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Research Article

Keywords: IgG4, HLA, etiology, MHC II, Pemphigus, Myasthenia gravis

Posted Date: October 6th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-638050/v1

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Genetic risk factors for pathogenic IgG4 autoantibodies: a systematic review and meta-analysis of HLA class II associations in patients with IgG4 autoimmune diseases

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Abstract

Autoimmune diseases caused by pathogenic IgG4 subclass autoantibodies (IgG4-AID) include diseases like MuSK myasthenia gravis, pemphigus vulgaris or thrombotic thrombocytopenic purpura. Their etiology is still unknown. Polymorphisms in the human leukocyte antigen (HLA) gene locus, particularly in HLA-DRB1, are known genetic susceptibility factors for autoimmune diseases.

We hypothesized a similar role for HLA polymorphisms in IgG4-AID and conducted a systematic review and meta-analysis with case-control studies on IgG4-AID based on MOOSE/ HuGENet guidelines.

Genotype (G) and allele (A) frequencies of *HLA-DQB1*05 (G: OR 3.8; 95% CI 2.44-5.9; p < 0.00001; A: OR 2.54; 95% CI 1.82-3.55; p < 0.00001) and *HLA-DRB1*14 (G: OR 4.31; 95% CI 2.82-6.59; p < 0.00001; A: OR 4.78; 95% CI 3.52-6.49; p < 0.00001) and the *HLA-DRB1*14-*DQB1*05 haplotype (OR 6.3; 95% CI 3.28-12.09; p < 0.00001 / OR 4.98; 95% CI 3.8-6.53; p < 0.00001) were increased while *HLA-DRB1*13 (G: OR 0.48; 95% CI 0.34-0.68; p < 0.00001; A: OR 0.46; 95% CI 0.34-0.62; p < 0.00001) was decreased in IgG4-AID patients.

In conclusion, the *HLA-DQB1*05, *HLA-DRB1*14 alleles and the *HLA-DQB1*05-*DRB1*14 haplotype could be genetic risk factors that predispose for the production of pathogenic IgG4 autoantibodies and the *HLA-DRB1*13 allele may protect from IgG4 autoimmunity.

**Keywords:** IgG4, HLA, etiology, MHC II, Pemphigus, Myasthenia gravis
Introduction

IgG4 autoimmune diseases (IgG4-AID) were first collectively described in 2015 (1) and include diseases such as muscle-specific kinase myasthenia gravis (MuSK MG), pemphigus vulgaris (PV) or thrombotic thrombocytopenic purpura (TTP)(2). IgG4-AID share pathophysiological and therapeutic commonalities (3, 4), and are distinct from other autoantibody-mediated autoimmune diseases, as IgG4 has unique properties including functional monovalency and lack of typical antibody effector mechanisms such as complement activation (5-8). IgG4 antibodies are considered as protective by competing with effector antibodies for binding of epitopes, e.g. in the context of allergy and autoimmunity (5, 9-13). Yet in IgG4-AID, the IgG4 autoantibodies are directly pathogenic by functional blocking of protein-protein interaction(1, 14). Their pathogenicity could be demonstrated by passive transfer of patient IgG4 to experimental animals in 1) MuSK MG (MuSK-IgG4), 2) PV (desmoglein 3-IgG4), 3) pemphigus foliaceus (PF, desmoglein 1 and/or 3-IgG4), 4) chronic inflammatory demyelinating polyneuropathy (CIDP, contactin-1-IgG4), 5) CIDP (neurofascin 155-IgG4), and 6) TTP (ADAMTS13-IgG4) (15).

Whether IgG4-AID have distinct genetic risk factors that may predispose for the production of pathogenic IgG4 is unknown. A major contributor to genetic susceptibility to autoimmunity are the highly polymorphic human leucocyte antigen (HLA) genes on chromosome 6p21.3 that encode the major histocompatibility complex (MHC)(16, 17). HLA-DR, HLA-DQ, and HLA-DP encode the MHC II molecules on antigen-presenting cells and thymic epithelial cells that present self- and foreign antigen peptides to CD4+ T helper cells,
which is essential for T-cell activation or the development and maintenance of tolerance (18, 19). *HLA-DR* has been linked to aberrant presentation of self-peptide to autoreactive T helper cells in the thymus (20), and a recent study showed that distinct *HLA-DR* variants may directly influence the immune response towards autoimmunity or tolerance (21). Furthermore, genetic polymorphisms in the *HLA-DRB1* gene are associated with a range of autoimmune diseases, such as rheumatoid arthritis, diabetes mellitus type I or systemic lupus erythematosus (22).

GWAS data suggests that HLA class II gene polymorphisms may also play a role for susceptibility to several different IgG4-AID (3), and specifically the *HLA-DRB1* and *DQB1* loci were associated with individual diseases (23, 24), but systematic data are lacking. Therefore, we wanted to investigate whether genetic susceptibility to develop pathogenic IgG4 autoantibodies may be linked to distinct HLA class II alleles. To this end, we conducted a systematic review and meta-analysis of case-control studies reporting HLA class II associations in individual IgG4-AID.

We found that patients with IgG4-AID had significantly increased frequencies of the *HLA-DQB1*\textsuperscript{*05} and *HLA-DRB1*\textsuperscript{*14} alleles and the *HLA-DRB1*\textsuperscript{*14-DQB1*05} haplotype, and a significant negative association with *HLA-DRB1*\textsuperscript{*13}. Notably, *HLA-DQB1*\textsuperscript{*05} is not positively associated with classical autoimmunity and could be a genetic risk factor for the production of IgG4 subclass autoantibodies.

2 Methods

The systematic review was based on recommendations by the HuGENet™ HuGE Review Handbook, version 1.0 (released by the EQUATOR network, 2015, (25)) and MOOSE guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (26). More detailed information on the different stages on the methods (study design, search strategy, screening, study selection, data extraction, statistical analysis) can be found in the supplementary methods.

2.1 Study design

In brief, the protocol was designed at the start of the study (see electronic supplementary materials page 74-79) and the research question was developed with guidance from the PICOS (PI(E)CO) method (27). Only case-control studies with patients with IgG4-AID of class I (MuSK MG, PV, PF, TTP and CIDP with autoantibodies against NF155 or CNTN1(15)) and ethnically, age- and gender-matched controls were included in the study.
2.2 Search strategy

Three individual researchers searched between May 5, 2020 and June 16, 2020 a total of 34 bibliographic databases, databases of systematic review and archives (table S1) and other sources including grey literature and hand searching, using pre-defined key words and Boolean search strategies (see supplementary methods). Due to the limited number of available studies, all studies were included without limitations for the publishing date.

2.3 Screening and study selection

After deduplication, three independent researchers screened the records blinded to each other to prevent bias for eligibility based on inclusion/exclusion criteria (see supplementary methods) using Rayyan software (28). Discrepancies in the assessment were resolved via discussion and the search and selection of studies was documented and visualized with a PRISMA flow chart (29).

2.4 Data extraction

Data including full bibliographic information, clinical and demographic information of patients and controls, HLA genotype, allele or haplotype frequency (see supplementary methods) was extracted from the manuscripts. Missing data was retrieved by contacting the corresponding authors of the study by email.

2.5 Statistics

Combinable data (haplotype, genotype and allele frequencies of HLA class II alleles, analyzed separately) was included in the analysis, and OR and 95% CI were calculated to determine strength of association. The null hypothesis that HLA class II alleles are not associated with class I IgG4-AID. The combined effect of the included studies (pooled OR) was calculated with a random-effects model, which was important to address heterogeneity in the studies and visualized using forest plots. The heterogeneity of the included studies was measured using $\chi^2$, $I^2$ and Tau$^2$. The publication bias was inspected by funnel plots. P values <.05 were considered statistically significant. The statistical analysis was conducted using RevMan software (Review Manager 5, 2015, The Cochrane Collection).
3 Results

3.1 Number and characteristics of included studies
After search and screening, 52 full-text articles with a total of 64 datasets (table 1, table S2) were included in the qualitative synthesis and 51 full-text articles with 62 datasets in the quantitative synthesis (figure 1). The following number of studies was identified: 36 on pemphigus, seven on TTP, five on MuSK MG, three on CIDP. Allele, genotype or haplotype frequencies were extracted and analyzed separately.

Due to lack of data on HLA-DP, only polymorphisms in the HLA-DR and HLA-DQ genes were extracted. The following studies and datasets were included in the qualitative synthesis but excluded from the meta-analysis as they did not fit all selection criteria: the study by Joly et al., 2020 (marked with (†)), and one dataset from the Delgado study (1997). Studies that did not differentiate between disease subgroups of pemphigus or CIDP were marked with (‡). Data from pemphigus studies using the same control for pemphigus foliaceus and pemphigus vulgaris were pooled and marked with (**). Studies marked with (*) were included after discussion with W.B..

3.2 HLA alleles with increased frequency in IgG4-AID
HLA associations with individual IgG4-AID (pemphigus, MuSK MG and TTP) are documented in the supplementary data (Figures S46-S105). To identify possible genetic risk factors that may predispose for the development of IgG4-AID, we analyzed HLA associations in all IgG4 patients (figure S19-28) and observed increased frequencies of HLA-DRB1*04 (figure S1, genotype: OR 2.72; 95% CI 1.81-4.10; p < 0.00001; allele: OR 2.72; 95% CI 1.94-3.81, p < 0.00001), HLA-DRB1*14 (figure 2, genotype: OR 4.31; 95% CI 2.82-6.59; p < 0.00001; allele: OR 4.78; 95% CI 3.52-6.49; p < 0.00001), HLA-DQB1*03 (figure S2, genotype: OR 2.53; 95% CI 1.67-3.97; p < 0.0001; allele: OR 1.65; 95% CI 1.24-2.19; p=0.0007) and HLA-DQB1*05 (figure 3, genotype: OR 3.8; 95% CI 2.44-5.9; p < 0.00001; allele: OR 2.54; 95% CI 1.82-3.55; p < 0.00001) as well as the HLA-DRB1*14-DQB1*05 haplotype (figure 4, n: OR 6.3; 95% CI 3.28-12.09; p < 0.00001, 2n: OR 4.98; 95% CI 3.8-6.53; p < 0.00001).

Since the predominance of pemphigus studies (36/52 studies) may have skewed the data towards pemphigus-specific risk alleles, the data was re-analyzed after excluding the pemphigus studies to validate the findings (figure S3-S7 and figure S29-S45).
While we could confirm the positive association with \textit{HLA-DRB1*14, HLA-DQB1*05} and the \textit{HLA-DRB1*14-DQB1*05} haplotype after exclusion of pemphigus patients (figure S5-S7), the frequency of \textit{HLA-DRB1*04} (figure S3) was significantly decreased, suggesting this association is specific for pemphigus. Further positive associations after exclusion of pemphigus were observed in \textit{HLA-DRB1*11, 12, 15 and 16} (figure S36-S39). These could play a role in a different subset of patients, perhaps in neurological IgG4-AID.

3.3. Reduced frequency of HLA alleles in IgG4-AID

Several HLA variants were significant decreased in patients with IgG4-AID, which is interesting as these may potentially contribute to a protection from IgG4 autoimmunity (figure 5, figure S8-S12). Reduced frequencies were observed for \textit{HLA-DRB1*03} (genotype: OR 0.54; 95\% CI 0.35-0.83; \(p=0.005\); allele: OR 0.46; 95\% CI 0.25-0.84; \(p=0.01\)), \textit{HLA-DRB1*07} (genotype: OR 0.49; 95\% CI 0.34-0.69; \(p < 0.00001\); allele: OR 0.52; 95\% CI 0.37-0.74; \(p=0.0003\)), \textit{HLA-DRB1*09} (genotype: OR 0.62; 95\% CI 0.47-0.82; \(p=0.0008\); allele: OR 0.70; 95\% CI 0.56-0.89; \(p=0.003\)), \textit{HLA-DRB1*13} (genotype: OR 0.48; 95\% CI 0.34-0.68; \(p < 0.0001\); allele: OR 0.46; 95\% CI 0.34-0.62; \(p < 0.00001\)), \textit{HLA-DQB1*02} (genotype: OR 0.5; 95\% CI 0.28-0.89; \(p=0.02\); allele: OR 0.51; 95\% CI 0.36-0.71; \(p<0.0001\)) and \textit{HLA-DQB1*06} (genotype: OR 0.61; 95\% CI 0.44-0.84; \(p=0.003\); allele: OR 0.59; 95\% CI 0.38-0.9; \(p=0.01\)).

The negative associations were less strong, and after exclusion of pemphigus (figure S30, S32, S34, S40, S43), only \textit{HLA-DRB1*13} (figure S4) was found at reduced frequency (genotype frequency: OR 0.41; 95\% CI 0.28-0.61; \(p < 0.00001\), allele frequency: OR: 0.49, 95\% CI 0.20-1.21, \(p=0.12\)).

In summary, accounting for the predominance of pemphigus studies, we observed a positive association with \textit{HLA-DRB1*14} and \textit{HLA-DQB1*05} alleles and the \textit{DRB1*14-DQB1*05} haplotype and a negative association with \textit{HLA-DRB1*13}.

3.4 Analysis of higher resolution data

We were interested to know whether the association was due to specific alleles, but high resolution data was only available for a fraction of studies as most studies only reported one-field resolution data (table S3 and S4). We analyzed the available datasets with higher resolution data, which were mostly from pemphigus studies. Data of the available variants (figure S13-S15) was analyzed and positive associations with \textit{HLA-DRB1*14:01, HLA-DRB1*14:04, HLA-DRB1*04:02} and \textit{HLA-DQB1*05:03} were observed.
3.5 Within ancestry analysis
To study the potential effect of ancestry, we conducted a within-ancestry analysis from the three countries with the highest number of datasets (Brazil: 6 studies, Turkey and Japan: each 5 studies) separately (figure S16-S18). A trend for similar outcomes could be observed in all three populations where enough data was available, but there was variation in the strength of the association, e.g. the OR for HLA-DRB1*14 was higher in Japan than in Brazil or Turkey. An across-ancestry analysis was not considered feasible with the available data.

3.6 Evaluation of heterogeneity and publication bias
The heterogeneity was assessed by Tau^2, X^2 and I^2 tests (table S5), whereas potential publication bias was assessed by funnel plots (figure 6, figure S106-112).
There was substantial heterogeneity for most of the alleles with the exception of HLA-DRB1*14 which showed a low level of heterogeneity only pemphigus allele frequency, but was highly heterogenic otherwise. HLA-DRB1*13 showed low heterogeneity in TTP and IgG4-AID excluding pemphigus, but moderate heterogeneity in all IgG4 AID collectively. Due to the high level of heterogeneity between the studies, the publication bias was assessed only by funnel plots. We found a low to moderate and mostly symmetrical publication bias in HLA-DQB1*05 and HLA-DRB1*14, with very few outliers in both directions, while 1-2 outliers towards lower ORs were found for HLA-DRB1*13.

4 Discussion
In recent years it was appreciated for the first time that IgG4 autoimmune diseases may be considered as a collective group of autoimmune diseases that share distinct pathophysiological and therapeutic commonalities (1, 3, 4), setting them apart from classical antibody mediated autoimmune diseases. Based on preliminary observations (3), we hypothesized that IgG4 AID may also share genetic associations with polymorphisms in the HLA class II genes. To address this possibility, we conducted a systematic review and meta-analysis on the genotype, haplotype and allele frequency of reported HLA class II alleles across IgG4-AID and found that HLA-DQB1*05, an allele that is not typically associated with autoimmunity, is significantly more frequent in patients with IgG4-AID. This suggests it may be a genetic susceptibility factor for IgG4-AID. In addition, HLA-DRB1*14, a known genetic susceptibility factor for autoimmunity, is also associated with IgG4 autoimmunity, as is the HLA-DQB1*05-DRB1*14 haplotype. HLA-DRB1*13, which is considered as
protective for autoimmunity in general, is also negatively associated with IgG4-AID. *HLA-DRB1*03 and 04, which are often associated with autoimmunity, did not correlate with IgG4-AID with the notable exception of pemphigus, which showed a strong association with *HLA-DRB1*04.

4.1 Genetic associations with individual IgG4 autoimmune diseases

This is to the best of our knowledge the first systematic review and meta-analysis investigating a potential association of *HLA class II* alleles with IgG4-AID. Systematic reviews on individual IgG4-AID (Pemphigus, MuSK MG) are in agreement with our findings (23, 24). A significant positive association of MuSK MG with *HLA-DRB1*14, *HLA-DRB1*16 and *HLA-DQB1*05 could be confirmed in our study (24). In contrast, a significant negative association for *HLA-DQB1*03 reported in the MuSK MG study could not be reproduced in our analysis, and the reported negative association with *HLA-DQB1*06 did not reach significance in our study. Possible reasons for this might be 1) the exclusion of one Italian study (30) from our analysis that was included in the Hong study as it did not match our inclusion/exclusion criteria and 2) the use of different statistical methodology (random- vs fixed-effects model).

Our analysis of pemphigus data is in line with previous meta-analyses. Increased frequencies of *HLA-DRB1*04 and *HLA-DRB1*14 and decreased frequencies of *HLA-DRB1*03, *HLA-DRB1*07 and *HLA-DRB1*15 were observed in the pemphigus patients (23). In contrast to the study from Yan et al., we found *HLA-DRB1*09, *HLA-DRB1*11 and *HLA-DRB1*13 also to be significantly decreased in pemphigus patients, but with a very broad 95% CI. In contrast to the Yan study, there was no positive association with *HLA-DRB1*08 and pemphigus, but analysis of pemphigus vulgaris studies only (data not shown) could reproduce the positive association for the genotype frequency. In a different study (31) *HLA-DQB1*05 and *HLA-DQB1*03 were positively associated with pemphigus vulgaris, which is in line with our findings.

There were only few studies with haplotype data in IgG4-AID available, but the increased frequency of the *HLA-DQB1*05-*DRB1*14 haplotype suggests linkage disequilibrium between the two genes.

Interestingly, while MuSK MG and pemphigus seem to have very similar genetic associations, TTP showed opposite effects for several alleles, and in *HLA-DRB1*04 and *HLA-DRB1*11 these were significant. Perhaps the different type and location of the antigen play a role: MuSK MG and pemphigus antibodies target antigens of the cell
surface/extracellular matrix (type II hypersensitivity reactions, Gell and Coombs classification (32)), while ADAMTS13 is a soluble antigen (type III hypersensitivity reactions). Another explanation could be that there are shared sequence motifs between e.g. MuSK and desmoglein 1/3 that facilitate binding to the peptide binding groove that are not present in ADAMTS13, causing a decreased affinity of ADAMTS13 derived peptides to specific HLA alleles.

Systematic reviews on genetic associations of the HLA with TTP or CIDP were not available. Although antibodies against CNTN1 and NF155 are known since the early 2000s (33, 34), possible associations with HLA polymorphisms have only recently been determined and investigated. A (non-systematic) review (35) also reports a handful of individual papers with genetic associations of neurological IgG4-AID with $HLA-DQB1^{*05}$, namely MuSK MG and IgLON5, but different alleles for IgG4-AID with antibodies against LGI1 ($HLA-DRB1^{*07:01}$), Caspr2 ($HLA-DRB1^{*11:01}$) or neurofascin ($HLA-DRB1^{*15}$). Whether these diseases are not associated with $HLA-DRB1^{*14}$ and $HLA-DQB1^{*05}$ cannot be concluded without further studies, as these were few studies with a low number of participants. Furthermore, the $DQB1$ locus was not investigated in all studies. Nevertheless, it is very likely that several different genetic associations may exist that may predispose for the production of IgG4 autoantibodies in different forms of IgG4-AID, also depending on the structure of the autoantigens.

4.2 Comparison of HLA associations between classical and IgG4 autoimmune diseases
We wanted to compare genetic HLA associations with classical autoimmune diseases (i.e. autoimmune diseases that are not caused by IgG4 autoantibodies) with the associations observed in IgG4-AID. In our study, $HLA-DQB1^{*05}$ was associated strongly with IgG4-AID, and where higher resolution data was available, it was the $HLA-DQB1^{*05:03}$ allele that was associated with IgG4-AID. Only few autoimmune diseases were reported to be associated with $HLA-DQB1^{*05}$, and these are mostly IgG4-AID, including MuSK MG, pemphigus and IgLON5 parasomnia. In other autoimmune diseases, negative associations were found with the $HLA-DQB1^{*05:02}$ in T1D (36, 37) and Sjögren’s syndrome (38). One single study reported $HLA-DQB1^{*05:02}$ to be positively associated with myelin oligodendrocyte glycoprotein-associated disorders (MOGAD), a rare neurological autoimmune disease (39). Overall this suggests that $HLA-DQB1^{*05}$ may be specifically associated with IgG4 autoimmune diseases.
4.3 HLA polymorphisms and the etiology of autoimmunity

Autoimmune diseases are thought to have a multifactorial etiology with a cumulative effect of genetic predispositions and environmental triggers. The shared pathophysiology indicates a common origin, leading to the investigation of common genetic factors in AIDs (49). One genetic compound suggested for this susceptibility are the HLA class II genes, which encode proteins required for antigen presentation to CD4+ T-cells in the thymus and the periphery, thereby affecting central tolerance development and T-cell activation in the periphery. HLA-DRB1, the most polymorphic gene with over 1800 alleles, is frequently associated with autoimmune diseases (20).

Different HLA alleles present distinct peptide repertoires, and may also affect T-cell fate by inducing regulatory T cells or conventional T-cells (21). Furthermore, MuSK MG patients with the HLA-DRB1*14 allele were found to have higher autoantibody titers and higher levels of the cytokine IL-10, which plays a role in IgG4 class switch, than patients with other HLA alleles (50). One hypothesis is that HLA-DRB1*14, HLA-DQB1*05 and/or other HLA alleles may have a direct effect on T-cell fate, favoring IL-10 producing T-cells independent of the presented peptide. Or alternatively, they indirectly favor induction of IgG4 autoantibodies by their distinct peptide repertoire.

4.4 Study limitations
The main limitation of the study was owed to the low prevalence of IgG4-AID, including 1) small numbers of patient per individual study (mostly between 30-100 patients), and 2) a low number of available studies, leading to 3) substantial heterogeneity, which was especially pronounced in studies on TTP. Pooling of data was not always possible due to different types of analysis and the differential use of nomenclature (e.g. genotype, haplotype, allele and phenotype frequency). Lack of information on homozygosity or heterozygosity in studies with genotype frequencies prevented a combined analysis for allele and genotype frequency, and since the HLA genes are in linkage disequilibrium, homo- and heterozygosity cannot be “re-calculated” by using the Hardy-Weinberg equilibrium. Therefore, we only included studies where the frequency was given in absolute and relative numbers and data for allele and genotype frequency were analyzed individually. Several studies used a single control group for two different datasets, and to avoid overestimating the number of controls, data of these studies were pooled where possible (52-55) (exception: two studies from Serbia (56, 57)). All studies included in the meta-analysis reported that the controls and patients derived from the same geographic location or that the controls were ethnically matched to the controls, but most studies did not provide further details on the ethnical matching.

Furthermore, high-resolution data was only available from a subset of studies, mostly on pemphigus, therefore the observed associations with the specific HLA-DQB1*05:03, HLA-DRB1*14:01 and DRB1*14:04 alleles need to be validated in further studies. Heterogeneity in ancestries across countries was addressed by only including studies with patients and controls that were ethnically matched and/or derived from the same population and use of the random-effects model for the meta-analysis.

Our understanding of the proposed kinship between individual IgG4-AID is very limited (1, 4, 14), and it is likely that there are different true effects of the HLA alleles in the distinct diseases. To account for this possibility, we used a random-effects model and also analyzed the diseases individually. Since there was a predominance of pemphigus studies (37/52 studies), we re-analyzed the data after exclusion of the pemphigus studies and could reproduce the associations with the HLA-DRB1*13, HLA-DRB1*14 and HLA-DQB1*05 alleles and the HLA-DRB1*14-DQB1*05 haplotype. In contrast, the HLA-DRB1*04 allele, which was more frequent in pemphigus patients, was not associated with the other diseases.

Antibody tests were not described in a substantial number of studies on pemphigus, but histopathologic diagnosis implicates the presence of the relevant IgG4 autoantibodies (mostly desmoglein 1 and desmoglein 3, < 0.5% of patients desmocollin), the inclusion criteria were changed during the second round of screening to include the pemphigus studies
in the quantitative analysis. The PRISMA statement acknowledges this iterative process and accepts that modifications in the review protocol during the synthesis may sometimes be inevitable (29).

5 Conclusions
With the limitations of this study in mind, we observed an increased frequency of HLA-DRB1*14 and HLA-DQB1*05 alleles as well as the HLA-DQB1*05-DRB1*14 haplotype in patients with IgG4 AID. These findings agree with the literature, where these alleles are also associated with individual IgG4-AIDs. Thus HLA-DRB1*14 and HLA-DQB1*05 individually - or in combination as haplotype - might pose a genetic risk factor for the susceptibility to develop IgG4 AID. HLA-DRB1*13 seems to be consistently less frequent in patients, indicating a possible protective effect. Nevertheless, the low number of individual studies and the relatively small patient cohorts contributed to the substantial heterogeneity, therefore further HLA association studies are needed to validate the findings.

Acknowledgements
We are grateful to Alexander Zimprich for scientific advice.

Declarations

Funding
I.K. was funded by a Hertha Firnberg project grant by the Austrian Science Fund (FWF) (grant number T996-B30).

Conflict of interest statement
The authors declare no conflict of interest.

Availability of data and material
To foster transparency, we provide all data generated in this study in the supplementary materials.

Code availability
Not applicable

Author’s contributions
I.K., A.E. and F.F. contributed to conception and design of the study. H.C. advised on neurological diseases, W.B. advised on dermatological diseases. A.P., G.L. and V.B. contributed to data collection. A.P. and F.F. conducted the statistical analysis. I.K. drafted the manuscript, F.F., A.E., W.B. and H.C. reviewed the manuscript for intellectual content.

**Ethics approval**
Not applicable

**Consent to participate**
Not applicable

**Consent for publication**
Not applicable

**Authors consent for publication**
All authors declare their consent for publication.

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Table 1: **Characteristics of included studies** PV, pemphigus vulgaris; PF, pemphigus foliaceus; CIDP, chronic inflammatory demyelinating polyneuropathy; TTP, thrombotic thrombocytopenic purpura; MuSK MG, muscle-specific kinase myasthenia gravis; PCR, polymerase chain reaction; SSP, sequence specific primer; SSO(P), sequence specific oligonucleotides (probes); RFLP, restriction fragment length polymorphism

| First author | Year | Country | Disease | Number of patients | Number of controls | HLA alleles (List of reported alleles) | HLA typing method | Genotype, Allele or haplotype frequency | Reference |
|--------------|------|---------|---------|--------------------|-------------------|--------------------------------------|------------------|----------------------------------------|-----------|
| Dere         | 2020 | Turkey  | PV      | 30                 | 30                | DRB1*01, *03, *04, *07, *08, *11, *12, *13, *14, *15, DQB1*02, *03, *04, *05, *06 | PCR-SSP     | Genotype frequency                      | (58)      |
| Ehsan        | 2015 | Iran    | MuSK MG | 24                 | 200               | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *1301, *1302, *1303, *14, *15, *16, DQB1*0201, *0301, *0302, *0303, *05, *0601, *0602, *0603, *0604 DRB1*14-DQA1*0104, DQB1*05, DRB1*15-DQA1*0102-DQB1*0601, DRB1*15-DQA1*0102-DQB1*0602, DRB1*15-DQA1*0103-DQB1*0601, DRB1*16-DQA1*0102-DQB1*05 | PCR-SSP | Allele frequency, haplotype frequency      | (59)      |
| Alahgholi     | 2013 | Turkey  | MuSK MG | 48                 | 250               | DRB1*03, DRB1*14, DRB1*16, DQB1*05 DRB1*14-DQB1*05, DRB1*16-DQB1*05 | PCR-SSP     | Genotype frequency, haplotype frequency      | (60)      |
| Harfouch      | 2014 | Syria   | PV      | 91                 | 270               | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSP     | Genotype frequency                        | (61)      |
| Gonzalez-     | 1998 | Spain   | PV      | 26                 | 200               | DR1, DR2, DR3, DR4, DR7, DR8, DR9, DR10, DR11, DR12, DR13, DR14 | PCR-SSOP, PCR-SSP | Genotype frequency                        | (62)      |
| Study          | Year | Country | Sample Size | DRB1 Alleles | DQB1 Alleles | Methodology | Genotype Frequency | Allele Frequency, Haplotype Frequency | References |
|---------------|------|---------|-------------|--------------|--------------|-------------|-------------------|---------------------------------------|------------|
| Brochado      | 2016 | Brazil  | 86 (172)    | DRB1*01:01, *01:02, *04:02, *07:01, *13:01, *14:01, *14:04 | DQB1*03:01, *03:02, *05:01, *05:03, *06:02, *06:03 | Commercial kits from One Lambda | Allele frequency, haplotype frequency | (63) |
| PV            | 82 (164) | 1592 (3184) | DRB1*01:01, *01:02, *04:02, *07:01, *08:04, *11:01, *13:01, *14:01, *14:04 | DQB1*03:01, *03:02, *05:01, *05:03, *06:02, *06:03 | DRB1*14-DQA1*01-DQB1*05, DRB1*16-DQA1*01-DQB1*05 | | |
| Martel        | 2002 | France  | 31          | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | DQB1*02, *03:02, *05:03 | PCR-SSO, PCR-SSP, PCR-RFLP | Genotype frequency | (64) |
| Párnická      | 2013 | Slovakia | 43 (86) | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | DQB1*02, *03, *04, *05, *06 | PCR-SSP | Allele frequency, haplotype frequency | (65) |
| Nikolic       | 2014 | Serbia  | 31 (62)     | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | DQB1*02, *03, *04, *05, *06 | PCR with sequence-specific oligonucleotides | Genotype frequency, allele frequency, haplotype frequency | (56) |
| De Sena Nogueira Maehara | 2017 | Brazil  | 42 (84)     | DRB1*02, *04, *05, *07, *16 | | PCR-SSO | Allele frequency | (66) |
| Author | Country | Region | Netherlands | PF | VCF | Genotype frequency | Genotype frequency, haplotype frequency | Allele frequency, haplotype frequency |
|--------|---------|--------|-------------|----|-----|-------------------|---------------------------------------|-------------------------------------|
| COPPO  | France  | TTP    | 17 (34)     | 447 (894) | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSO | Genotype frequency (67) |
| KANAI  | Japan   | MuSK MG| 14          | 100   | DRB1*01, *04, *08, *09, *11, *12, *13, *14, *15, 16 | PCR-SSP | Genotype frequency, haplotype frequency (68) |
| PICCINELLI | Italy  | CIDP   | 24 (48)     | 216 (432) | DRB1*01, *03, *04, *07, *08, *10, *11, *13, *14, *15, *16 | PCR-SSP | Allele frequency, haplotype frequency (69) |
| ZIVANOVIC | Serbia | PV     | 72 (144)    | 1992 (3984) | DRB1*01, *03, *04, *07, *11, *12, *13, *14, *15, *16 | PCR-SSP | Allele frequency, haplotype frequency (57) |
| Saha   | UK      | PF (Caucasian white British) | 25 (50) | 100 (200) | DRB1*01, *04, *14, *16 | PCR-SSP | Allele frequency (70) |
| Saha   | UK      | PF (Indo-Asians) | 10 (20) | 59 (118) | DRB1*01, *04, *14, *16 | PCR-SSP | Allele frequency (70) |
| Gil    | Brazil  | PV     | 102         | 594   | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSP | Genotype frequency (71) |
| TORZECKA | Poland | PF     | 15 (30)     | 152 (304) | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15 | PCR-SSP | Allele frequency (52) |
| Authors          | Year | Country | Disease | PV | Sample Size            | DRB1 Alleles          | DQB1 Alleles                  | Methodology                   | Method                          | Frequencies                        | Notes                                |
|------------------|------|---------|---------|----|------------------------|-----------------------|-----------------------------|-------------------------------|---------------------------------|------------------------------------|-------------------------------------|
| Abida            | 2009 | Tunisia |         | PV | 38 (76)                | DRB1*01, *03, *04, *07, *08, *09, *10 *11, *12, *13, *14, *15 | DQB1*03, *04, *11, *13, *15 DQB1*0301, *0302, *06 | Dynal RELI SSO HLA-DRB Test | PCR-SSP | Allele frequency (72) |
| Ogata            | 2020 | Japan   | CIDP    | PV | 90 (180)                | DRB1*01, *03, *04, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06 DQB1*14:05-DQB1*05:03, DRB1*15:01-DQB1*06:02, DRB1*15:02-DQB1*06:01 | Next-generation sequencing | Allele frequency, haplotype frequency (73) |
| Priyadarsini     | 2018 | India   | PV      | PV | 22 (44)                | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06 | PCR-SSOP | Genotype frequency, haplotype frequency (74) |
| Tunca            | 2010 | Turkey  | PV      | PV | 25, 113                | DRB1*01, *03, *04, *05, *06, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06 | PCR-SSP | Genotype frequency (75) |
| Haase            | 2015 | Germany | PV (German) | PV | 46 (92) 74 (148)       | DRB1*01, *02, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSP | Allele frequency (76) |
| Haase            | 2015 | Germany | PV (Egypt) | PV | 47 (94) 73 (146)       | DRB1*01, *02, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSP | Allele frequency (76) |
| Martinez-Martinez| 2017 | Spain   | CIDP    | PV | 13, 941               | DRB1*15               | DRB1*15-DQB1*06              | DNA sequence analysis and SSP methodology | Genotype frequency, haplotype frequency (77) |
| Glorio           | 1999 | Argentina | PV     | PV | 30, 199               | DR3, DR4, DR8, DR14, DR15 DQB1*03, *05 | PCR-SSO | Genotype frequency (78) |
| Author | Year | Country | Ethnicity | DRB1 Haplotype | Genotyping Method | Genotyping Technique | Reference |
|--------|------|---------|-----------|----------------|-------------------|----------------------|-----------|
| Pavoni | 2003 | Brazil  | Fogo selvagem | DRB1*01, *03, *04, 07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSOP | Genotype frequency | (79) |
| Thomas | 1998 | Spain   | PV        | DR1, DR2, DR3, DR4, DR7, DR8, DR9, DR10, DR11, DR12, DR13, DR14 | PCR-SSOP, PCR-SSP | Genotype frequency | (80) |
| Zhang  | 2019 | China   | PF, PV    | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | Affymetrix axio | Genotype frequency, allele frequency | (53) |
|        |      |         |           | DQB1*02, *03, *04, *05, *06 | precision medicine research array based GWAS |                   |           |
| Moraes | 1991 | Brazil  | Fogo selvagem | DRB1*01, *15 | PCR-SSP | Genotype frequency | (81) |
| Lee    | 1998 | South Korea | PF, PV | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSP | Genotype frequency | (54) |
| Shams  | 2008 | Iran    | PV        | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSP | Allele frequency, haplotype frequency | (82) |
|        |      |         |           | DQB1*02, *03, *04, *05, *06 | DRB1*15-DQA1*01-DQB1*06 |                   |           |
|        |      |         |           |                      | DRB1*16-DQA1*01-DQB1*05 |                   |           |
| Orouji | 2014 | Mid-east origin | PV | DQB1*02, *03, *04, *05, *06 | PCR-SSP | Genotype frequency, allele frequency | (83) |
| Miyagawa | 1997 | Japan   | PF, PV    | DRB1*04, *14 | NA | Genotype frequency, haplotype frequency | (55) |
| Author  | Year | Location | Disease | n (N) | DRB1, DQB1 Genotypes | Method | Approach | Reference |
|---------|------|----------|---------|-------|----------------------|--------|----------|-----------|
| Joly†   | 2020 | France   | TTP     | 26    | 172                  | PCR-SSP| Genotype frequency, allele frequency | (84) |
| Glorio  | 2002 | Argentina| PV      | 47    | 199                  | PCR-SSO| Genotype frequency              | (85) |
| Sakai   | 2020 | Japan    | TTP     | 52 (104) | 523 (1046)          | Commercial kits with Illumina MiSeq technology | Allele frequency | (86) |
| Koc     | 2012 | Turkey   | Pemphigus | 60    | 60                  | PCR-SSP| Genotype frequency              | (87) |
| Scully  | 2010 | UK       | TTP     | 50    | 200                  | PCR-SSP, PCR-SSOP | Genotype frequency              | (88) |
| Mobini  | 1997 | Iran     | PV      | 38    | 57                  | PCR-SSOP| Haplotype frequency              | (89) |
| Delgado | 1997 | Pakistan | PV (Pakistan) | 19 (38) | 13 (26)          | PCR-SSOP| Allele frequency              | (90) |
|         |      |         | Europe  | PV (Europe) | 19 (38) | 248 (496) |                      |          |
| Yamashina | 1998 | Japan    | PV      | 17    | 525                  | PCR-RFLP| Genotype frequency, haplotype frequency | (91) |
| Al Haddad | 2019 | Lebanon  | TTP     | 30    | 30                  | PCR-SSP| Genotype frequency              | (92) |
| Name               | Year | Country | Disease | TTP | DQB1*02, *03, *04, *05, *06 | DRB1*01, *03, *04, *07, *08, *09, *11, *12, *13, *14 | Method                    | Genotype frequency | Allele frequency |
|--------------------|------|---------|---------|-----|-----------------------------|------------------------------------------------------|---------------------|------------------|
| John               | 2011 | Germany | TTP     | 54  | 11407                       | DRB1*04, *05                                         | PCR-SSP, PCR-SSO    | (93)             |
|                    |      |         |         | 50  | 174                         | DQB1*02                                              |                      |                  |
|                    |      |         |         | 54  | 174                         | DQB1*04, *05                                        |                      |                  |
|                    |      |         |         | 47  | 174                         | DQB1*03                                              |                      |                  |
|                    |      |         |         | 52  | 174                         | DQB1*06                                              |                      |                  |
| Martino            | 2016 | France  | TTP     | 26  | 663 (1326)                  | DRB1*04, DRB1*11                                     | PCR-SSO             | (94)             |
|                    |      |         |         | 26  | 437 (874)                   | DQB1*03                                              |                      |                  |
|                    |      |         |         | 24  | 100 (200)                   | DRB1*04, DRB1*11, DQB1*03                            |                      |                  |
| Cerna              | 1993 | Brazil  | Fogo selvage | 10  | 74                          | DRB1*04, *08, *14, *16, DQB1*03, *04                 | PCR-SSOP            | (95)             |
| Birol              | 2002 | Turkey  | Pemphigus | 33  | 100                         | DR4, DR11, DR14, DQ2, DQ4                           | Microdroplet lymphocyte test | (96)             |
| Rangel-Gamboa      | 2015 | Mexico  | PV      | 43  | 99 (198)                    | DR1, DR4, DR7, DR8, DR11, DR13, DR14, DR16          | PCR-SSO             | (97)             |
| Khan               | 2015 | Pakistan | PV     | 28  | 150                         | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | PCR-SSP             | (98)             |
| Carcassi           | 1996 | Italy   | PV (Sardinians) | 16  | 91 (182)                   | DRB1*03, *04, *08, *14, DQB1*02, *03, *05           | PCR-SSO             | (99)             |
|                    |      |         |         | 16  | 284 (568)                   | DRB1*03, *04, *08, *14                                |                      |                  |
| Study     | Year | Country       | Method | Primer/Probe/Genotyping | Sample Size | Genotypes/Alleles | Technique | Frequency Type | References |
|-----------|------|---------------|--------|-------------------------|-------------|-------------------|-----------|----------------|------------|
| Lombardi  | 1996 | Italy         | PV     |                         | 16 (32)     | 406 (812)         | DQB1*02, *03, *05 | Genotype frequency | (100)     |
|           |      |               |        |                         |             |                   |           |                |            |
| Saha      | 2010 | UK            | PV     | 33                      | 96 (192)    | 100 (200)         | DRB1*03, *04, *07, *14, *15 | Allele frequency | (101)     |
|           |      |               |        |                         |             |                   | DQB1*02, *03, *05, *06 |                |            |
|           |      |               | PV     |                         | 57 (114)    | 59 (118)          |                        |                |            |
| Niks      | 2006 | Netherlands   | MuSK   | 23                      | 23 (46)     | 321 (642)         | DR1, DR3, DR14, DR16, DQ5, DQ6 | Genotype frequency, Haplotypic frequency | (102)     |
| Sinkovits | 2017 | Hungary       | TTP    | 75                      | 75          | 162               | DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 | Genotype frequency, Haplotypic frequency | (103)     |
Table 2: **HLA class II associations identified in IgG4-AID.** Bold: significant results only for either genotype or allele frequency.

| Disease                              | Positive association                              | Negative association |
|--------------------------------------|--------------------------------------------------|----------------------|
| Pemphigus                            | DRB1*04, *14, DQB1*03, *05                       | DRB1*03, *07, *09, *11, *13, *15, DQB1*02, *06 |
| TTP                                  | DRB1*11, *12, *15                                | DRB1*04, *13         |
| MuSK myasthenia gravis               | DRB1*14, *16, DQB1*05, DRB1*14-DQB1*05, DRB1*16-DQB1*05 | No significant associations |
| All IgG4-AID                         | DRB1*04, *14, DQB1*03, *05, DRB1*14-DQB1*05      | DRB1*03, *07, *09, *11, *13, *15, DQB1*02, *06 |
| MuSK, TTP, CIDP combined             | DRB1*11, *12, *14, *15, *16, DQB1*05, DRB1*14-DQB1*05 | DRB1*04, *13,         |
Figure Legends

Figure 1: PRISMA flow chart of study identification and eligibility screening. For specific inclusion and exclusion criteria see text, section 2.3). Figure modified from Moher et al. 2009(104).

Figure 2: Forest plot depicting allele and genotype frequency of HLA-DRB1*14 and patients with class I IgG4 autoimmune diseases. Cumulative meta-analysis with a random-effects model demonstrated a significant increased frequency in patients compared to controls.

Figure 3: Forest plots of the allele and genotype frequency for HLA-DQB1*05 in patients with class I IgG4 autoimmune diseases. Meta-analysis analysis using a random-effects model demonstrated a significant increased frequency in patients compared to controls.

Figure 4: Forest plots of haplotype frequencies for HLA-DRB1*14-DQB1*05 in patients with class I IgG4 autoimmune diseases. Meta-analysis using a random-effects model showed a significant positive association in patients throughout all six IgG4 AIDs. n, calculations similar to the genotype frequency by dividing the number of individuals with a specific haplotype by the number of total individuals; 2n calculations similar to the allele frequency by dividing the total number of a specific haplotype by the total number of alleles in the cohort

Figure 5: Forest plots of allele and genotype frequency of HLA-DRB1*13 and patients with class I IgG4 autoimmune diseases. Meta-analysis using a random-effects model demonstrated a significant decreased frequency in patients compared to controls.

Figure 6: Funnel plot analysis of genotype and allele frequency data for HLA-DQB1*05, DRB1*13 and HLA-DRB1*14 in all IgG4 patients. A funnel plot analysis was undertaken to assess publication bias. Odds ratios (OR) were plotted against the standard error (SE) and the studies demonstrated symmetrical scattering along the funnel axis (pooled effect estimate from meta-analysis).
Figure 1: PRISMA flow chart of study identification and eligibility screening. For specific inclusion and exclusion criteria see text, section 2.3). Figure modified from Moher et al. 2009(104).
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Meta-analysis analysis using a random-effects model demonstrated a significant increased frequency in patients compared to controls.

#### Allele frequency

| Study or Subgroup            | Allele | Total | Odds Ratio M-H, Random, 95% CI |
|------------------------------|--------|-------|--------------------------------|
| CIPD (Pissinelli, 2019)†      | 48     | 42    | 1.40 [0.70, 2.81]              |
| CIPD, NF-155 (Ogata, 2020)   | 2      | 10    | 0.31 [0.08, 1.32]              |
| MusK MG (Ehsani, 2015)       | 10     | 5     | 4.82 [2.59, 8.96]              |
| MusK MG (Nikolic, 2014)      | 32     | 30    | 2.16 [1.25, 3.76]              |
| Pemphigus (Brochado, 2016)** | 60     | 57    | 3.76 [2.70, 5.23]              |
| Pemphigus (Zhang, 2019)**    | 223    | 184   | 3.91 [3.04, 5.03]              |
| PF, Indo-Asian (Saha, 2019)  | 10     | 10    | 3.72 [1.39, 9.93]              |
| PF, White British (Saha, 2019)| 19    | 10    | 2.38 [1.22, 4.63]              |
| PV (Oroz, 2014)              | 10     | 10    | 0.92 [0.40, 2.09]              |
| PV (Parnicka, 2013)          | 29     | 46    | 1.89 [1.09, 3.27]              |
| PV (Shams, 2008)             | 59     | 144   | 1.54 [0.94, 2.53]              |
| PV (Zivanovic, 2016)         | 19     | 38    | 5.28 [2.67, 10.42]             |
| PV, Europe (Delgado, 1997)   | 58     | 51    | 3.65 [2.17, 6.44]              |
| PV, Indo-Asians (Saha, 2010)*| 12     | 32    | 1.41 [0.94, 2.11]              |
| PV, Italians (Carcassi, 1996)| 5      | 35    | 1.83 [1.13, 2.95]              |
| PV, Sardinians (Carcassi, 1996)| 53   | 55    | 2.84 [2.08, 3.62]              |
| PV, White Europeans (Saha, 2010)*| 11  | 104   | 2.54 [1.82, 3.55]              |

Total (95% CI): 2052

| Study or Subgroup            | Events | Total | Odds Ratio M-H, Random, 95% CI |
|------------------------------|--------|-------|--------------------------------|
| Patient                      | 48     | 42    | 1.40 [0.70, 2.81]              |
| Control                      | 10     | 5     | 4.82 [2.59, 8.96]              |
| Odds Ratio                   |       |       |                                |

Total events: 674

Heterogeneity: Tau^2 = 0.60; Chi^2 = 107.24, df = 17 (P < 0.00001); I^2 = 84%

Test for overall effect: Z = 5.45 (P < 0.00001)
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Supplementary Files

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- SupplementaryMaterial.pdf