scientific reports

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A systematic review and meta-analysis of HLA class II associations in patients with IgG4 autoimmunity

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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.

Abbreviations

CIDP	Chronic inflammatory demyelinating polyneuropathy
HLA	Human leukocyte 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

IgG4 autoimmune diseases (IgG4-AID) were first collectively described in 2015[1] and include diseases such as myasthenia gravis with antibodies against muscle-specific kinase (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 activation[3–6]. IgG4 is thought to play a protective role, e.g. in allergy or autoimmunity, by

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competing with effector antibodies for epitope binding[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 by 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 diseases[14] that are therefore not part of our study. IgG4-AID share also further important pathophysiological and therapeutic commonalities[15–17] including severe disease course, low disease prevalence (equal or less than 5/10,000) and good response to B-cell depletion therapy with rituximab[17].

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 leukocyte antigen (HLA) genes on chromosome 6p21.3 that encode the major histocompatibility complex (MHC)[18,19]. *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[20,21].

HLA-DR has been linked to aberrant presentation of self-peptide to autoreactive T helper cells in the thymus[22], and 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[23]. There is also evidence that the HLA can influence the production of IgG4: distinct HLA variants were shown to determine the immune response towards autoimmunity or tolerance in animal models[24,25] by directly affecting T-cell fate towards conventional (Tconv) or regulatory T cells (Tregs), and production of pro- or anti-inflammatory cytokines, including interleukin-10 (IL-10). IL-10, which is in part produced by Tregs[26], induces activation, IgG4 class switch and antibody production in naïve CD40-primed B cells and is therefore a key regulator of IgG4 production[26–31]. Increased IgG4 production was linked to *HLA-DRB1*15* in patients with IgG4-related disease[32]and MuSK MG patients carrying *HLA-DRB1*14* expressed elevated levels of IL-10 and MuSK antibodies compared to patients with other *HLA* variants[33]. Furthermore, IL-10 was found to be elevated in patients with pemphigus[34,35], MuSK-MG[36] and thrombotic thrombocytopenic purpura[37]. This suggests a link between HLA polymorphisms and production of IgG4 via IL-10[29–31,38]. In a previous review, we observed that individual IgG4-AID were frequently reported to be associated with the same recurrent HLA alleles: *HLA*DRB1* 04, 11, 14 or 15*, and/or *HLA-DQB1*05*[15]. GWAS data also suggests that HLA class II gene polymorphisms play a role for susceptibility to several different IgG4-AID[15], and specifically the *HLA-DRB1* and *DQB1* loci were associated with individual diseases[39,40]. We hypothesized that distinct HLA variants may contribute to a genetic susceptibility resulting in a predominant production of IgG4 subclass antibodies and may therefore be associated with several distinct IgG4-AID. Therefore, we wanted to investigate HLA associations first in individual IgG4-AID to identify disease- specific variants, and then across diseases to identify which HLA variants are shared among different IgG4 associated diseases that may predispose to developing pathogenic IgG4 autoantibodies. 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.

Methods

The systematic review was based on recommendations by the HuGENet™ HuGE Review Handbook, version 1.0 (released by the EQUATOR network, 2015[41]), and MOOSE guidelines for Meta-Analyses and Systematic Reviews of Observational Studies[42].

Study design. The protocol, including the research question, search strategy, inclusion/exclusion criteria, data to be extracted, and the planned statistical analysis and bias assessment, was designed at the start of the study. The research question was developed with guidance from the PICOS (PI(E)CO) method[43]. The population (P) was defined as the participants in case–control studies and the intervention/exposure (I/E) was defined as the presence of distinct HLA alleles. The comparators (C) were the participants (patients and controls) without the distinct HLA allele and the outcome (O) was the occurrence of one of the six class I IgG4 AID. Regarding the study design, only case–control studies were considered, due to the rare nature of the disease. 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 (A.P., G.L. and V.B.) used electronic search of 34 bibliographic databases and archives (supplementary Table S1), including PubMed/MEDLINE, Cochrane CENTRAL and Cochrane CDSR, Web of Science (core collection and all databases), BIOSIS, Scopus, Ovid Global Health, clinical trial registries (ClinicalTrials.gov and WHO ICTRP), and databases of systematic reviews (Epistemonikos, PROSPERO), BioOne, Centre for Reviews and Dissemination, CINAHL, DOAJ, EMBASE, EU Clinical Trials Register, GlaxoSmithKline's Clinical Study Register, Godort, HSRProj, JSTOR, Mendeley, metaRegister of Controlled Trials (Current controlled trials), Research gate, Science Citation Index (ISI), Science direct, TRIP Database, U.S. Government Documents, Worldcat, Biorxiv and Medrxiv as well as using other sources including grey literature (open grey) and hand searching. The search strategy included the search for key words, MeSH terms, including the use of a truncation operator (*, e.g. "antibod*" to identify the terms "antibody" and "antibodies"), and misspelling including the terms "HLA," "human leucocyte antigen", "DRB1", "DQB1","MuSK myas-

thenia gravis", "pemphigus", "thrombotic thrombocytopenic purpura", " CIDP", "chronic inflammatory demyelinating polyneuropathy", "MuSK", "Desmoglein 3", "Desmoglein 1", "blistering skin disease", "ADAMTS13", Neurofascin 155", "NF155", "Contactin-1", "CNTN1″ and related terms in titles and abstracts and full text using Boolean search strategies. The search was conducted between May 5, 2020 until June 16, 2020. As only a limited number of studies investigating HLA associations in IgG4-AID exist, no restrictions for the date of publication were made and all studies available at the time of the search were included. Due to the language proficiency of the researchers, studies in German, English, Italian and Spanish were considered, if applicable using wildcards (*) for the search terms.

Screening and study selection. After deduplication, three researchers screened the obtained records for eligibility independently of each other, based on inclusion/exclusion criteria in two phases (first phase: screening of title/abstract, second phase: screening of the full text) using Rayyan software[44]. The inclusion criteria for selecting the studies were as follows:

a. Studies in humans with a case-control design that
b. Reported the association of gene variants of the HLA class II gene locus, including allele, genotype or haplotype frequency.
c. Studies in which cases were patients with class I IgG4-AID that were tested positive for the corresponding antibodies ((MuSK myasthenia gravis (antibodies to MuSK) pemphigus vulgaris (antibodies to desmoglein 3), pemphigus foliaceus (antibodies to desmoglein 1 and/or 3), peripheral neuropathies, including CIDP, (antibodies against Contactin 1), peripheral neuropathies, including CIDP, (antibodies against Neurofascin 155), thrombotic thrombocytopenic purpura (antibodies against ADAMTS13)) by standardized laboratory tests, including the following tests: ELISA, cell-based assay (CBA), radioimmuno(precipitation)assay (RIA), direct or indirect immunofluorescence test.
d. Studies with a minimum of 1 control per case, that were age and gender matched, and that described the controls as either ethnically matched or with controls from the same geographical region as the patient cohort.
e. Studies with controls that are either healthy individuals or patients with a different type of the same disease that were negative for their relevant autoantibodies, as well as any other IgG4 associated autoantibody or with an unrelated disease.

The exclusion criteria were as follows:

f. Studies in which the controls had any immunodeficiencies/abnormalities in the HLA locus,
g. Studies in which data on an individual patient level was not available,
h. Studies including subjects already included in other published studies,
i. Studies where a full text version was not available and
j. Studies where insufficient data was available to calculate an odds ratio.

During the two screening phases, the three researchers were blinded to each other's decisions in order to prevent bias. Any discrepancies in the assessment after unblinding were resolved via discussion. The search and selection of studies was documented and visualized with a PRISMA flow chart[45].

Data extraction. Data was extracted from tables and running text in the included manuscripts and collected in Excel (Microsoft Office, USA). If data was incomplete, unpublished or unavailable, it was attempted to retrieve the data by contacting the corresponding authors of the study by email. The following information from each included study was extracted: primary author, year of publication, full bibliographic information, demographic information of patients and controls (sex, age), country of study site, type of IgG4-AID and/or type of autoantibody, affected organ, type of control, HLA typing method, sample size, genotype frequency, allele frequency, haplotype frequency, HLA supertype frequency, OR and 95% CI. Combinable data was analysed by meta-analysis for association between HLA alleles (genotype or allele frequency) and class I IgG4-AID individually and collectively.

Statistics. Combinable data (haplotype, genotype and allele frequencies of HLA class II alleles, analyzed separately) was included in the analysis. To study genetic associations with the HLA class II alleles, we used the dominant genetic model of association to analyze genotype frequencies and the allelic model of association to analyze allele frequencies[46]. Depending on the information provided in the individual studies, haplotype analysis was conducted either with the dominant genetic model of association (based on haplotype frequency, defined as the number of individuals with a specific haplotype out of the number of total individuals (n)), or using the allelic model of association (based on haplotype frequency, defined as the total number of a specific haplotype out of the total number of alleles of all study participants (2n)). Both datasets were analyzed and presented separately.

The combined effect of the included studies (pooled OR) was calculated using the Review Manager ((RevMan) [Computer program] Version 5.4.1 The Cochrane Collaboration, 2020).

Mantel–Haenszel tests for the ORs were performed with a random-effects model for different studies, which was important to address heterogeneity in the studies between diseases, and visualized using forest plots.

The heterogeneity of the included studies was measured using X^2, I^2 and Tau^2. The publication bias was inspected by funnel plots. To overcome bias due to the predominance of pemphigus studies, which comprised > 50% of the studies, the analysis was repeated, excluding studies on pemphigus. Uncorrected p values < 0.05 were reported as statistically significant. To correct for multiple testing, we applied a Bonferroni-correction for k = 40 tests (20 marker positions, analyzed either as alleles or genotypes), which leads to a corrected significance level of $p < 0.00125$. Results that were only significant at the uncorrected level are shown in italics.

Consent for publication. All authors declare their consent for publication.

Results

Number and characteristics of included studies. After search and screening, 52 full-text articles with a total of 64 datasets (Tables 1,2) were included in the qualitative synthesis and 51 full-text articles with 62 datasets in the quantitative synthesis (Fig. 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, and one dataset from the Delgado study (1997).

Genetic associations with individual IgG4-AID. We wanted to study genetic HLA associations of the individual diseases. Data of 15 *HLA-DRB1* alleles (*DRB1*01–16*) and five *HLA-DQB1* alleles (*DQB1*02–06*) could be extracted from studies on pemphigus, MuSK MG and TTP (summarized in Tables 1,2). Due to a lack of data, no separate analysis for CIDP was undertaken.

Pemphigus. In a substantial proportion of the studies, there was little to no distinction between pemphigus vulgaris and pemphigus foliaceus. In this study, we therefore analyzed all subtypes of pemphigus collectively (supplementary Figs. S46–S66). The pooled ORs and 95% CIs indicated that four HLA variants were associated with a significantly increased frequency in pemphigus patients: *HLA-DRB1*04* (genotype: OR 4.86; 95% CI 3.61–6.54; $p < 0.00001$; allele: OR 4.18; 95% CI 3.14–5.56; $p < 0.00001$), *HLA-DRB1*14* (genotype: OR 4.81; 95% CI 2.88–8.05; $p < 0.00001$; allele: OR 6.14; 95% CI 4.98–7.58), *HLA-DQB1*03* (genotype: OR 2.77; 95% CI 1.56–4.92; $p = 0.0005$; allele: OR 1.99; 95% CI 1.39–2.83; $p = 0.0002$) and *HLA-DQB1*05* (genotype: OR 4.3; 95% CI 2.53–7.28; $p < 0.00001$; allele: OR 3.04; 95% CI 2.10–4.41; $p < 0.00001$). Eight variants were significantly decreased in pemphigus patients, suggesting a protective role: *HLA-DRB1*03* (genotype: OR 0.34; 95% CI 0.25–0.47; $p < 0.00001$; allele: OR 0.35; 95% CI 0.17–0.70; *p = 0.003*), *HLA-DRB1*07* (genotype: OR 0.38; 95% CI 0.25–0.58; $p < 0.00001$; allele: OR 0.45; CI 95% 0.32–0.61; $p < 0.00001$), *HLA-DRB1*09* (genotype: OR 0.57; 95% CI 0.43–0.77; $p = 0.0002$; allele: OR 0.62; 95% CI 0.47–0.81; $p = 0.0005$), *HLA-DRB1*11* (genotype: OR 0.42; 95% CI 0.27–0.65; $p < 0.0001$; allele: OR 0.47; 95% CI 0.31–0.72; $p = 0.0005$), *HLA-DRB1*13* (genotype: OR 0.51; 95% CI 0.31–0.82; *p = 0.006*; allele: OR 0.44; 95% CI 0.32–0.6; $p < 0.00001$), *HLA-DRB1 *15* (genotype: OR 0.47; 95% CI 0.37–0.59; $p < 0.00001$; allele: OR 0.37; 95% CI 0.3–0.47; $p < 0.00001$), *HLA-DQB1*02* (genotype: OR 0.33; 95% CI 0.24–0.45; $p < 0.00001$; allele: OR 0.4; 95% CI 0.31–0.52; $p < 0.00001$) and *HLA-DQB1*06* (genotype: OR 0.48; 95% CI 0.31–0.74; $p = 0.0009$; allele: OR 0.43; 95% CI 0.36–0.53; $p < 0.00001$).

Thrombotic thrombocytopenic purpura (TTP). Seven TTP studies were analyzed, but due to a lack of data, quantitative analysis was only conducted on genotype frequency of alleles with data from at least three studies, and allele frequency was only analyzed qualitatively. We observed significantly increased genotype frequencies of *HLA-DRB1*11* (genotype: OR 3.38; 95% CI 2.04–5.60; $p < 0.00001$), *HLA-DRB1*12* (genotype: OR 2.52; 95% CI 1.32–4.84; $p = 0.005$), *HLA-DRB1*15* (genotype: OR 1.67; 95% CI 1.11–2.51; *p = 0.01*) and significantly decreased genotype frequencies, and a trend towards a reduced allele frequency of *HLA-DRB1*04* (genotype: OR 0.38; 95% CI 0.25–0.56; $p < 0.00001$) and *HLA-DRB1*13* (genotype: OR 0.43, 95% CI 0.29–0.64; $p < 0.0001$) (supplementary Figs. S67–S84).

MuSK Myasthenia gravis. Five studies were available on MuSK MG, and quantitative analysis was only performed for alleles with a minimum of three studies per allele. MuSK MG patients had a strong, significant increase in genotype frequency of *HLA-DRB1*14* (genotype: OR 6.36, 95% CI 2.75–14.75, $p < 0.0001$), *HLA-DRB1*16* (genotype: OR 5.03, 95% CI 3.16–7.99; $p < 0.00001$) and *HLA-DQB1*05* (genotype: OR 7.94, 95% CI 3.44–18.30, $p < 0.00001$). The haplotypes *HLA-DRB1*14-DQB1*05* and *HLA-DRB1*16-DQB1*05* showed an increased frequency in the two studies that defined the haplotype frequency like the genotype frequency (n), and a significant increase in the three studies that defined the haplotype frequency like the allele frequency (2n, *HLA-DRB1*14-DQB1*05*: OR: 4.78; 95% CI 2.65–8.62; $p < 0.00001$; *HLA-DRB1*16-DQB1*05*: OR 3.47, 95% CI 2.16–5.57; $p < 0.00001$). A tendency towards a decreased frequency of *HLA-DQB1*06* was observed (supplementary Figs. S85–S105).

HLA alleles with increased frequency across IgG4-AID. To identify possible genetic risk factors that may be shared across diseases and that may predispose for the development of IgG4 autoantibodies, we analyzed HLA associations in all IgG4 patients (Fig. S19–28). Only figures with results that remained statistically significant after additional analysis (described below) are shown in the main manuscript, the remaining results are shown in the supplementary. We observed increased frequencies of *HLA-DRB1*14* (Fig. 2, genotype: OR 4.31;

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	[80]
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	[81]
Alahgholi-Hajibehzad	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	[82]
Harfouch	2014	Syria	PV	91	270	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16	PCR-SSP	Genotype frequency	[83]
Gonzalez-Escribano	1998	Spain	PV	26	200	DR1, DR2, DR3, DR4, DR7, DR8, DR9, DR10, DR11, DR12, DR13, DR14	PCR-SSOP, PCR-SSP	Genotype frequency	[84]

Continued

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
Brochado	2016	Brazil	PF	86 (172)	1592 (3184)	DRB1*01:01, DRB1*01:02, DRB1*04:02, DRB1*07:01, DRB1*08:04, DRB1*11:01, DRB1*13:01, DRB1*14:01, DRB1*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	Commercial kits form One Lambda	Allele frequency, haplotype frequency	85
			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*15-DQA1*01-DQB1*06, DRB1*14-DQA1*01-DQB1*05, DRB1*16-DQA1*01-DQB1*05			
Martel	2002	France	PF	31	84	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16,	PCR-SSO, PCR-SSP, PCR–RFLP	Genotype frequency	86
				30	64	DQB1*02, *03:02, *05:03			
Párnická	2013	Slovakia	PV	43 (86)	113 (226)	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06 DRB1*14-DQB1*05:03, DRB1*14:54-DQB1*05:03, DRB1*14:04-DQB1*05:03, DRB1*14:05-DQB1*05:03	PCR-SSP	Allele frequency, haplotype frequency	87
Nikolic	2014	Serbia	MuSK MG	31 (62)	1992 (3984)	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16	PCR with sequence-specific oligonucleotides	Genotype frequency, allele frequency, haplotype frequency	78
				31 (62)	159 (318)	DQB1*02, *03, *04, *05, *06 DRB1*14-DQB1*05, DRB1*16-DQB1*05, DRB1*15-DQB1*06			
De Sena Nogueira Maehara	2017	Brazil	Fogo selvagem	42 (84)	478 (956)	DRB1*02, *04, *05, *07, *16	PCR-SSO	Allele frequency	88
		Netherlands	PF	17 (34)	447 (894)	DRB1*04			
Coppo	2010	France	TTP	61	172	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16	PCR-SSO	Genotype frequency	89
				60	172	DQB1*02, *03, *04, *05, *06			

Continued

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
Kanai	2016	Japan	MuSK MG	14	100	DRB1*01, *04, *08, *09, *11, *12, *13, *14, *15, 16 DQB1*03, *04, *05, *06	PCR-SSP	Genotype frequency, haplotype frequency	[90]
Piccinelli	2019	Italy	CIDP	24 (48)	216 (432)	DRB1*01, *03, *04, *07, *08, *10, *11, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06 DRB1*15-DQB1*06	PCR-SSP	Allele frequency, haplotype frequency	[91]
Zivanovic	2016	Serbia	PV	72 (144)	1992 (3984)	DRB1*01, *03, *04, *07, *11, *12, *13, *14, *15, *16	PCR-SSP	Allele frequency, haplotype frequency	[79]
				72 (144)	159 (318)	DQB1*02, *03, *04, *05, *06 DRB1*14-DQB1*05, DRB1*16-DQB1*05, DRB1*15-DQB1*06			
Saha	2019	UK	PF (Caucasian white British)	25 (50)	100 (200)	DRB1*01, *04, *14 DQB1*0302, *0501, *0502, *0503	PCR-SSP	Allele frequency	[92]
			PF (Indo-Asians)	10 (20)	59 (118)	DRB1*01, *04, *14 DQB1*0302, *0501, *0503			
Gil	2017	Brazil	PV	102	594	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06	PCR-SSP	Genotype frequency	[93]
Torzecka	2003	Poland	PF	15 (30)	152 (304)	DRB1*01, *03, *04, *07, *08, *09, *10 *11, *12, *13, *14, *15	Dynal RELI SSO HLA-DRB Test	Allele frequency	[74]
			PV	38 (76)	152 (304)	DRB1*01, *03, *04, *07, *08, *09, *10 *11, *12, *13, *14, *15			
Abida	2009	Tunisia	PF	90 (180)	270 (540)	DRB1*03, *04, *11, *13, *15 DQB1*0301, *0302, *06	PCR-SSP	Allele frequency	[94]
Ogata	2020	Japan	CIDP	22 (44)	418 (836)	DRB1*01, *03, *04, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06 DRB1*14:05-DQB1*05:03, DRB1*15:01-DQB1*06:02, DRB1*15:02-DQB1*06:01	Next-generation sequencing	Allele frequency, haplotype frequency	[95]
Priyadarshini	2018	India	PV	50	50	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06 DRB1*14-DQB1*05, DRB1*15-DQB1*06	PCR-SSOP	Genotype frequency, haplotype frequency	[96]
Tunca	2010	Turkey	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	[97]

Continued

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
Haase	2015	Germany	PV (German)	46 (92)	74 (148)	DRB1*01, *02, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16	PCR-SSP	Allele frequency	98
			PV (Egypt)	47 (94)	73 (146)				
Martinez-Martinez	2017	Spain	CIDP	13	941	DRB1*15	DNA sequence analysis and SSP methodology	Genotype frequency, Haplotype frequency	99
				13	35	DRB1*15-DQB1*06			
Glorio	1999	Argentina	PV	30	199	DR3, DR4, DR8, DR14, DR15 DQB1*03, *05	PCR-SSO	Genotype frequency	100
Pavoni	2003	Brazil	Fogo selvagem	128	402	DRB1*01, *03, *04, 07, *08, *09, *10, *11, *12, *13, *14, *15, *16	PCR-SSOP	Genotype frequency	101
Thomas	1998	Spain	PV	26	200	DR1, DR2, DR3, DR4, DR7, DR8, DR9, DR10, DR11, DR12, DR13, DR14	PCR-SSOP, PCR-SSP	Genotype frequency	102
Zhang	2019	China	PF	72	501	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06	Affymetrix axiom precision medicine research array based GWAS	Genotype frequency, allele frequency	75
			PV	255	501				
Moraes	1991	Brazil	Fogo selvagem	37	49	DR1, DR16, DQ2	PCR-SSP	Genotype frequency	103
				38	46	DRB1*15			
				38	41	DQB1*06			
Lee	1998	South Korea	PF	15	100	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06	PCR-SSP	Genotype frequency	76
			PV	15	100				
Shams	2008	Iran	PV	52 (104)	180 (360)	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06 DRB1*15-DQA1*01-DQB1*06 DRB1*16-DQA1*01, DQB1*05	PCR-SSP	Allele frequency, haplotype frequency	104
Orouji	2014	Mid-east origin	PV	54	85	DQB1*02, *03, *04, *05, *06	PCR-SSP	Genotype frequency, allele frequency	105
Miyagawa	1997	Japan	PF	9	525	DRB1*04, *14 DQB1*03, *05 DRB1*14-DQA1*01-DQB1*05	NA	Genotype frequency, haplotype frequency	77
			PV	7	525				
Joly †	2020	France	TTP	26	172	DRB1*04, *11 DQB1*03	PCR-SSP	Genotype frequency, allele frequency	106
Glorio	2002	Argentina	PV	47	199	DR3, DR4, DR8, DR14, DR15 DQB1*03, *05	PCR-SSO	Genotype frequency	107
Sakai	2020	Japan	TTP	52 (104)	523 (1046)	DRB1*01, *04, *08, *09, *11, *12, *13, *14, *15 DQB1*03, *04, *05, *06	Commercial kits with Illumina MiSeq technology	Allele frequency	108
Koc	2012	Turkey	Pemphigus	60	60	DRB1*04, *11, *14 DQB1*02, *05, *06	PCR-SSP	Genotype frequency	109
Scully	2010	UK	TTP	50	200	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06	PCR-SSP, PCR-SSOP	Genotype frequency	110

Continued

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
Mobini	1997	Iran	PV	38	57	DRB1*14-DRB3*02-DQB1*05-DQA1*01, DRB1*15-DRB5*01-DQB1*06-DQA1*01, DRB1*15-DRB5*01-DQB1*06-DQA1*05	PCR-SSOP	Haplotype frequency	111
Delgado	1997	Pakistan	PV (Pakistan)	19 (38)	13 (26)	DRB1*01, *02, *03, *04, *07, *10, *11, *13, *14 DQB1*02, *03, *04, *05, *06	PCR-SSOP	Allele frequency	112
		Europe	PV (Europe)	19 (38)	248 (496)	DRB1*01, *02, *04, *07, *08, *11, *12, *13, *14 DQB1*02, *03, *05, *06			
Yamashina	1998	Japan	PV	17	525	DRB1*04, *14 DQB1*03, *05	PCR–RFLP	Genotype frequency, haplotype frequency	113
Al Haddad	2019	Lebanon	TTP	30	30	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06	PCR-SSP	Genotype frequency	114
John	2011	Germany	TTP	54	11,407	DRB1*01, *03, *04, *07, *08 *09, *11, *12, *13, *14	PCR-SSP, PCR-SSO	Genotype frequency	115
				50	174	DQB1*02			
				54	174	DQB1*04, *05			
				47	174	DQB1*03			
				52	174	DQB1*06			
Martino	2016	France	TTP	26 (52)	663 (1326)	DRB1*04, DRB1*11	PCR-SSO	Allele frequency	116
				26 (52)	437 (874)	DQB1*03			
				24 (48)	100 (200)	DRB1*04, DRB1*11 DQB1*03			
Cerna	1993	Brazil	Fogo selvagem	10	74	DRB1*04, *08, *14, *16 DQB1*03, *04	PCR-SSOP	Genotype frequency	117
Birol	2002	Turkey	Pemphigus	33	100	DR4, DR11, DR14 DQ2, DQ4	Microdroplet lymphocyte test	Genotype frequency	118
Rangel-Gamboa	2015	Mexico	PV	43 (86)	99 (198)	DR1, DR4, DR7, DR8, DR11, DR13, DR14, DR16	PCR-SSO	Allele frequency	119
Khan	2015	Pakistan	PV	28	150	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16	PCR-SSP	Genotype frequency	120
Carcassi	1996	Italy	PV (Sardinians)	16 (32)	91 (182)	DRB1*03, *04, *08, *14 DQB1*02, *03, *05	PCR-SSO	Allele frequency	121
			PV (Italians)	16 (32)	284 (568)	DRB1*03, *04, *08, *14			
				16 (32)	406 (812)	DQB1*02, *03, *05			
Lombardi	1996	Italy	PV	33	102	DRB1*01, *03, *04, *07, *08, *11, *13, *14, *15, *16 DQB1*02, *03, *04, *05, *06	PCR-SSO	Genotype frequency	122
Saha	2010	UK	PV (white Europeans)	96 (192)	100 (200)	DRB1*03, *04, *07, *14, *15 DQB1*02, *03, *05, *06	PCR-SSP	Allele frequency	123
			PV (Indo-Asians)	57 (114)	59 (118)				

Continued

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
Niks	2006	Netherlands	MuSK MG	23	2440	DR1, DR3, DR14, DR16, DQ5, DQ6	PCR-amplified fragments and biotin labelled oligonucleotides	Genotype frequency, Haplotype frequency	[124]
				23 (46)	321 (642)	DRB1*14-DQB1*05, DRB1*15-DQB1*05			
Sinkovits	2017	Hungary	TTP	75	204	DRB1*01, *03, *04, *07, *08, *09, *10, *11, *12, *13, *14, *15, *16	PCR-SSO	Genotype frequency, Haplotype frequency	[125]
				75	162	DRB1*14-DQB1*05, DRB1*16-DQB1*05, DRB1*15-DQB1*06			

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. † Study was included in the qualitative synthesis, but excluded from the meta-analysis as it did not fit all selection criteria.

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,*

Table 2. HLA class II associations identified in IgG4-AID. Bold: significant results only for either genotype or allele frequency.

95% CI 2.82–6.59; $p < 0.00001$; allele: OR 4.78; 95% CI 3.52–6.49; $p < 0.00001$), *HLA-DQB1*05* (Fig. 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 (Fig. 4, n: OR 6.3; 95% CI 3.28–12.09; $p < 0.00001$, 2n: OR 4.98; 95% CI 3.8–6.53; $p < 0.00001$). Further associations were found in *HLA-DQB1*03* (Fig. 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-DRB1*04* (Fig. S1, genotype: OR 2.72; 95% CI 1.81–4.10; $p < 0.00001$; allele: OR 2.72; 95% CI 1.94–3.81, $p < 0.00001$).

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 (Figs. S3–S7 and 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 (Fig. S5–S7), the frequency of *HLA-DRB1*04* (Fig. 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* (Fig. S36–S39).

Reduced frequency of HLA alleles in IgG4-AID. Several HLA variants were significantly decreased in patients with IgG4-AID, which is interesting as these may potentially contribute to a protection from IgG4 autoimmunity (Figs. 5; Suppl Fig. 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; $p = 0.01$).

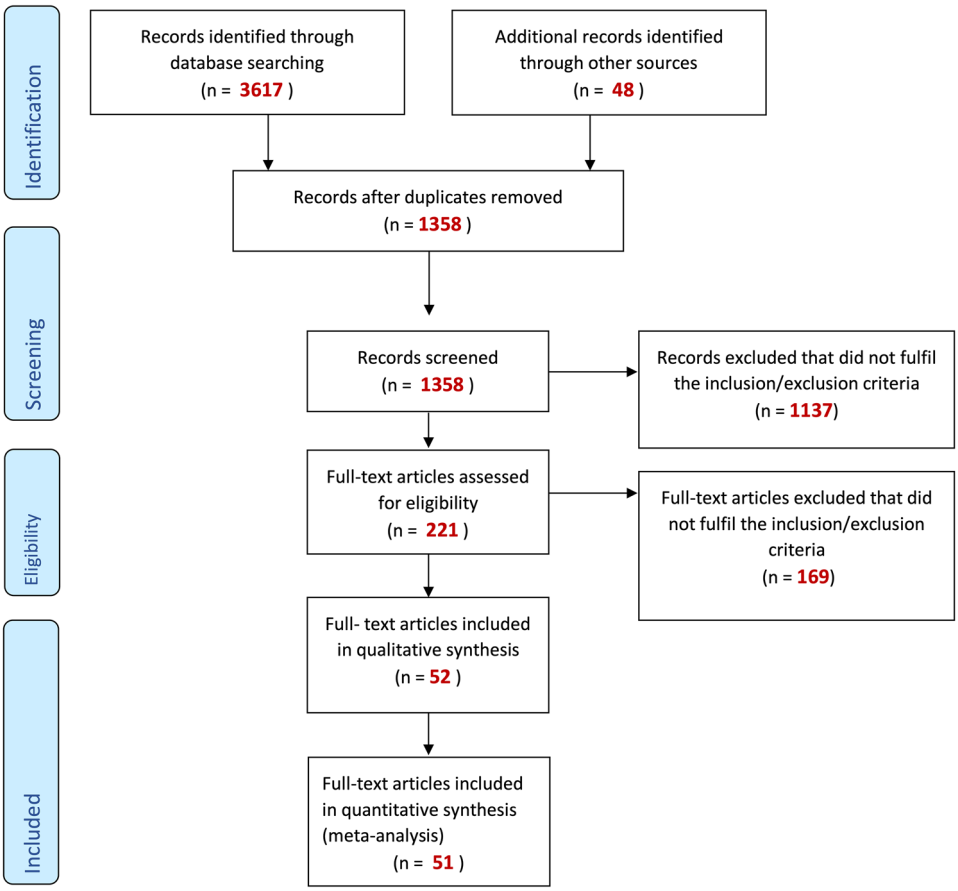

Figure 1. PRISMA flow chart of study identification and eligibility screening. For specific inclusion and exclusion criteria see methods. Figure modified from Moher et al.[47].

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

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 S3 and S4). We analyzed the available datasets with higher resolution data, which was mostly derived from pemphigus studies. Data of the available variants (Fig. 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 (Fig. 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 Tau^2, X^2 and I^2 tests (supplementary Table S5), whereas potential publication bias was assessed by funnel plots (Figs. 6; Suppl Figs.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 in the 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*.

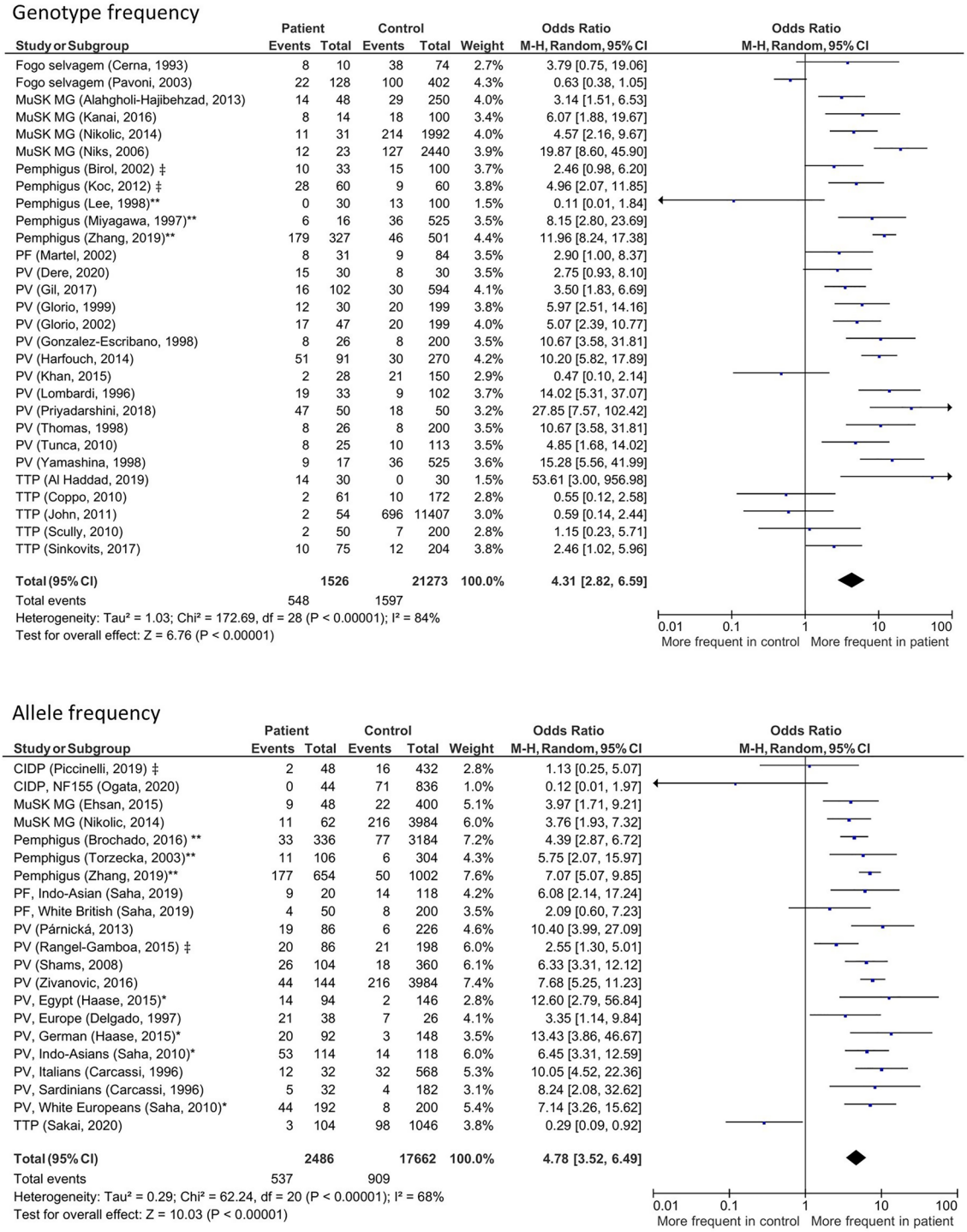

Figure 2. Forest plot depicting allele and genotype frequency of *HLA-DRB1*14* in patients with class I IgG4-AID. Cumulative meta-analysis with a random-effects model demonstrated a significant increased frequency in patients compared to controls. ‡ Study did not differentiate between disease subgroups of pemphigus or CIDP. * Study was included after discussion with W.B. **Study in which the same control group was used for pemphigus foliaceus and pemphigus vulgaris, here data was pooled for analysis.

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

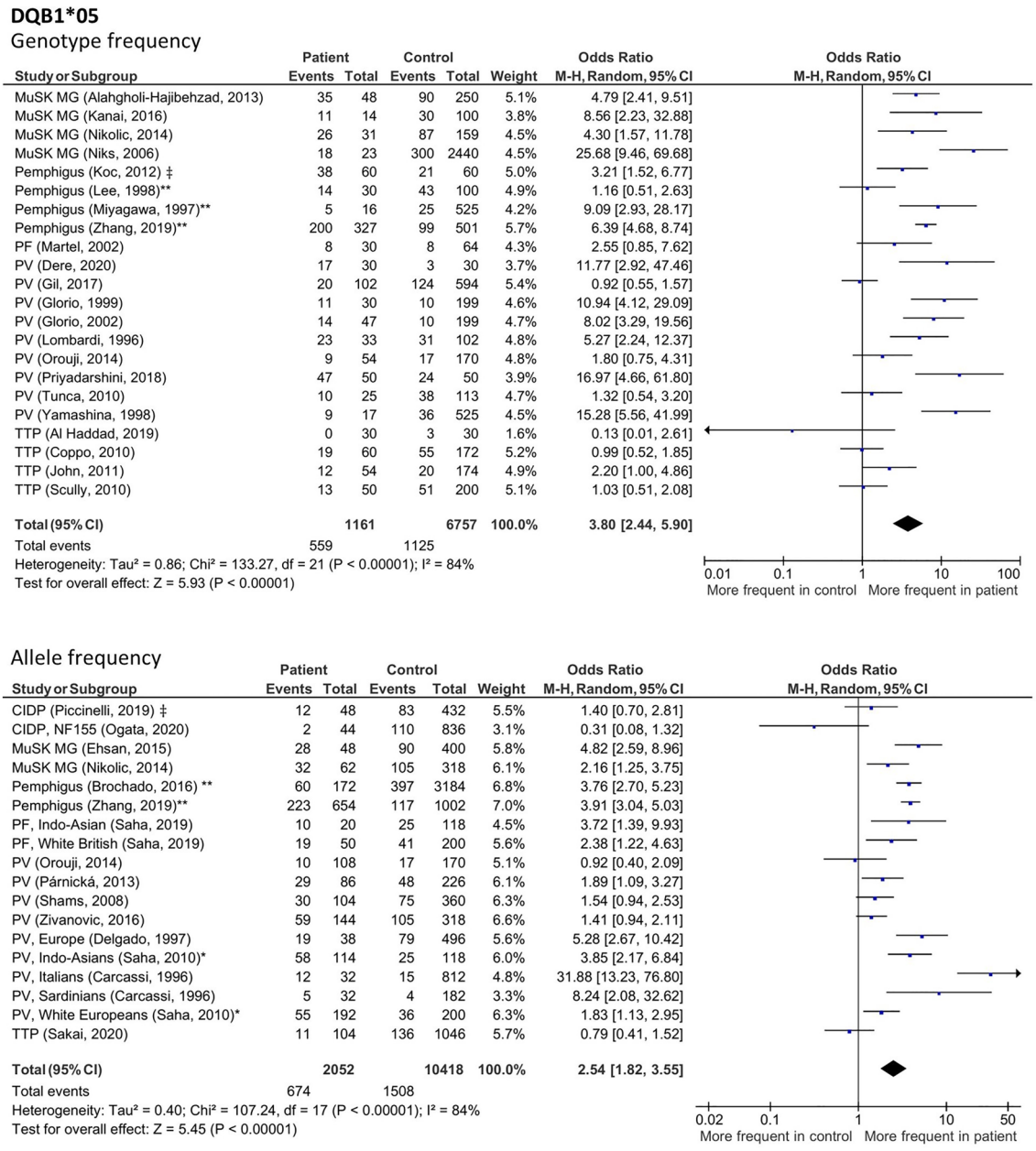

Figure 3. Forest plots of the allele and genotype frequency for *HLA-DQB1*05* in patients with class I IgG4-AID. Meta-analysis using a random-effects model demonstrated a significant increased frequency in patients compared to controls. ‡ Study did not differentiate between disease subgroups of pemphigus or CIDP. * Study was included after discussion with W.B. ** Study in which the same control group was used for pemphigus foliaceus and pemphigus vulgaris, here data was pooled for analysis.

with autoimmunity, is significantly more frequent in patients with IgG4-AID. This suggests it may be a genetic susceptibility factor for the production of IgG4 subclass antibodies. 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[39,40]. A

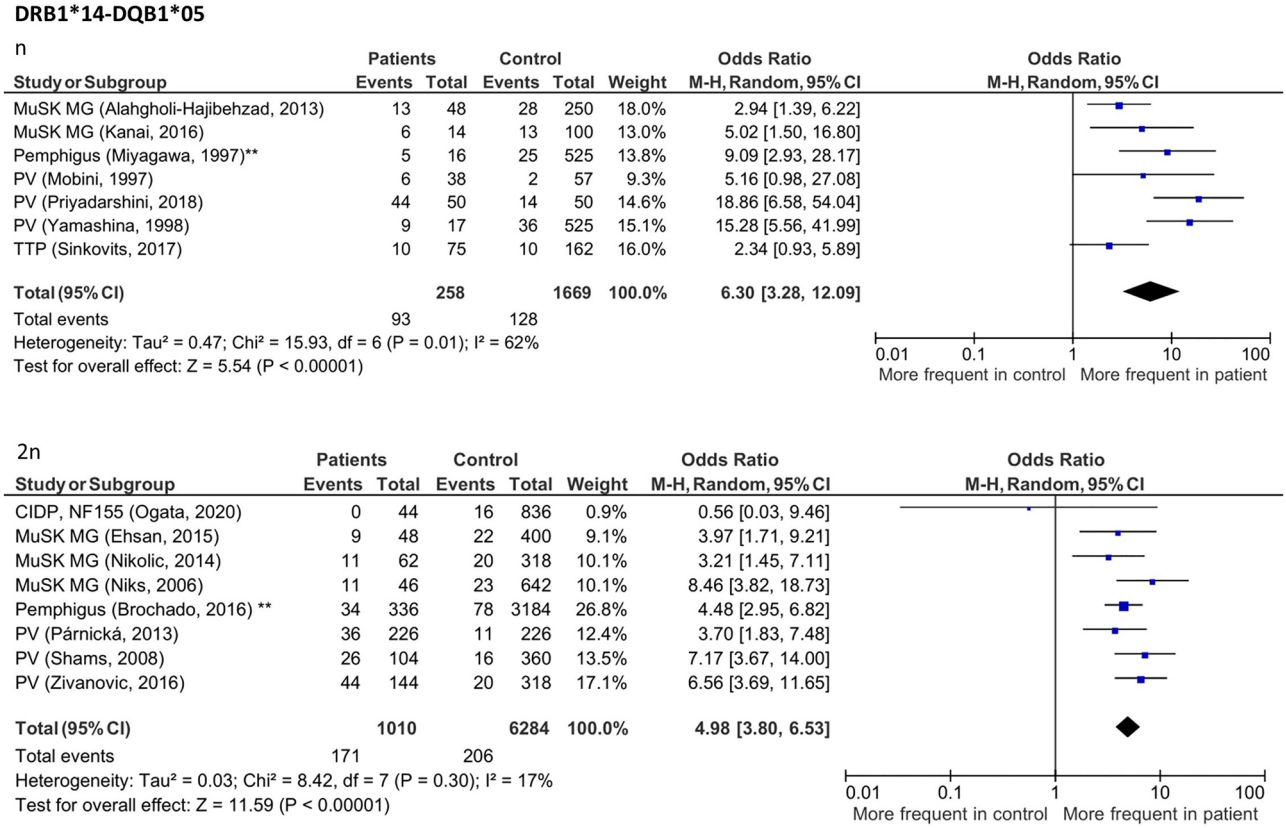

Figure 4. Forest plots of haplotype frequencies for *HLA-DRB1*14-DQB1*05* in patients with class I IgG4-AID. Meta-analysis using a random-effects model showed a significant positive association in patients throughout all six diseases. (n): haplotype frequency was defined as the number of individuals with a specific haplotype out of the number of total individuals; (2n): haplotype frequency was defined as the total number of a specific haplotype out of the total number of alleles of all study participants. ** Study in which the same control group was used for pemphigus foliaceus and pemphigus vulgaris, here data was pooled for analysis.

significant positive association of MuSK MG with *HLA-DRB1*14*, *HLA-DRB1*16* and *HLA-DQB1*05* could be confirmed in our study[40]. 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[48] from our analysis that was included in the Hong study[40] 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[39]. In contrast to the latter study, 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[39], 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[49] *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 may be due to 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[50]), 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[51,52], possible associations with HLA polymorphisms have only recently been determined and investigated. A (non-systematic) review[53] also reports a handful of individual papers with genetic associations of neurological IgG4-AID with *HLA-DQB1*05*, namely MuSK MG and anti-IgLON5 disease, but different alleles for IgG4-AID with antibodies against LGI1 (*HLA-DRB1*07:01*),

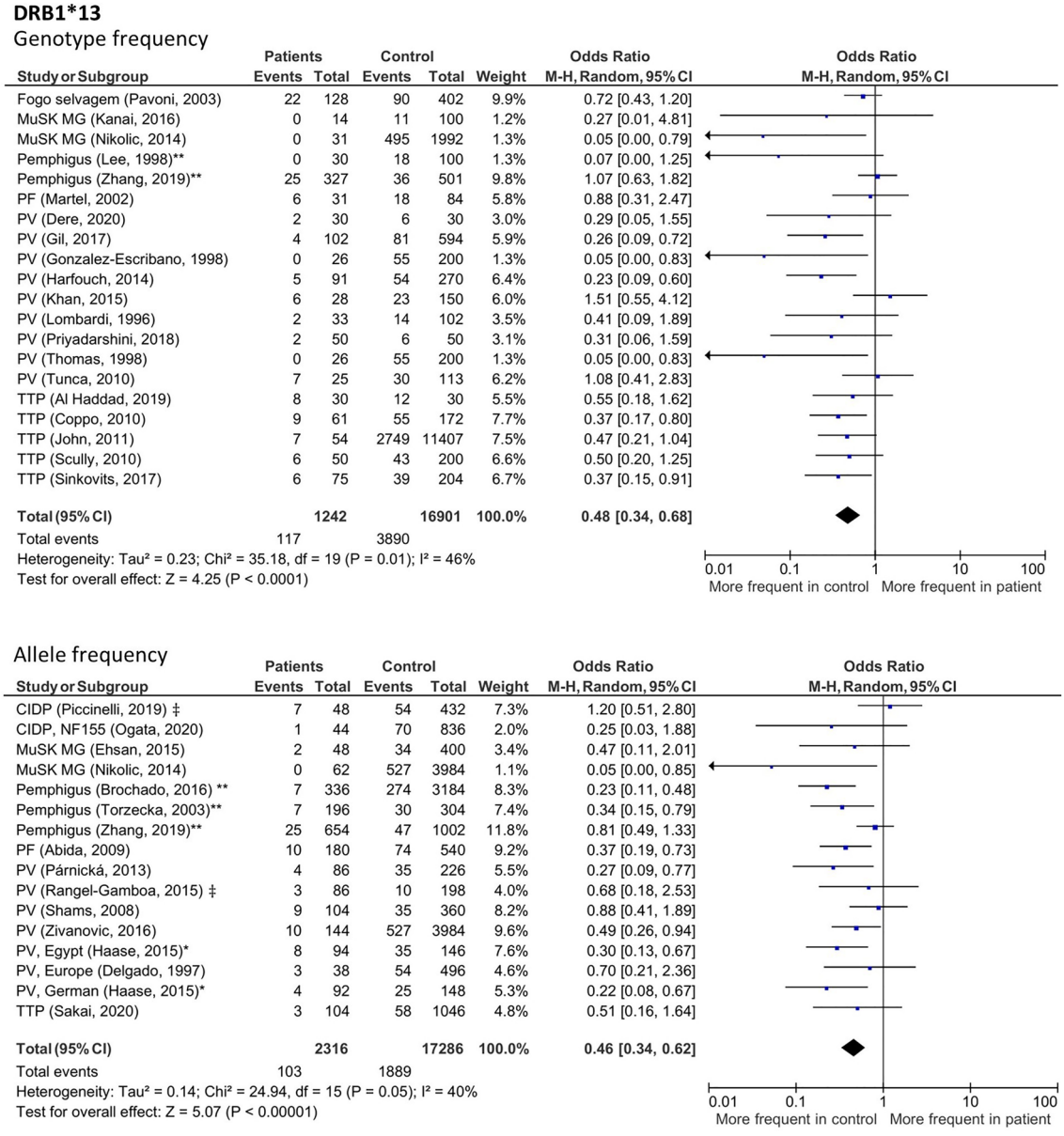

Figure 5. Forest plots of allele and genotype frequency of *HLA-DRB1*13* in patients with class I IgG4-AID. Meta-analysis using a random-effects model demonstrated a significant decreased frequency in patients compared to controls. ‡ Study did not differentiate between disease subgroups of pemphigus or CIDP. *Study was included after discussion with W.B. **Study in which the same control group was used for pemphigus foliaceus and pemphigus vulgaris, here data was pooled for analysis.

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 anti-

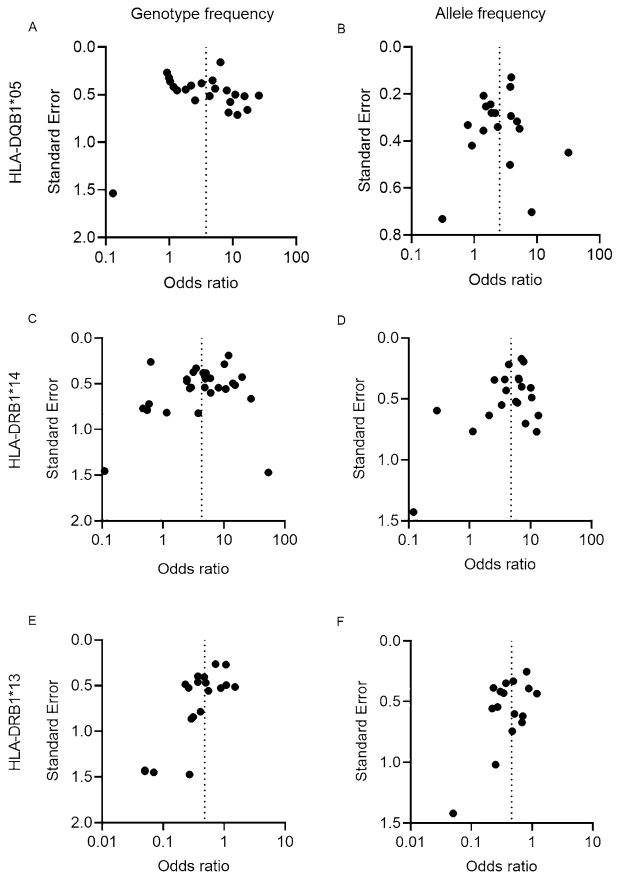

Figure 6. Funnel plot analysis of genotype and allele frequency data for *HLA-DQB1*05, DRB1*13* and *HLA-DRB1*14* in all IgG4 patients. A funnel plot analysis was undertaken to assess publication bias. Odds ratios were plotted against the standard error and the studies demonstrated symmetrical scattering along the funnel axis (pooled effect estimate from meta-analysis).

IgLON5 disease. In other autoimmune diseases, negative associations were found with the *HLA-DQB1*05:02* in T1D[54,55] and Sjögren's syndrome[56]. One single study reported *HLA-DQB1*05:02* to be positively associated with myelin oligodendrocyte glycoprotein-associated disorders (MOGAD), a rare neurological autoimmune disease[57]. Overall this suggests that *HLA-DQB1*05* may be specifically associated with IgG4-AID.

*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 MG[22], 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 hepatitis[58–60].

The *HLA-DRB1*03* allele frequency is increased in classical AID, including diabetes mellitus type 1[54,55], multiple sclerosis[61], neuromyelitis optica[62], systemic lupus erythematosus[63], Graves' disease[64] and Sjögren's syndrome[56], 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[58,65], but decreased in IgG4-AID (MuSK, TTP and CIDP)—with the exception of pemphigus, where a strong association was observed.

HLA polymorphisms and the induction of IgG4 autoantibodies. 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[66]. 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[22]. Different HLA alleles present distinct peptide repertoires, and may directly affect T-cell fate by inducing Tconv or Tregs and a proinflammatory or tolerogenic cytokine environment[24,25]. The latter also includes IL-10, which is an important regulator for IgG4 production[26–31]. MuSK MG patients with the *HLA-DRB1*14* allele were found to have higher autoantibody titers and higher levels of the cytokine IL-10 than patients with other HLA alleles[33], and elevated IL-10 levels were found in several IgG4-AID, including pemphigus[34,35], MuSK-MG[36] and thrombotic thrombocytopenic

purpura[37]. We hypothesize that *HLA-DRB1*14*, *HLA-DQB1*05* and/or other HLA alleles may have therefore a direct effect on T-cell fate, favoring IL-10 producing Tregs and the production of tolerogenic cytokines which then induce class switch of B-cells to IgG4 and the production of IgG4 autoantibodies. How may HLA variants affect T-cell fate? The mechanism could depend for example on characteristics of the peptide repertoires presented in the different MHC II variants[25,67–69], by differential interactions between the TCR and the HLA that may affect peptide recognition[70] or by different cell type specific expression levels of the MHC II depending on the HLA variant[71].

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-AID[14]. 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-AID[14]. In line with these findings, HLA associations also differ for IgG4-RLD, which was found to be associated with *HLA-DRB1*04 allele*[72].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[13,15,17].

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 and 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[73], 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 was 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 was pooled where possible[74–77] (exception: two studies from Serbia[78,79]). 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 patients, 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[1,12,16], 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[45].

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.

Data availability

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

Received: 28 October 2021; Accepted: 13 May 2022
Published online: 02 June 2022

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Acknowledgements
We are grateful to Alexander Zimprich for scientific advice.

Author 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., R.H., 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 No. T996-B30). R.H. was funded by a grant from the Austrian Science Fund (FWF) (Grant No. I4685-B, SYNABS).

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-13042-2.

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