

A Systematic Review and Meta-Analysis of HLA-Class-II Associations in Patients with IgG4 Autoimmunity

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Research Article

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

Posted Date: November 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-638050/v2>

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Version of Record: A version of this preprint was published at Scientific Reports on June 2nd, 2022. See the published version at <https://doi.org/10.1038/s41598-022-13042-2>.

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; $p < 0.0001$; 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.

Introduction

IgG4 autoimmune diseases (IgG4-AID) were first collectively described in 2015¹ and include diseases such as muscle-specific kinase myasthenia gravis (MuSK MG), pemphigus vulgaris (PV) or thrombotic thrombocytopenic purpura (TTP)². IgG4-AID are distinct from other autoantibody-mediated autoimmune diseases, as IgG4 is normally considered as an anti-inflammatory antibody that has structural differences to other IgG subclasses (including functional monovalency) and lacks typical antibody effector mechanisms, such as complement activation³⁻⁶. IgG4 is thought to play a protective role, e.g. in allergy or autoimmunity, by competing with effector antibodies for epitope binding autoimmunity^{3,7-11}. Interestingly, in IgG4-AID the autoantibodies belong predominantly to the IgG4 subclass, and they are directly pathogenic by functional blocking of protein-protein interaction.^{1,12} IgG4 pathogenicity could be demonstrated in passive transfer 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)¹³. Notably, IgG4-AID differ from clinically distinct IgG4-related diseases¹⁶ that are therefore not part of our study. IgG4-AID share also further important pathophysiological and therapeutic commonalities^{14,15} including severe disease course, low disease prevalence (equal or less than 5/10,000) and good response to B-cell depletion therapy with rituximab¹³.

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)^{17,18}. *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^{19,20}. *HLA-DR* has been linked to aberrant presentation of self-peptide to autoreactive T helper cells in the thymus²¹, and a recent study showed that distinct *HLA-DR* variants may directly influence the immune response towards autoimmunity or tolerance²². 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 erythematosus²³.

GWAS data suggests that HLA class II gene polymorphisms may also play a role for susceptibility to several different IgG4-AID¹⁴, and specifically the *HLA-DRB1* and *DQB1* loci were associated with individual diseases^{24,25}, 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*05* and *HLA-DRB1*14* alleles and the *HLA-DRB1*14-DQB1*05* haplotype, and a significant negative association with *HLA-DRB1*13*. Notably, *HLA-DQB1*05* is not positively associated with classical autoimmunity and could be a genetic risk factor for the production of IgG4 subclass autoantibodies.

Results

Number and characteristics of included studies

After search and screening, 52 full-text articles with a total of 64 datasets (supplementary table S1, Table 1) 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.

Table 1

HLA class II associations identified in IgG4-AID. Bold: significant results only for either genotype or allele frequency.

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

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..

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 (Supplementary 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 *HLA-DRB1*14*, *HLA-DQB1*05* and the *HLA-DRB1*14-DQB1*05* haplotype after exclusion of pemphigus patients (figure S5-S7), the frequency of *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 *HLA-DRB1*11*, 12, 15 and 16 (figure S36-S39).

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 *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), *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), *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), *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), *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 *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 *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 *HLA-DRB1*14* and *HLA-DQB1*05* alleles and the *DRB1*14-DQB1*05* haplotype and a negative association with *HLA-DRB1*13*.

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 (supplementary table S4 and S5). 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 *HLA-DRB1*14:01*, *HLA-DRB1*14:04*, *HLA-DRB1*04:02* and *HLA-DQB1*05:03* were observed.

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.

Evaluation of heterogeneity and publication bias

The heterogeneity was assessed by τ^2 , χ^2 and I^2 tests (supplementary table S6), 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*.

Discussion

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*.

Therefore, *HLA-DRB1*14* and *HLA-DQB1*05* may be genetic risk factors for IgG4 AID, and *HLA-DRB1*13* may have a protective effect.

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) agree with our findings^{24,25}. A significant positive association of MuSK MG with *HLA-DRB1*14*, *HLA-DRB1*16* and *HLA-DQB1*05* could be confirmed in our study²⁵. 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 study²⁷ 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 patients²⁴. 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 study²⁸ *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 classification²⁹), 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^{30,31}, possible associations with HLA polymorphisms have only recently been determined and investigated. A (non-systematic) review³² 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. *HLA-DRB1*11* and *15* were also positively associated with IgG4-AID after exclusion of pemphigus (in addition to *HLA-DRB1*12* and *16*), these could play a role in a different subset of patients, perhaps in neurological IgG4-AID.

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.

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^{33,34} and Sjögren's syndrome³⁵. One single study reported *HLA-DQB1*05:02* to be positively associated with myelin oligodendrocyte glycoprotein-associated disorders (MOGAD), a rare neurological autoimmune disease³⁶. Overall this suggests that *HLA-DQB1*05* may be specifically associated with IgG4 autoimmune diseases.

*HLA-DRB1*14* also is strongly associated with IgG4-AID in our study, and was also reported as increased in patients with rheumatoid arthritis, Guillain-Barré syndrome and MuSK MG³⁷, suggesting it may be a genetic risk factor to develop autoimmune diseases. *HLA-DRB1*13* was found to be less frequent in IgG4-AID in our study, and this was also observed in classical AID, including T1D and autoimmune hepatitis³⁸⁻⁴⁰.

The *HLA-DRB1*03* allele frequency is increased in classical AID, including diabetes mellitus type 1^{33,34}, multiple sclerosis⁴¹, neuromyelitis optica⁴², systemic lupus erythematosus⁴³, Graves' disease⁴⁴ and Sjögren's syndrome³⁵, but we observed no association across IgG4-AID, only a decrease in studies on pemphigus. A similar difference could be found for *HLA-DRB1*04*, which is increased in classical AID diabetes mellitus type 1, rheumatoid arthritis and autoimmune hepatitis patients^{38,45}, but decreased in

IgG4-AID (MuSK, TTP and CIDP) - with the exception of pemphigus where a strong association was observed.

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 AIDs⁴⁶. 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 diseases²¹.

Different HLA alleles present distinct peptide repertoires, and may also affect T-cell fate by inducing regulatory T cells or conventional T-cells²². 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 alleles⁴⁷. 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.

IgG4-AID, IgG4-related diseases and IgG4 subclass

IgG4-related disease (IgG4-RLD) is the umbrella term for a distinct group of diseases associated with the IgG4 subclass, that is unrelated to IgG4-AID⁴⁸. IgG4-RLD are clinically distinct from IgG4-AID, their pathogenic mechanism is unknown, the role of IgG4 in these diseases is unclear, and clinical characteristics of IgG4-RLD include fibrosis, IgG4+ plasma cell infiltrates in the tissue, organ swelling and increased serum IgG4 concentrations, which are not characteristic for IgG4-AID⁴⁸. In line with these findings, HLA associations also differ for IgG4-RLD, which was found to be associated with *HLA-DRB1*04 allele*⁴⁹. The pathogenic mechanisms of IgG4 and the regulatory mechanisms that lead to the production of pathogenic IgG4 in IgG4-AID are not well understood, and are subject of an ongoing review series^{13,14}.

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 disequilibrium⁵⁰, 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^{51–54} (exception: two studies from Serbia^{55,56}). 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^{1,12,15}, 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 inevitable⁵⁷.

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.

Methods

The systematic review was based on recommendations by the HuGENet™ HuGE Review Handbook, version 1.0 (released by the EQUATOR network, 2015, ⁵⁸) and MOOSE guidelines for Meta-Analyses and Systematic Reviews of Observational Studies ⁵⁹. 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.

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 ⁶⁰. 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 ¹³) and ethnically, age- and gender-matched controls were included in the study.

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 (supplementary table S2) 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.

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 ⁶¹. Discrepancies in the assessment were resolved via discussion and the search and selection of studies was documented and visualized with a PRISMA flow chart ⁵⁷.

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.

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 χ^2 , I^2 and Tau². 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).

Abbreviations

CIDP

chronic inflammatory demyelinating polyneuropathy

HLA

human leucocyte antigen

IgG4-AID

IgG4 autoimmune diseases

FS

fogo selvagem

MuSK

muscle-specific kinase

MuSK MG

MuSK myasthenia gravis

MHC

major histocompatibility complex

PF

pemphigus foliaceus

PV

pemphigus vulgaris

TTP

thrombotic thrombocytopenic purpura

Declarations

Acknowledgements

We are grateful to Alexander Zimprich for scientific advice.

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.

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

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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Figures

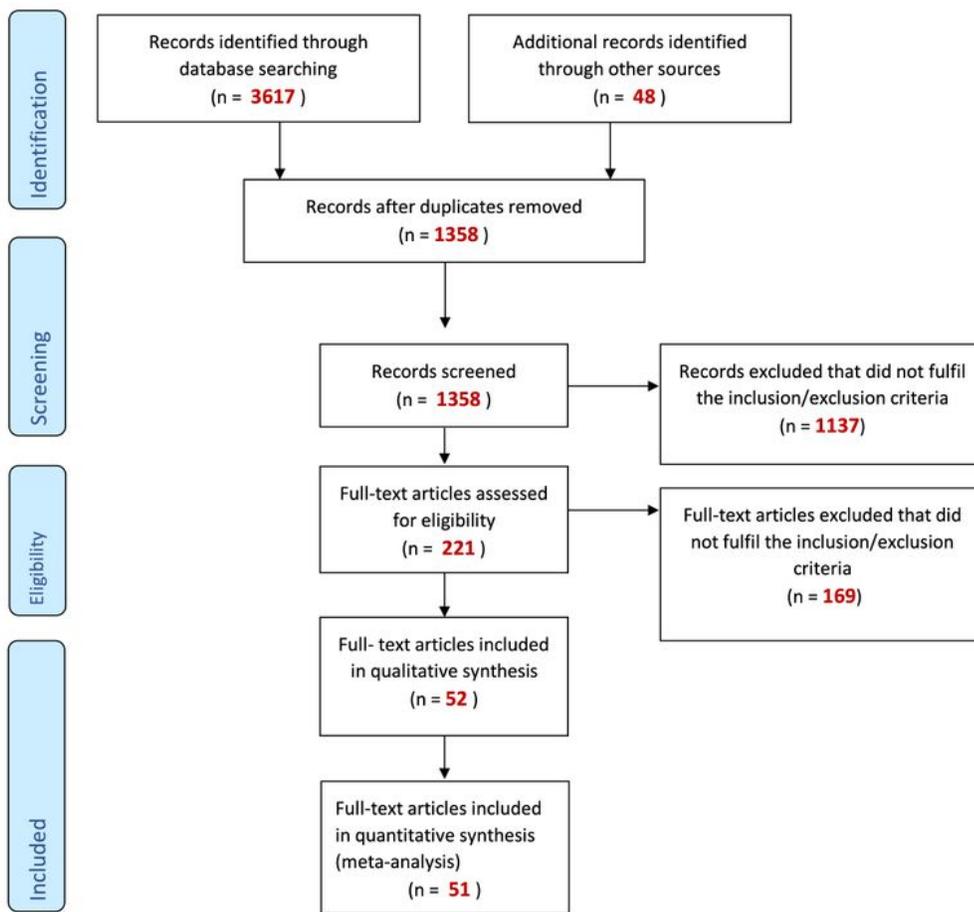
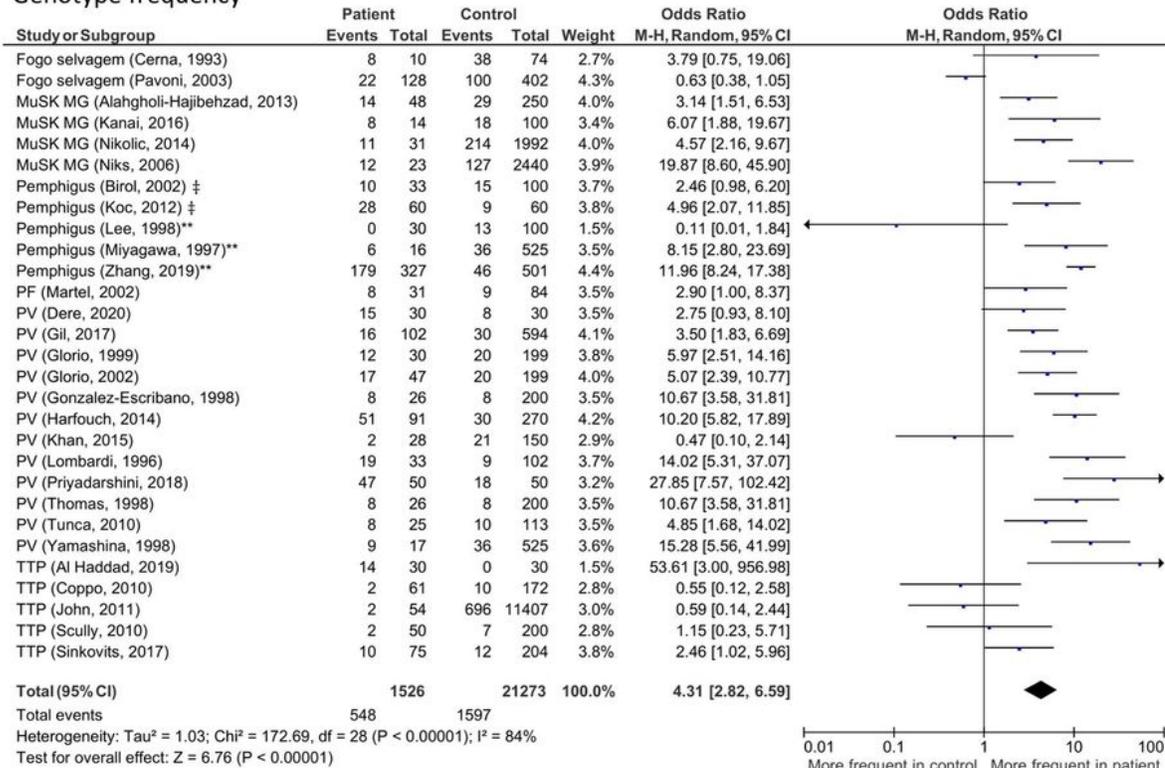


Figure 1

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. 200926.

DRB1*14

Genotype frequency



Allele frequency

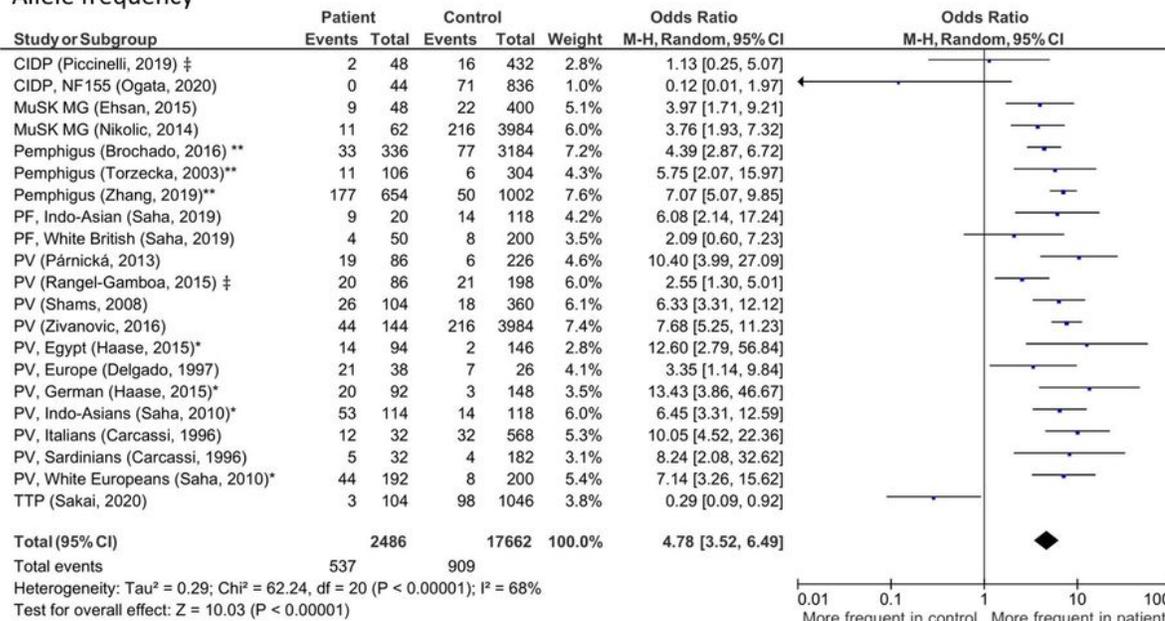
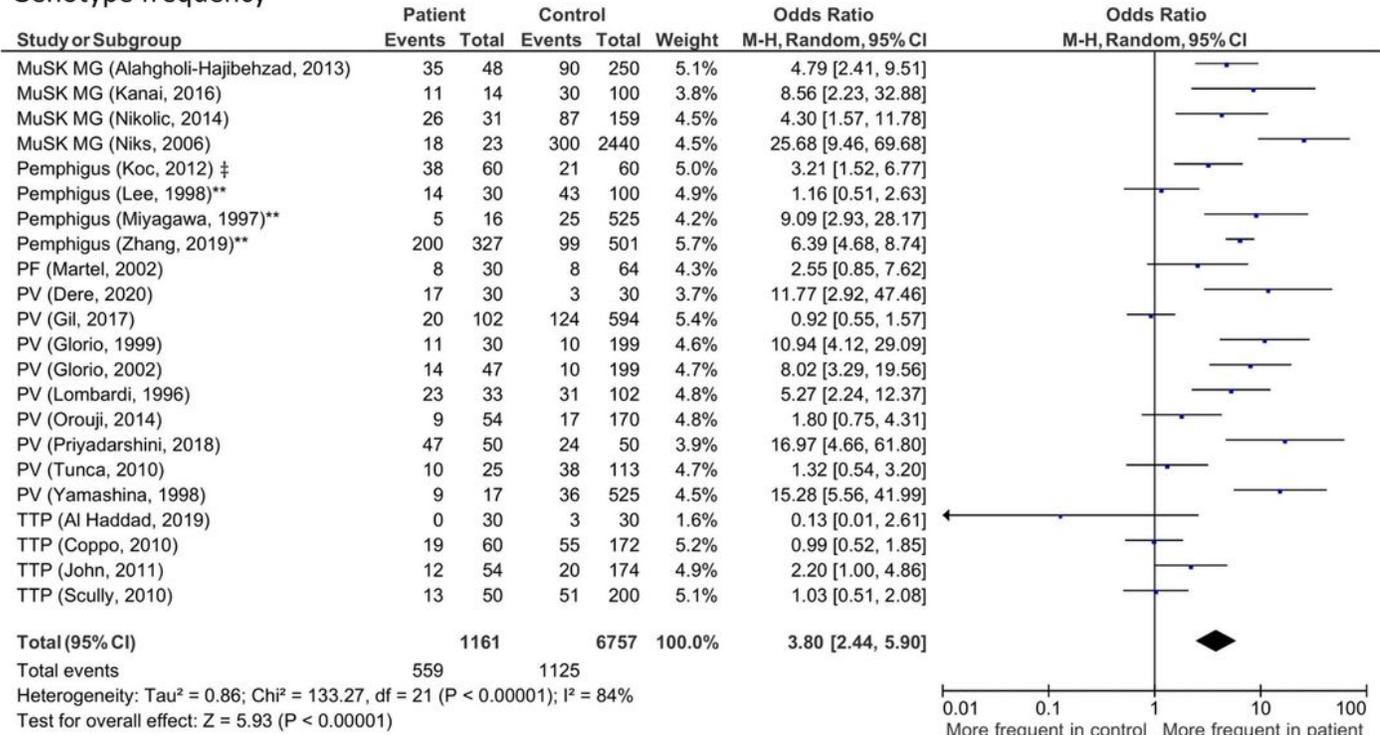


Figure 2

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.

DQB1*05

Genotype frequency



Allele frequency

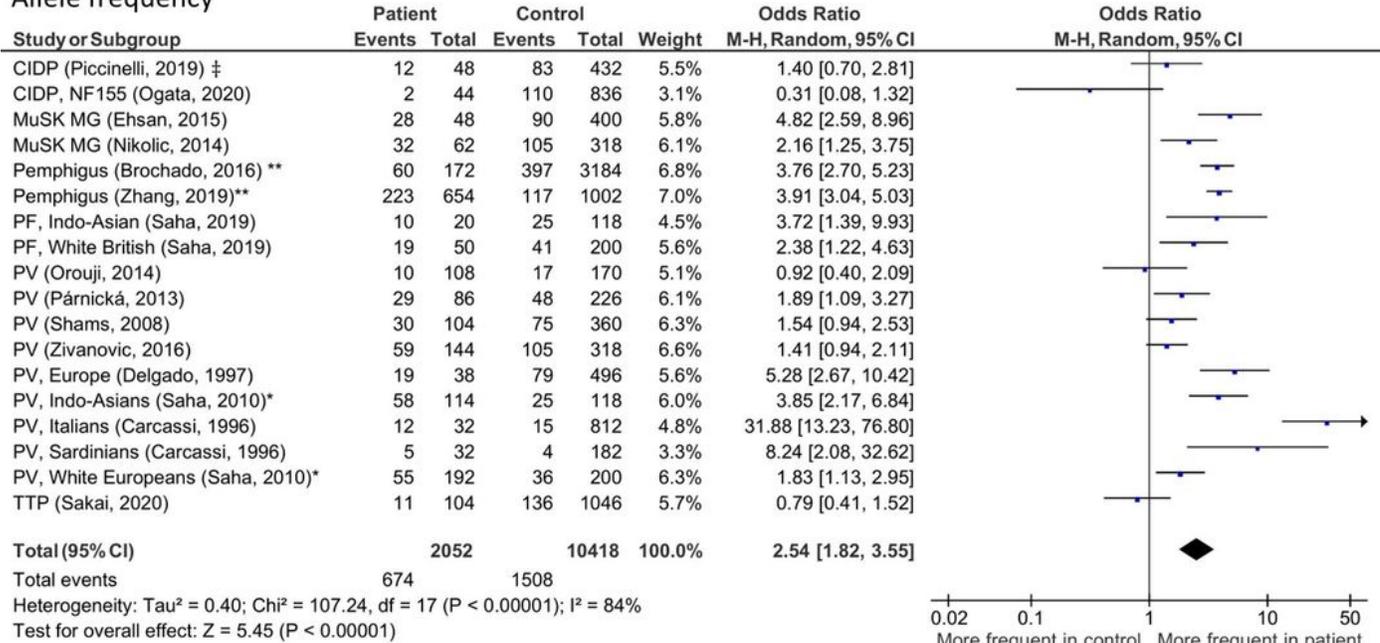


Figure 3

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.

DRB1*14-DQB1*05

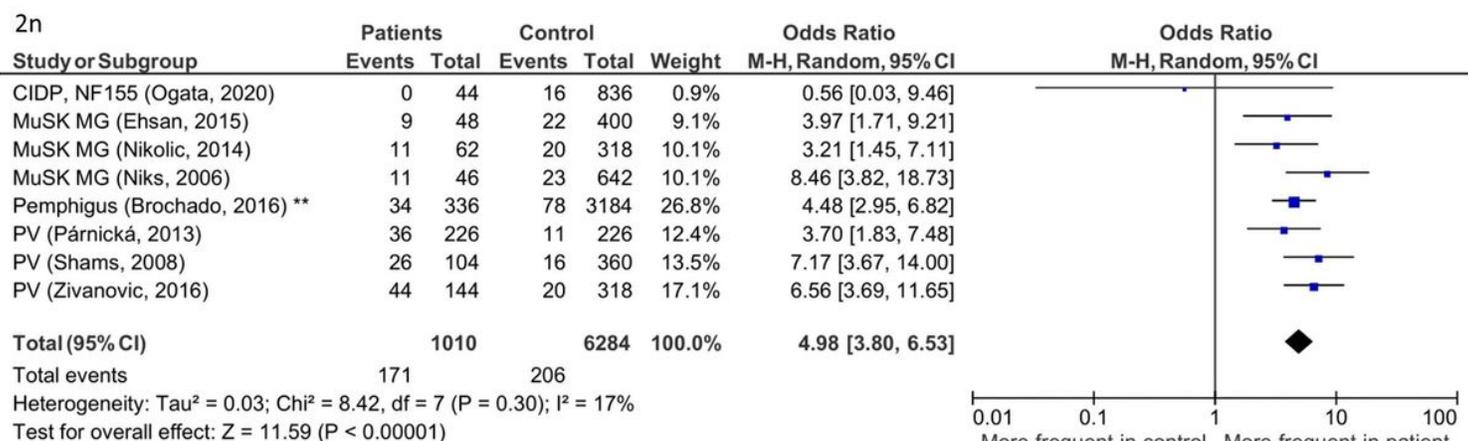
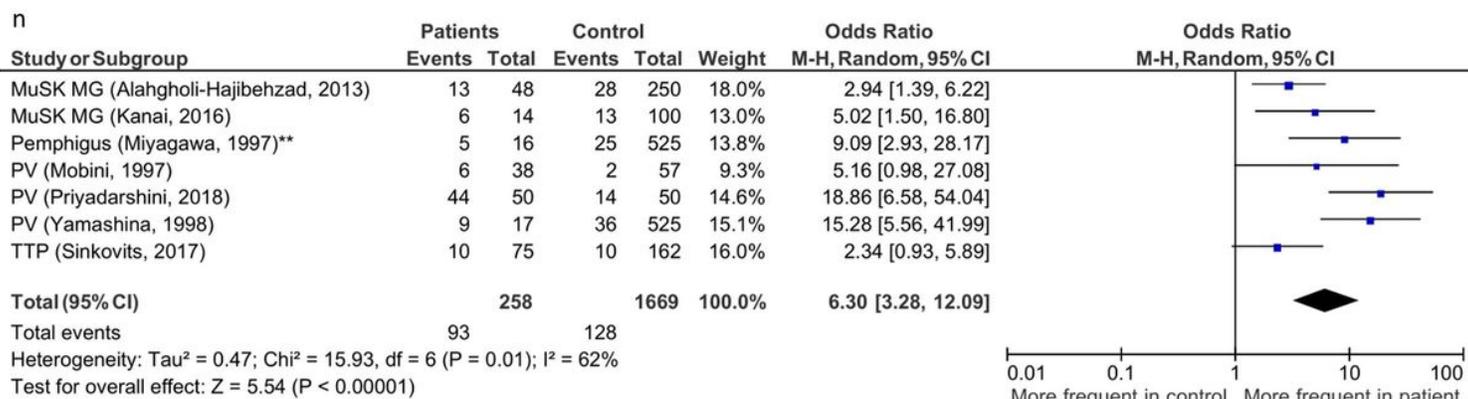
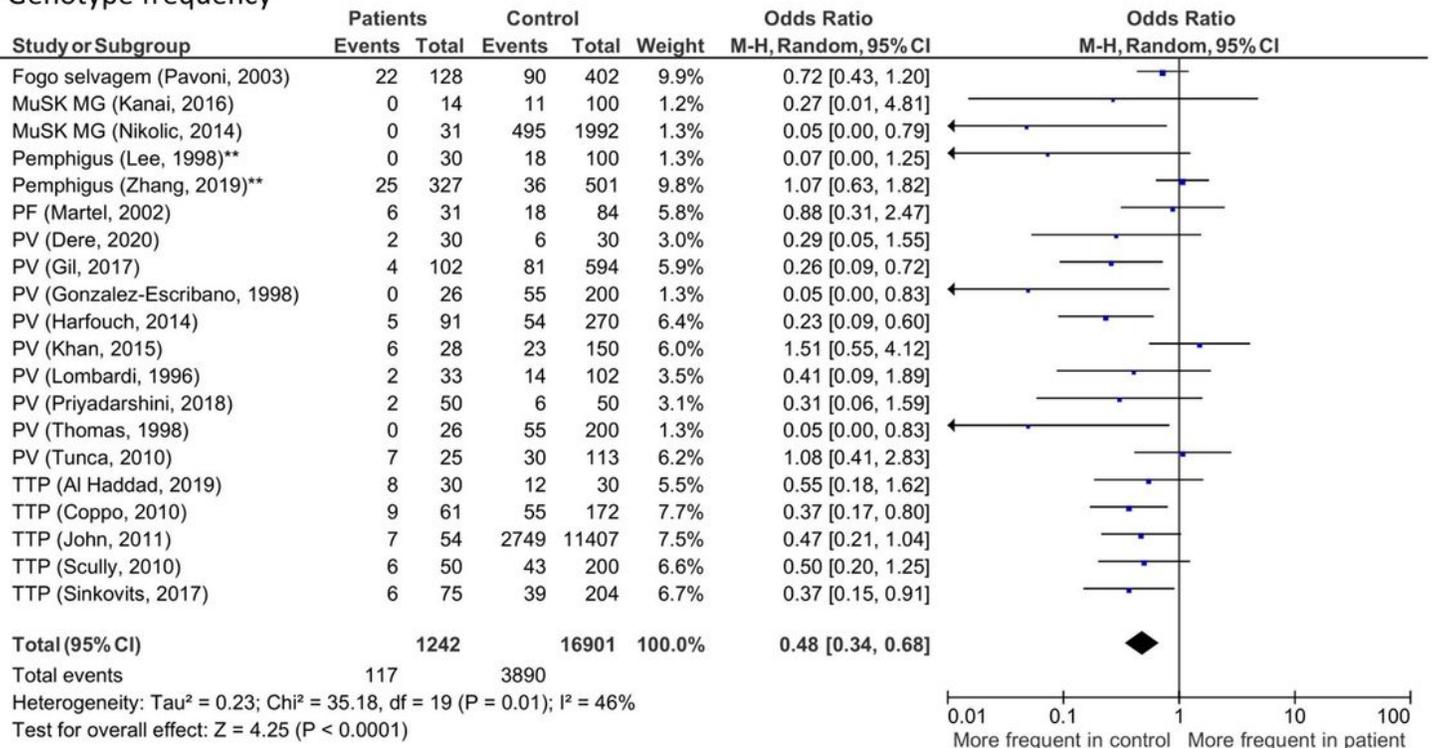


Figure 4

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

DRB1*13

Genotype frequency



Allele frequency

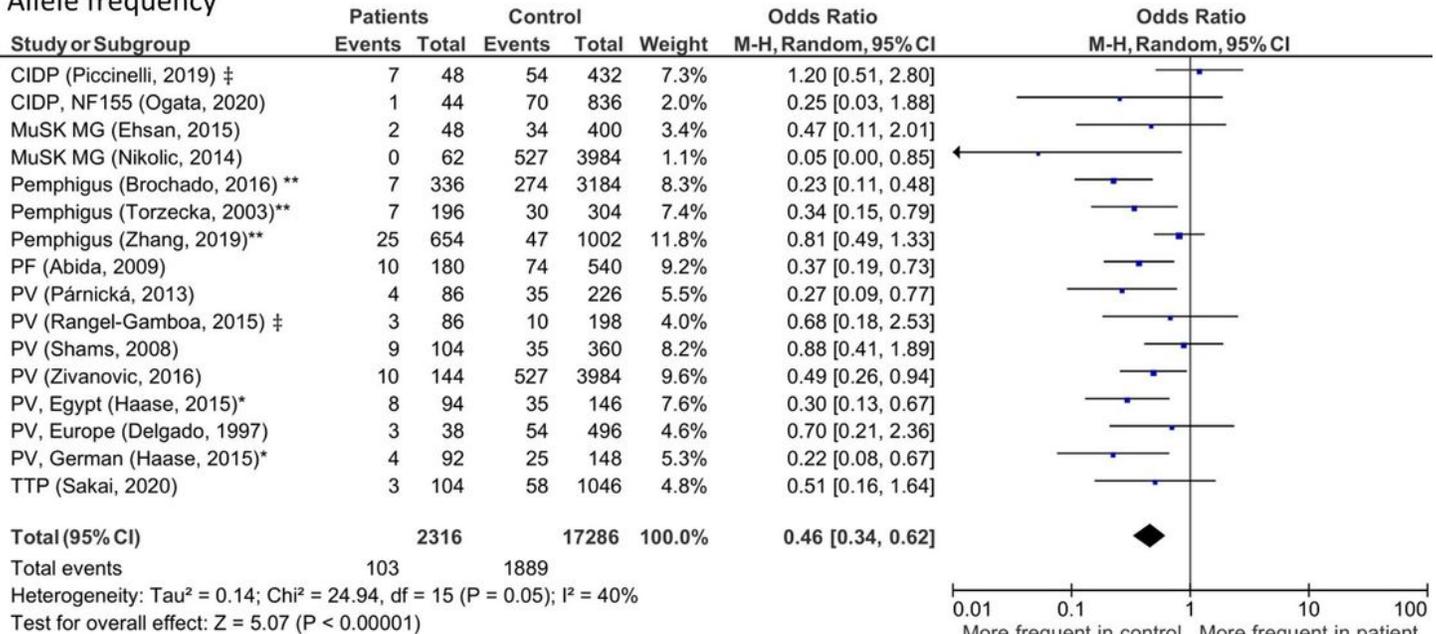


Figure 5

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.

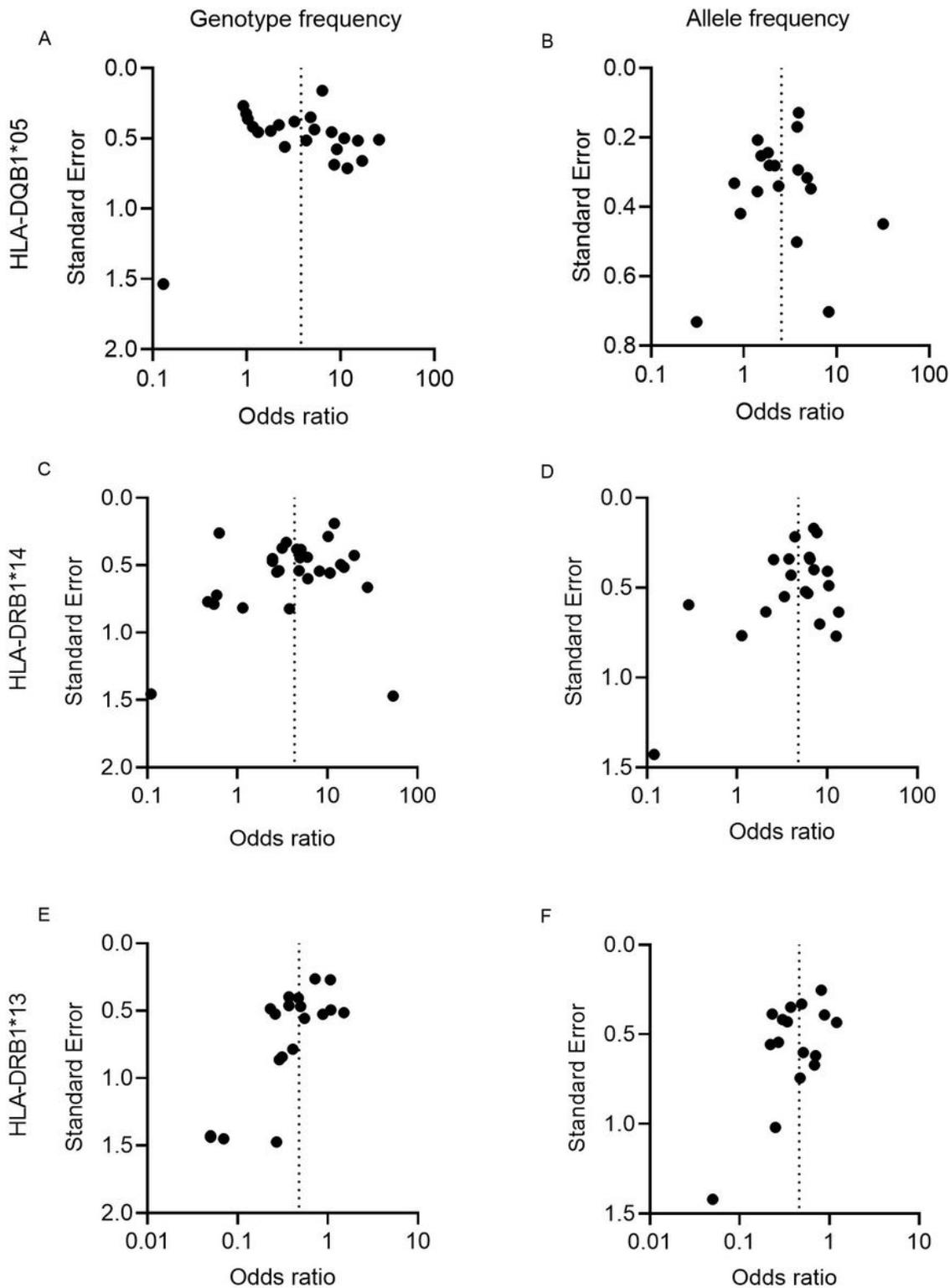


Figure 6

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).

Supplementary Files

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- [SupplementaryMaterial3.11.21.pdf](#)