fine-mapping did not help us to pinpoint the causal variants in this region. The set for the region around rs3821236 had rs3821236 at the top (posterior inclusion probability 0·13), which was also second in the corresponding pan-ancestry set (posterior inclusion probability 0·10).

In the eQTL Catalogue, we identified similar associations for the variants in our European study to those identified in the pan-ancestry study: rs1270942 is a pQTL and eQTL for multiple proteins and genes, including MICB, C4A, and C4B; rs607929 is an eQTL for multiple HLA genes, most significantly for *HLA-DRB1*; and rs3821236 is significantly associated with increased expression of *STAT4* across multiple RNA studies and tissue types (appendix 2 p 13). Subsequent Bayesian colocalisation analysis showed that the most likely colocalised signals for the xMHC were the GWAS signal tagged by rs1270942 and an eQTL signal for *C4A* (posterior probability 0·93; appendix 2 p 14). The GWAS signal tagged by rs1270942 also had a high posterior probability of colocalisation with QTL signals for *C4A* in three additional eQTL Catalogue studies (posterior probability 0·64–0·92; appendix 2 p 14). For the GWAS signal tagged by rs7454108 and rs3957146, the most likely colocalisation was with an eQTL signal for *HLA-DQB1* (posterior probability 0·89; appendix 2 p 14). Finally, the GWAS signal tagged by rs3821236 was confidently colocalised with an eQTL signal for *STAT4* (posterior probability 0·93; appendix 2 p 14).

For both studies, the independently associated variants identified by the comprehensive xMHC analyses were the same MHC SNPs as in the genome-wide analyses (appendix 2 pp 15–16). Overall, 8562 significant associations were identified within the xMHC at the 10^{-5} level in the pan-ancestry study, of which 6028 reached genome-wide significance (appendix 2 p 17). In Europeans, 8070 significant associations were identified within the xMHC at the 10^{-5} level, 5151 of which reached genome-wide significance, with rs1270942 ranking first (figure 2A; appendix 2 p 18). Upon conditioning on rs1270942 (ie, testing for association that is not explained by rs1270942), 1084 significant associations were identified at the 10^{-5} level, none of which reached genome-wide significance, with rs607929 ranking first (figure 2B; appendix 2 p 18). Upon conditioning on both rs1270942 and rs607929, no significant associations remained (figure 2C; appendix 2 p 18).

We found the top independently associated SNP in our European cohort, rs1270942, to be a proxy for two groups of risk-conferring extended HLA variants; the variants within each group were all highly correlated (r^2 of approximately 0·99) to each other, suggesting that they

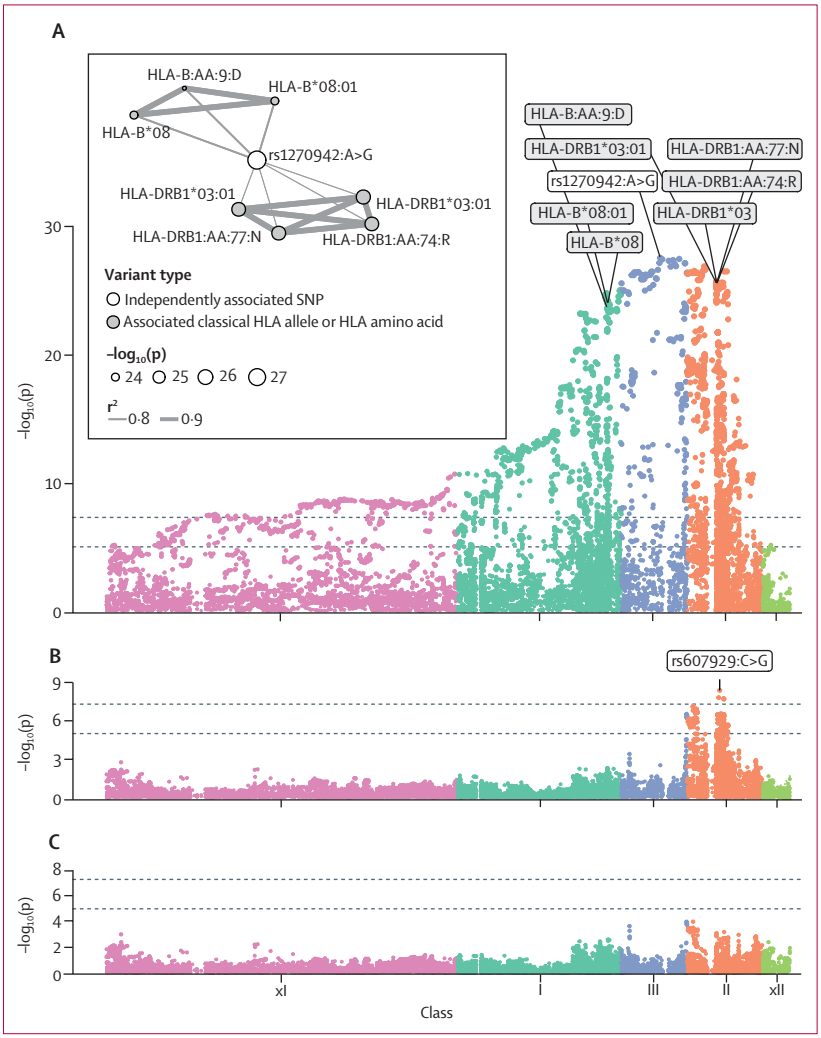

Figure 2: **Comprehensive xMHC analysis of AQP4-positive NMOSD in European individuals**
(A) Manhattan plot of xMHC variants. The top variant, rs1270942, is labelled in white. Also labelled, in grey, are HLA classical alleles and HLA amino acids that are associated with the disease and are proxies for rs1270942 in European populations. Inset: Graph of the labelled variants. Node size is proportional to $-\log_{10}(p)$. Variants that are proxies for each other are connected by an edge with thickness proportional to r^2, and the distance between them is approximately inversely proportional to r^2. (B) Manhattan plot conditional on rs1270942. The top variant, rs607929, is labelled in white. (C) Manhattan plot conditional on rs1270942 and rs607929. In all plots, horizontal lines correspond to the 10^{-5} and 5×10^{-8} (genome-wide) significance levels. AQP4=aquaporin 4. NMOSD=neuromyelitis optica spectrum disorder. SNP=single nucleotide polymorphism. xMHC=extended MHC.

all represent the same biological signal (figure 2A). The first group comprised four variants, all of which were related to the same MHC class II gene, *HLA-DRB1*. The first and second variants were gene allele *HLA-DRB1*03* ($p=1·93\times10^{-26}$, OR 2·78, 95% CI 2·30–3·35) and its suballele *HLA-DRB1*03:01* ($p=2·80\times10^{-26}$, OR 2·79, 95% CI 2·30–3·37; appendix 2 p 18). The third and fourth variants were amino acids of the HLA-DRB1 protein: arginine at amino acid position 74 (HLA-DRB1:AA:74:R, $p=2·86\times10^{-26}$, OR 2·76, 95% CI 2·29–3·34) and asparagine at amino acid position 77 (HLA-DRB1:AA:77:N, $p=2·51\times10^{-26}$, OR 2·77, 95% CI 2·29–3·34). We further explored the relationship

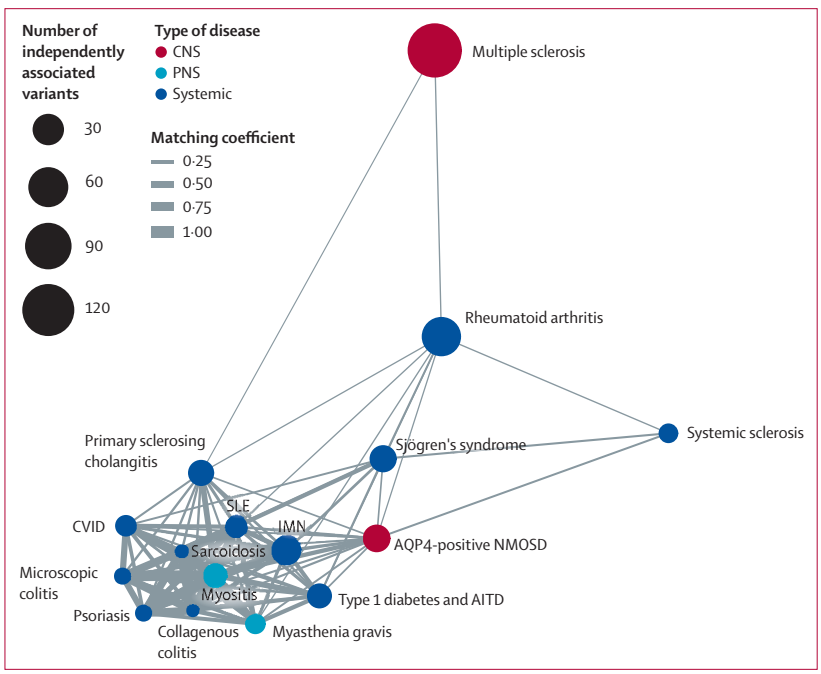

Figure 3: **Graph of shared genetic risk across selected autoimmune diseases**
Nodes comprise AQP4-positive NMOSD, autoimmune diseases with a non-zero matching coefficient with AQP4-positive NMOSD, and multiple sclerosis (appendix 1 p 6). Node size is proportional to the number of independent associations in the corresponding study. Pairs of diseases with a non-zero matching coefficient are connected by an edge with thickness proportional to the matching coefficient, and the distance between them is approximately inversely proportional to the matching coefficient. AITD=autoimmune thyroid diseases. AQP4=aquaporin 4. CVID=common variable immunodeficiency. IMN=idiopathic membranous nephropathy. NMOSD=neuromyelitis optica spectrum disorder. PNS=peripheral nervous system. SLE=systemic lupus erythematosus.

between *HLA-DRB1* alleles and amino acids in appendix 1 (p 24). The second group of risk variants comprised *HLA-B* allele *HLA-B*08* ($p=9{\cdot}68\times10^{-25}$, OR 2·68, 95% CI 2·22–3·24), its suballele *HLA-B*08:01* ($p=1{\cdot}02\times10^{-24}$, OR 2·68, 95% CI 2·22–3·24), and aspartate at amino acid position 9 of the HLA-B protein (HLA-B:AA:9:D, $p=2{\cdot}05\times10^{-24}$, OR 2·65, 95% CI 2·20–3·21). We did not find any extended HLA variants that are proxies for rs607929 and associated with AQP4-positive NMOSD in Europeans.

Using the GWAS Catalog, we identified direct matches for our top pan-ancestry and European C4A associations, rs1150753 and rs1270942, in systemic lupus erythematosus (appendix 2 pp 19–20). The rs1270942 association was directly matched in a study for type 1 diabetes and autoimmune thyroid diseases. The European STAT4 association, rs3821236, was directly matched in three systemic sclerosis studies and one systemic lupus erythematosus study (appendix 2 p 20). Several autoimmune diseases with indirect matches in both of our studies were also identified, including Sjögren's syndrome, systemic lupus erythematosus, and myasthenia gravis (appendix 2 pp 21–22), supporting that these comorbid diseases share a degree of genetic risk. Both rs1150753 and rs1270942 are also proxies for rs1150757 (r^2 of 1·00 and 0·96, respectively; appendix 2 pp 21–22), which was found to be significantly associated with AQP4-positive NMOSD but not AQP4 antibody-negative NMOSD in the previous NMOSD GWAS by Estrada and colleagues.[9]

Our analysis of genetic risk sharing among autoimmune diseases in Europeans showed that AQP4-positive NMOSD is most similar (as measured by matching coefficient) to myositis, systemic lupus erythematosus, and idiopathic membranous nephropathy (appendix 1 p 6; figure 3). Subsequent genetic correlation analysis of autoimmune diseases with available summary statistics found AQP4-positive NMOSD to be significantly genetically correlated with sarcoidosis ($p=6{\cdot}08\times10^{-9}$, $r_g=0{\cdot}81$, 95% CI 0·54–1·00]) and systemic lupus erythematosus ($p=1{\cdot}96\times10^{-6}$, $r_g=0{\cdot}77$, 95% CI 0·45–1·00; appendix 1 pp 6, 14). No significant correlation was identified between AQP4-positive NMOSD and rheumatoid arthritis, collagenous colitis, microscopic colitis, or multiple sclerosis.

The lack of genetic sharing between AQP4-positive NMOSD and multiple sclerosis is supported by the discordance observed in the efficacy of several pharmacological treatments (appendix 1 p 15, appendix 2 p 23). By contrast, drugs that show efficacy across other autoimmune diseases sharing genetic risk with AQP4-positive NMOSD might be targeting shared disease pathways; for example, inhibitors of tyrosine kinase 2 (TYK2), which mirror the effect of the *TYK2* variant P1104A (rs34536443, chr19:10352442:G>C).[26,27] Accordingly, we tested the a priori hypothesis that rs34536443 is associated with AQP4-positive NMOSD. We found that the variant is indeed protective ($p=0{\cdot}0008$, OR 0·52, 95% CI 0·35–0·76 in the pan-ancestry study; $p=0{\cdot}0015$, OR 0·54, 95% CI 0·36–0·79 in the European study).

Discussion

To our knowledge, this was the largest GWAS of AQP4-positive NMOSD to date. Our findings provide new insights into disease cause, validate and consolidate previous findings, and clarify our understanding of commonly occurring comorbidities in NMOSD.

The AQP4-positive NMOSD risk signal that reached highest genome-wide significance drives differential expression and copy number of *C4*. Reduced C4 serum levels have previously been observed in people with AQP4-positive NMOSD compared with those with myelin oligodendrocyte glycoprotein antibody-associated disease or multiple sclerosis, or healthy controls.[28] Reduced C4 has also been associated through a previous genetic analysis, which demonstrated that the association was specific to individuals with NMOSD with AQP4 antibodies. C4 maintains peripheral B cell tolerance in a myeloid cell-dependent manner, the failure of which is likely to lead to increased numbers of autoreactive B cells that are able to enter lymph node follicles and differentiate into antibody-producing cells.[29] This

potential mechanism by which reduced C4 might lead to autoreactive B cell survival is supported by a study showing that the integrity of the central and peripheral B cell tolerance checkpoints in people with APQ4-positive NMOSD is compromised[30] and by studies in systemic lupus erythematosus[31] and other systemic autoimmune diseases, which are associated with low copy numbers of *C4*, C4A-deficiency, or both.[32] We show that these systemic autoimmune diseases are genetically similar to APQ4-positive NMOSD in our genetic risk sharing analysis.

The subsequent immune safety checkpoint that is likely to be affected in AQP4-positive NMOSD patients is the failure to prevent autoreactive CD4+ T cells from providing help to autoreactive B cells. Central to this hypothesis is the increased disease risk associated with carrying the *HLA-DRB1*03:01* allele—in particular, the structure of its P4 peptide-binding pocket. *HLA-DRB1*03:01* is highly correlated with the presence of arginine at position 74, which forms part of the peptide binding pocket of the HLA class II allele, and the presence of asparagine at position 77, which is adjacent to position 74 in the tertiary complex of the structure. This would suggest that the risk is mediated by the peptide repertoire that is presented to CD4+ T cells and, by inference, supports that AQP4-positive NMOSD is a T cell-dependent, antigen-driven disease.[33] At a structural level, the impact of MHC polymorphisms on T-cell receptor recognition have been demonstrated to occur via direct and indirect means.[34] In the context of HLA-mediated autoimmunity, a correlation between HLA polymorphisms and their selection for specific autoreactive T-cell receptors has recently been established.[35] How HLA polymorphisms affect T-cell receptor repertoires in the context of NMOSD will require future detailed investigations. *HLA-DRB1*03:01* is also associated with increased risk of several autoimmune diseases, including myositis,[36] systemic lupus erythematosus,[37] and myasthenia gravis;[38] it is also associated with multiple sclerosis, albeit at a lower risk than for the aforementioned diseases.[39]

Outside the MHC, we show that the largest genetic risk for AQP4-positive NMOSD is on chromosome 2 and is an eQTL for *STAT4*. Of note, we show that this risk is also shared with common comorbid autoimmune diseases, including Sjögren's disease, systemic lupus erythematosus, and myasthenia gravis, as well as systemic sclerosis, sarcoidosis, and myositis.

The rs35593987 variant sits within a region of DNA that is active in T follicular helper cells,[40] a population of CD4+ T cells that are required for B cells to transform into high-affinity antibody producing cells. Importantly, the amount of STAT4 produced by T cells determines their commitment to this role,[41] as well as balancing the fate of their counterparts, T follicular regulatory cells, which hinder the production of autoantibodies against self-antigens or allergens.[42] Thus, a genetic regulator of STAT4 in T follicular helper cells is likely to be instrumental in determining the fate of diseases that are driven by the generation of autoantibodies. Additional evidence shows that autoreactive CD4+ T cells, including those in patients with AQP4-positive NMOSD, have an exhausted phenotype, owing to chronic self-antigen exposure. However, as has also been shown in other auto-antibody diseases, including autoimmune hepatitis and bullous pemphigoid, these exhausted cells remain highly effective at providing the help needed for autoreactive B cells to produce autoantibodies.[43]

Our study is limited by sample size in drawing further conclusions from additional associations that were significant at the 10^{-5} level but not at the genome-wide level and we anticipate that increasing the sample size would provide further statistical power to tease apart the top signal (tagged by rs1150753). We were also limited by our sample size in detecting any cell type or tissue enrichment in disease heritability.

When taking our findings together, and within the context of supporting studies, we propose that autoantibody production in patients with AQP4-positive NMOSD is precipitated by an inherent impairment to remove B cells that are reactive to self, at which several safety checkpoints appear to be at fault. The specificity of this failure in the context of AQP4-positive NMOSD is likely to be dependent on the peptide specificity of the HLA class I and class II associations (*HLA-B*08:01* and *HLA-DRB1*03:01*, respectively), but the genetic sharing between AQP4-positive NMOSD and several other autoimmune diseases indicates that these diseases are precipitated through similar cumulative failings within the immune system. This also raises the possibility that existing therapies for other diseases might hold promise for treating AQP4-positive NMOSD. Having demonstrated that the TYK2-STAT4 pathway is associated with such shared vulnerability, this could be a promising therapeutic target for treating patients with AQP4-positive NMOSD.

International NMOSD Genetics Consortium

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Contributors

KEA, SBK, CAD, JP, and LF contributed to study conceptualisation, project administration, and sample acquisition. MIL and PW

contributed to diagnostic testing and recruitment. BGW contributed to sample collection. APA, KEA, RF, KJK, BMN, GM, JP, and LF contributed to data analysis, data interpretation, methodology, and visualisation. KEA, APA, RF, LTJ, JR, RG, TK, GM, JP, and LF contributed to writing the manuscript. JP and LF established the International NMOSD Genetics Consortium and were responsible for funding acquisition and supervision. All authors contributed to critical review. All authors had access to the study data and had final responsibility for the decision to submit the manuscript for publication. KEA and APA accessed and verified the data underlying the study.

Declaration of interests

RF has received support from Guarantors of Brain. PW has received grants from the Guthy-Jackson Foundation, received royalties from WO/2010/046716, received honoraria for teaching talks for the University of British Columbia and Union Chimique Belge and has the following issued patents: WO2015177512A1, WO2019211633A1, WO2014202978A1, and WO2022189788A1. BGW has royalties or licenses with RSR, Hospices Civils de Lyon, MVZ Labor PD Dr Volkmann und Kollegen, and Oxford University, has received consulting fees from Roche, Chugai, Genetech, Horizon Therapeutics, CANbridge Pharmaceuticals, has received honoraria from Roche and Horizon, has a patent for NMO-IgG for diagnosis of neuromyelitis optica, and participates on a data safety monitoring board or advisory board for Alexion, Medimmune, VielaBio, Horizon, and UCB Biosciences. KJK has received consulting fees from Tome Biosciences, AlloDX, and Vor Biosciences, serves on the *Nature Genomics* scientific advisory board and has stocks or stock options in *Nature Genomics*. TK has received support from Deutsche Forschungsgemeinschaft and Gemeinnützige Hertie-Stiftung, received honoraria from Sanofi, Roche, and Merck, and received a travel grant as an invited speaker for the European Committee for Treatment and Research in Multiple Sclerosis and the Consortium of Multiple Sclerosis Centers. BMN serves on the scientific advisory board for and has stocks or stock options in Deep Genomics and Neumora. GM has received support from the Li Ka Shing Foundation. JP has received honoraria for scientific meetings and advisory work from Merck Seronon, Novartis, Chugai, Alexion, Roche, Medimmune/Horizon, Argenx, Sanofi, UCB Pharma, Mitsubishi, Amplo Biotechnology, and Janssen. JP also holds a patent (reference P37347WO) and a licence agreement with Numares for multimarker multiple sclerosis diagnosis (without income). JP's neuromyelitis optica service is funded by the Highly Specialised Services NHS England.

Data sharing

Summary statistics for the pan-ancestry study and the European study are available in the GWAS Catalog (accession numbers GCST90572740 and GCST90572741, respectively).

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Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps.

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