Network meta-analysis of genes highly correlated with the onset of bullous pemphigoid

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Introduction. Study on genes highly related to the pathogenesis of bullous pemphigoid
Methods. Search papers in PubMed, Web of Science, Cochrane Library, Google Scholar, CNKI, Wanfang, Embase, and VIP databases. The search time limit is from the establishment of the database to May 2023. Randomized controlled trials (RCTs) were collected, in which the subjects were BP patients, and the experimental content was to detect BP-related genes. Meta-analysis and network meta-analysis were performed.
Results. We screened out 8 studies, among which traditional Meta-analysis results showed that the genes related to BP in 8 studies belonged to HLA-DRB1*. The network results show that 4 studies have proven that DRB1*10 is a highly related gene to BP. Three of the studies showed that DQB1* 0301 is also the main related gene of BP.
Conclusion. The known and determined gene that is highly related to BP is DRB1*10. And DQB1* 0301 is also the main related gene of BP.
Keywords. bullous pemphigoid, related genes, HLA-II, Meta-Analysis

INTRODUCTION

Pemphigoid (Pg) is a potentially fatal subepidermal blistering autoimmune disease. Most patients are elderly (Sagi et al. 2011). There are two main phenotypes of Pg, namely BP and mucosal pemphigoid (MMP), also known as cicatricial pemphigoid (Hammers and Stanley 2020).

Elderly patients are the main affected population of this disease, which is manifested by severe bullae on the entire skin and limbs(Amber et al. 2017; Tolaymat and Hall 2023). The main manifestation is severe itching at the location of the bullae [3]. After the blister ruptures, it is easy to leave a large and easily infected wound. This is because the composition of the blister fluid is very similar to that of serum, so it is easy to be infected(Daniel and Murrell 2019; Didona and Di Zenzo 2018). When widespread infection occurs, the patient's mortality rate will reach 19%-30% (Daniel and Murrell 2019). Post-inflammatory hypopigmented or hyperpigmented macules often remain after the lesion heals (Tolaymat and Hall 2023).

[3] Bullous pemphigoid (BP) is an autoimmune bullous disease that occurs in the elderly. Its clinical manifestations are generalized tension bullae throughout the body, negative Nissl sign, and repeated delays in the course of the disease, which seriously threatens the patient's life and health.

[4] BP is also considered an autoimmune disease. Because immunopathology shows deposition of IgG and/or C3 in the basement membrane zone and autoantibodies against basement membrane zone components are also present in the serum, the disease has a good prognosis. The specific pathogenesis of BP is unclear, given the presence of autoantibodies against the basement membrane zone in the serum of most patients. Immunoelectron microscopy also shows that this antibody is bound to the clear layer of the basement membrane zone, so this disease is also called an organ-specific autoimmune disease. Studies have found that BP is mainly related to the autoimmune response to hemidesmosomal proteins (Amber et al. 2017; Witte et al. 2018). Circulating autoantibodies in BP patients exhibit heterogeneous specificity for several hemidesmosomal components, including BP230, an intracellular component of hemidesmosomal plaques, and the transmembrane protein BP180/collagen type XVII (Fang et al. 2018b; Kamaguchi and Iwata 2019). In addition to being mainly related to hemidesmosome autoantibodies, the disease is also related to complement activation at the dermal-epidermal junction and dermal granulocyte infiltration.

The causes of disease can be mainly divided into two aspects: internal causes and external causes. Internal causes are so-called genetic factors, while external causes are environmental factors. These include pathogenic microorganisms, living environment, improper diet, drug abuse, irregular work and rest, etc. The complex interactions between genetic factors and environmental factors have long exceeded people's imagination and understanding. To us, some sporadic diseases seem to be accidental, but their essence is composed of many necessities.

The HLA complex is also known as the human major histocompatibility complex (MHC). This gene complex is a highly polymorphic genomic region of over 3Mb on chromosome 6p21. And it is highly enriched in immune response genes. MHC genetic variation is the highest in the human genome and is associated with tissue transplant compatibility and many genetic diseases. HLA can be divided into 4 types, including HLA class I and class II alleles. Among them, the class I gene region is located at the distal end of the centromere, and mainly includes HLA-A, B, C, E, F, G, H, K and L loci and other newly proposed new loci recently. Class II alleles are located proximal to the centromere and are the most complex structural region, mainly composed of three subregions: DR, DQ, and DP. Research has found that HLA complexes may be closely related to autoimmune diseases. One study used GWAS to study susceptibility genes for systemic lupus erythematosus in four Latin American countries. HLA-related alleles such as DQA1*01:02, DQB1*06:02, and DRB1*15:01 were found to have the strongest association with systemic lupus erythematosus. It was also found that DQB1*03:01 and DQB1*03:02 may have a protective effect in the Mexican population (Alarcón-Riquelme et al. 2016). In Asian populations, it has also been found that HLA-DQA1 (rs9271366) can increase the risk of lupus erythematosus, while HLA-DQA2 (rs9275328) can reduce the risk of lupus erythematosus (Chai et al. 2012). At the same time, some researchers also found that HLA-DQA2 is associated with the onset of Sjogren's syndrome(Fang et al. 2015). These all indicate that HLA alleles are highly correlated with autoimmune diseases. In the study of BP-

related genetic susceptibility gene loci, it was found that HLA-DQB1*0301 is closely related to the onset of BP(Zakka et al. 2011).

Someone studied the genetic factors of BP, and they found that HLA-A*11:01, HLA-B*37:01, HLA-G*01:01, HLA-G*01:06, HLA-DQA1*01:05, HLA -DQA1 * 05:05, HLA-DQA1 * 05:08, HLA-DQB1 * 03:01, HLA-DQB1 * 05:01, HLA-DRB1 * 10:01 are significantly positively correlated with the onset of BP. And HLA-DQA1 * 01:02, HLA-DQA1 * 01:03, HLA-DQB1 * 02:02, HLA-DRB1 * 07:01 are significantly negatively correlated with the onset of BP (Fang et al. 2018a). Azis et al. also found that alleles HLA C*17, DQB1*03:01, DQA1*01:03 and DQA1*05:05 are closely related to the onset of BP in the Brazilian population (Chagury et al. 2017). At the same time, some people have found that polymorphisms in the ABCB1 gene not only affect the therapeutic effect of drugs on BP, but also affect the development of various diseases such as BP (Rychlik-Sych et al. 2018; Rychlik-Sych et al. 2017).

Network Meta analysis mainly uses indirect comparison techniques to simultaneously comprehensively evaluate and rank all interventions in the same body of evidence. The so-called "indirect comparison" refers to the evaluation of the effects of two different interventions that lack direct comparative clinical evidence with the help of other relevant studies that have been carried out.

As we have described above the genes related to the pathogenesis of BP, there has been no research on integrating these genes. Therefore, this study hopes to conduct research on BP-related genes published in domestic and foreign professional journals in recent years by searching relevant literature. Use Network Meta (Brignardello-Petersen et al. 2018; White 2015) and traditional Meta analysis methods to further understand the BP related genes, and the functions of these genes. This can provide targeted treatment for future clinical treatments, and select different clinical assessment and treatment methods for different genotypes of BP.

MATERIALS AND METHODS

Literature Search Strategy

Specific and systematic searches were carried out on the webpage, databases PubMed, Embase, Web of Science, Google Scholar, CNKI, Wanfang and VIP databases; the search terms were: as “bullous pemphigoid ”,"related genes ” and "HLA-II ” . the search time limit is from the establishment of the database to May 2023, the search results are limited to clinical research, and are not restricted by language or race, and manual searches are performed by reading relevant works and summarizing references. Search strategies need to be adjusted for compling with the relevant regulations in every database.

Literature Inclusion Criteria

(1) Randomized clinical trial (RCT), no matter whether it is single-blind, double-blind or non-blind. (2) The trial includes a parallel control group. (3) The subjects of the study are patients with BP. (4) Outcome indicators include all BP related genes.

Literature Exclusion Criteria

(1) Non-RCT study. (2) Duplicate publications or data duplication. (3)Studies without a control group. (4) Animal experiments. (5) Research methods, results, and conclusions that cannot be explained or do not correspond to each other. (6) Statistical methods and data analysis that have obvious errors. (7) Literature with imperfect experimental design. (8) Literature for which data could not be extracted or data were incomplete. (9) The test results and conclusions are obviously inconsistent with the reality. (10) Outcome indicators do not include any BP related genes.

literature Screening and Data Extraction

literature screening : Two researchers on the basis of the inclusion and exclusion criteria independently screened the literature, targeting titles and abstracts, including primary screening, secondary screening, and cross-checking to determine possible relevant studies. Firstly, conduct a preliminary screening: read and analyze the titles and the abstracts of the articles, and eliminate the literature that apparently does not including in the inclusion criteria or duplicate studies. Second, re-screening: read the full text of the papers obtained from the primary screening, and then further screen the literature according to the inclusion criteria. Finally, check the papers: cross-check the obtained literature. For documents with incomplete or questionable information, it is necessary to contact the corresponding authors for detailed information. Finally, it was judged whether the literature was included in the study. If two researchers have different opinions on some articles, they will discuss together until a consensus is reached; if no consensus can be reached, a third researcher will participate in the judgment. Finally, the selected documents are included in the table for extraction and summary.

Data extraction: The content of data extraction includes title, first author, year of publication, research type, and observation indicators.

Efficacy Index

① HLA-II

② BP related genes: HLA-DRB*

Quality Evaluation

Eligible literature was assessed for methodological quality using the Jadad scoring scale, scored on a scale of 1 to 7, assessing random sequence generation, blinding, allocation concealment, and patient withdrawal or withdrawal. A Jadad score of 4–7 was considered high-quality literature, and 1–3 was considered low-quality literature.

Statistical Method

the analyzes were pooled using RevMan 5.4 and Stata statistical software, with ratio (OR) and 95% confidence intervals (CI) for continuous data. The heterogeneity index (I2) is used to evaluate the heterogeneity of the treatment effect. When there is no

significant heterogeneity among the studies (I2<50%), the fixed effect model is used; when there is significant heterogeneity among the studies (I2 ≥50%), use a random effects model. Egger's test was used to assess the potential risk of publication bias, with a test level of P = 0.05. Sensitivity analysis were performed on factors that may cause heterogeneity, and literature with high sensitivity was excluded. A descriptive analysis was performed for those who could not perform a meta-analysis.

RESULTS

Literature search results

Systematically retrieved the original literature on Bullous pemphigoid, HLA and related gene published in databases such as CNKI, Wanfang, VIP, EMBASE, web of science, and PubMed, using subject headings combined with free words for systematic retrieval, and manually retrieved 558 literature; 48±138 articles that were repeatedly published or animal experiments were obtained, and 192 articles were obtained; after reading the full text, 132±38 literatures that could not obtain the full text and incomplete experimental design were eliminated, and finally 8 literatures were obtained(Esmaili et al. 2013; Jiang Haiyan et al. 2005; Jin Yan et al. 2003; Jin Yan et al. 2002; Okazaki et al. 2000; Su Riguga et al. 2015; Zhang Kejin et al. 2008; Zhou Shuhua et al. 2007). The literature screening process is shown in Fig 1.

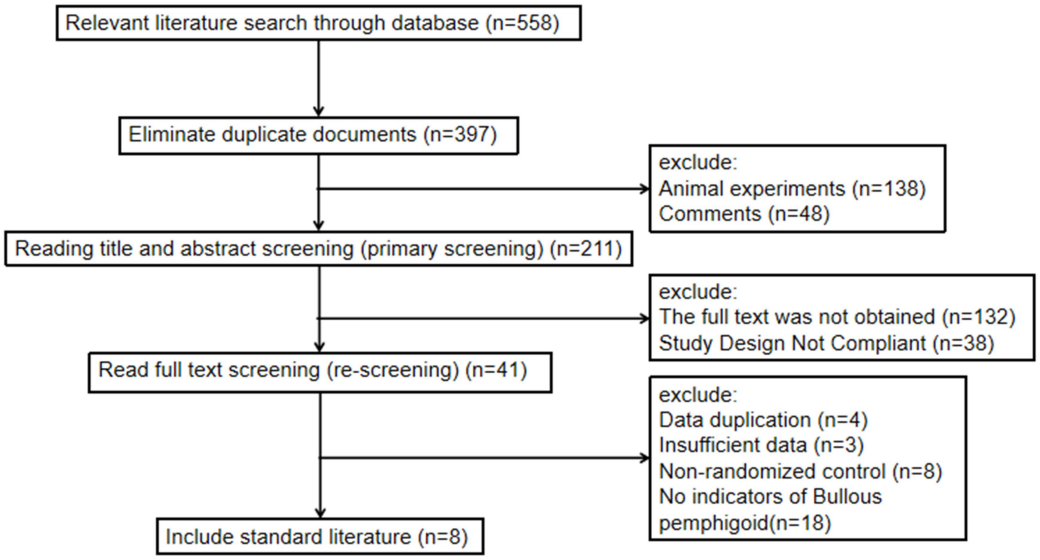

Figure 1 flow chart of literature search of network meta analysis.

Basic characteristics and quality evaluation of included literature

The demographic characteristics and baseline characteristics of the patients are shown in Table 1. The Jadad score of the included literature was 4 to 5, which was high-quality literature, and none of the 8 included studies had withdrawal or withdrawal.

Researcher	Number of cases(BP group/control)	Age range (years)	Disease course	Gene name	Identification method	Efficacy index	Jadad score
Zhang Kejin（2008）	43/125	5-83	-	DRB1*10, DRB1*11	PCR	①②	4
Jiang Haiyan（2005）	30/168	37-83	-	DRB1*110X,DRB1*120X	PCR-SSP	①②	5
Zhou Shuhua (2007)	98/140	44-83	-	DRB1*10, DRB1*0302	PCR	①②	5
Su Riguga (2015)	30/30	57-85	-	DQB1* 0301	PCR-SSP	①②	4
Jin Yan (2003)	112/300	-	-	DRB1*04, DRB1*1001	PCR	①②	5
Jin Yan (2002)	112/300	66.64±14.09	5.55±144	DRB1*10	PCR-SSO	①②	5
Aiko Okazaki (2000)	23/23	-	-	DRB1*04, DRB1 *1101	PCR-RFLP	①②	5
Nafiseh Esmaili（2013）	50/180	-	-	DQA1*0501,DQB1*0301,DQB1*0401	PCR	①②	5

Table 1. Basic characteristics and Jadad score of included studies. “-”not available.

Risk of bias results

In order to assess the risk of bias, we used the Cochrane risk assessment tool to conduct an item-by-item evaluation of each included study through the following 6 evaluation criteria.

1) Random sequence generation
2) Allocation concealment
3) Blinding of participants and personnel
4) Blinding of outcome assessment
5) Incomplete outcome data
6) Selective reporting

Analysis of the results for risk of bias (Figs 2, 3) indicated that each of the included studies correctly described the generation of the random sequence and had relatively comprehensive outcome data. As for Blinding of outcome assessment, none of the

articles assessed outcome blinding. Since the studies selected this time are mainly related to genes, the blinding of patients in clinical practice is not applicable in this study.

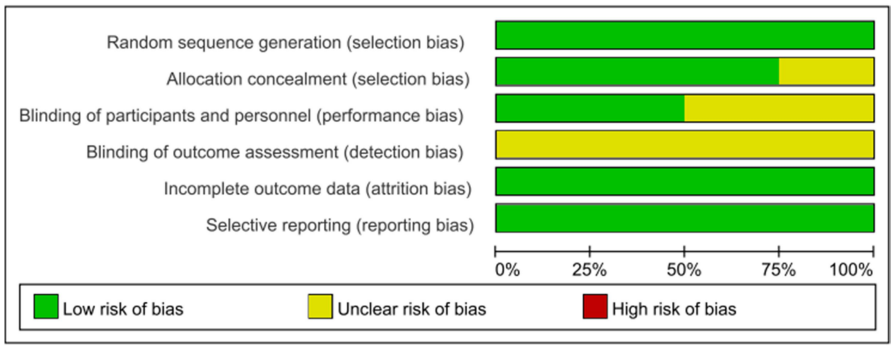

Fig 2. Risk of bias bar plot

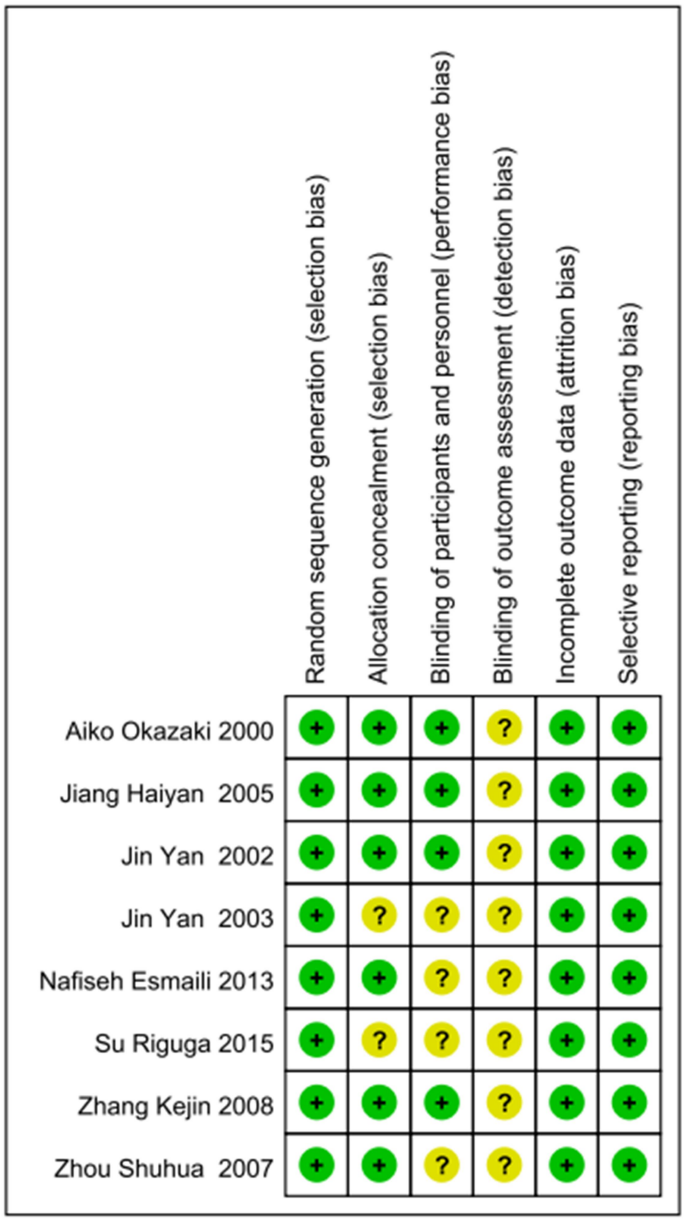

Fig 3. Risk of bias summary

Efficacy index results

HLA-II

According to Figure 4 it shows that in the 8 studies the most frequently occurring HLA-II class genes of the BP group and the control group (RR=2.55, 95% CI 2.06-3.15).

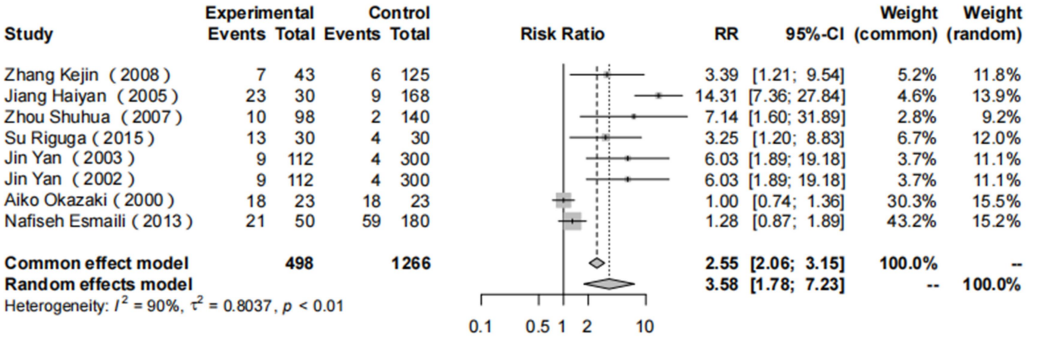

Fig 4. Meta-analysis forest plot of the most frequently occurring HLA-II class genes in 2 groups.

Dyspepsia

8 included studies specifically described the second most frequently occurring HLA-II gene(HLA-DRB*) in the BP and control groups (RR=2.06, 95% CI 1.67-2.53) (Fig 5).

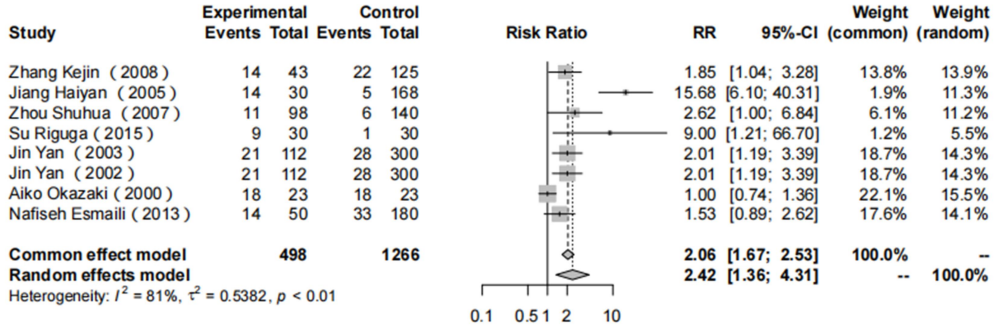

Fig 5. Meta-analysis forest plot of the second most frequently gene in 2 groups.

Network meta graph analysis

The Network Meta diagram of different genes is shown in Figure 6. All studies were based on the HLA-II gene. The HLA-DRB study had the largest total sample size (P < 0. 01).

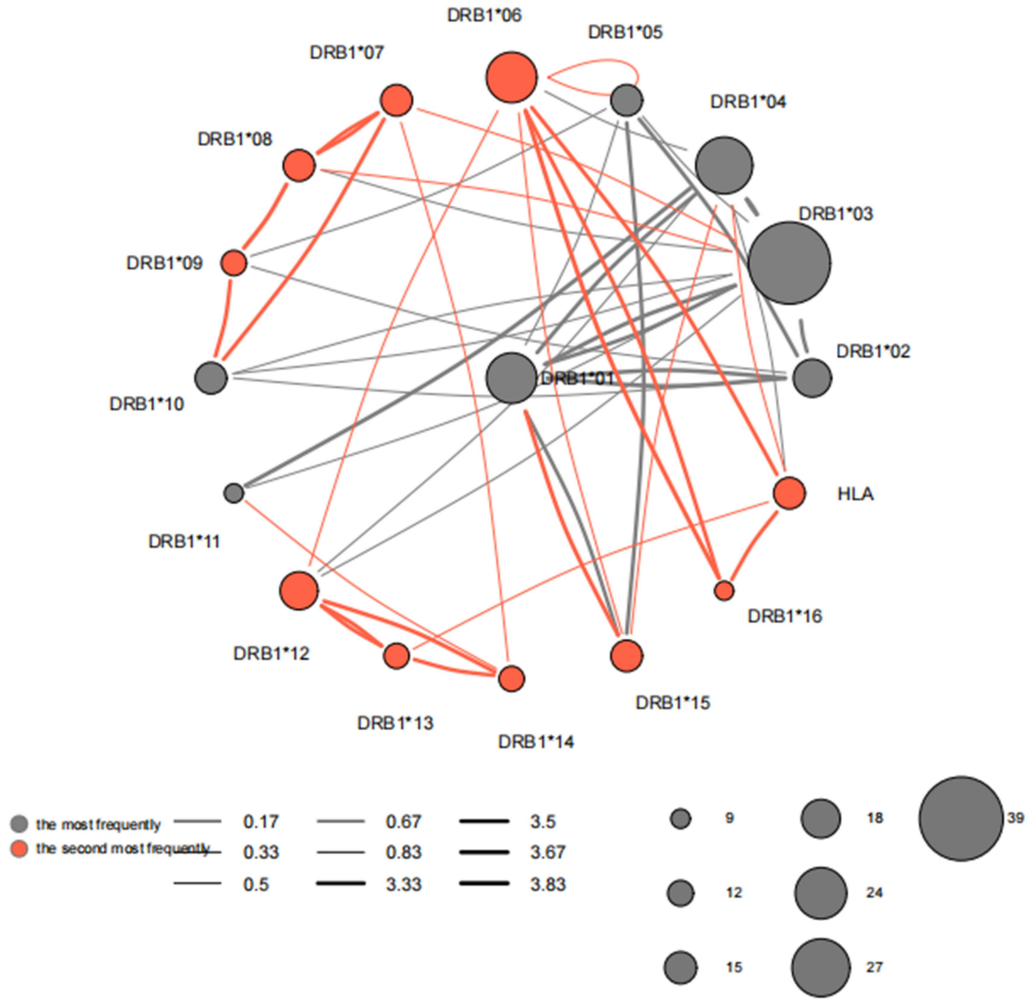

Fig.6 Network Meta relationship diagram

DISCUSSION

Bullous pemphigoid (BP) is an autoimmune skin disease (Hammers and Stanley 2020). It is more common in people over 60 years old and is easy to relapse. If the disease is too severe and left untreated, it can lead to death from co-infection and multiple organ failure (Pennington et al. 2021). Studies have found that HLA-DRB1 and DQB1 alleles are related to BP, but the susceptibility genes of BP patients in different ethnic groups, races and regions are not the same.

This study collected all current detection tests for genes related to BP disease. The result obtained is that traditional Meta-analysis results show that there are very few reports on the correlation between HLA-I genes and BP, and most reports have no correlation between HLA-I genes and BP (Lo Schiavo et al. 2013). At present, the most reported BP susceptibility gene is the HLA-DR/DQ allele, but the conclusions are not exactly the same.

(Okazaki et al. 2000) used the PCR-RFLP method to conduct HLA-DR and DQ genotype analysis and found that the frequency of HLA-DRB1* 04, DRB1* 1101 and DQB1* 0302 in Japanese BP patients was significantly higher than that in the normal control group. Among them, the frequency of DRB1 * 04 /DQA1 *0301 /DQB1 * 0302 and DRB1 * 1101 /DQA1 * 0505 /DQB1* 0302 haplotypes and DRB1* 04 /DQA1* 0301 /DQB1* 0302 haplotypes was significantly higher than that in the normal control group. . (Esmaili et al. 2013) found that HLA-DQB1*0301 is a genetic susceptibility gene for Iranian BP patients, while HLA-DRB1 has no correlation with BP. There are similar reports in China. Some scholars used the PCR-SSOP method to conduct HLA-DRB1, DQA1, and DQB1 allele typing on BP patients in Shanghai and found that HLA-DRB1* 1001 and DRB1* 04 may be susceptibility genes for BP patients in Shanghai. (Zhou Shuhua et al. 2007) found that HLA-DRB1*10 may be the genetic susceptibility gene for BP in Shandong Han people. (Zhang Kejin et al. 2008) reported that there is no correlation between BP patients in Shandong Han and HLA-DRB1. In addition, a study in Inner Mongolia showed that HLA-DQB1* 0301 may be the genetic susceptibility gene of BP patients in Inner Mongolia Han, while HLA-DRB1* 16 and DQB1* 0501 may be protective genes in Inner Mongolia Han(Su Riguga et al. 2015).

According to all the reports retrieved by this study, the BP-related genotypes studied are basically HLA-DRB1*. However, the string search results show that there are also HLA-A, HLA-G, HLA-F and other related genes (Fig 7). At present, domestic and foreign studies have shown that HLA-A and HLA-G may also be related to BP, but there are no very clear research results on their specific correlation. In addition to HLA-DQB, there are also related genes such as HLA-DQA1, HLA-DQA2, HLA-DRA1*, etc. (Fig 8). According to the relevant literature used in this study, we can know that HLA-DRB1 is also involved in BP disease. The remaining genes need to be proven in future clinical experiments.

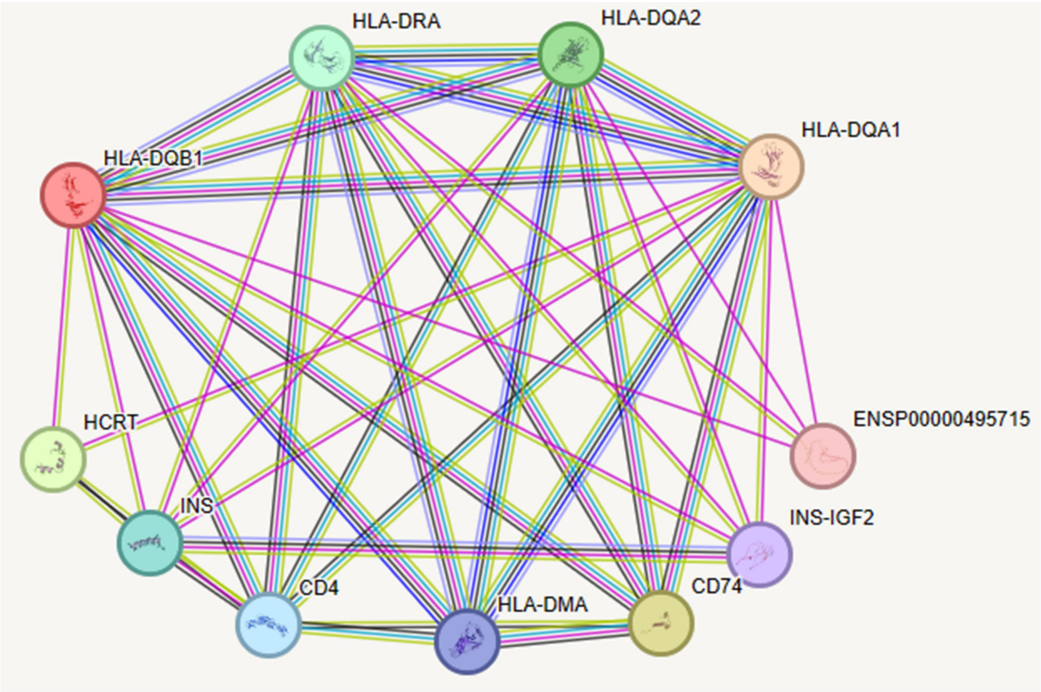

Fig 7.String search result of HLA-DRB related genes

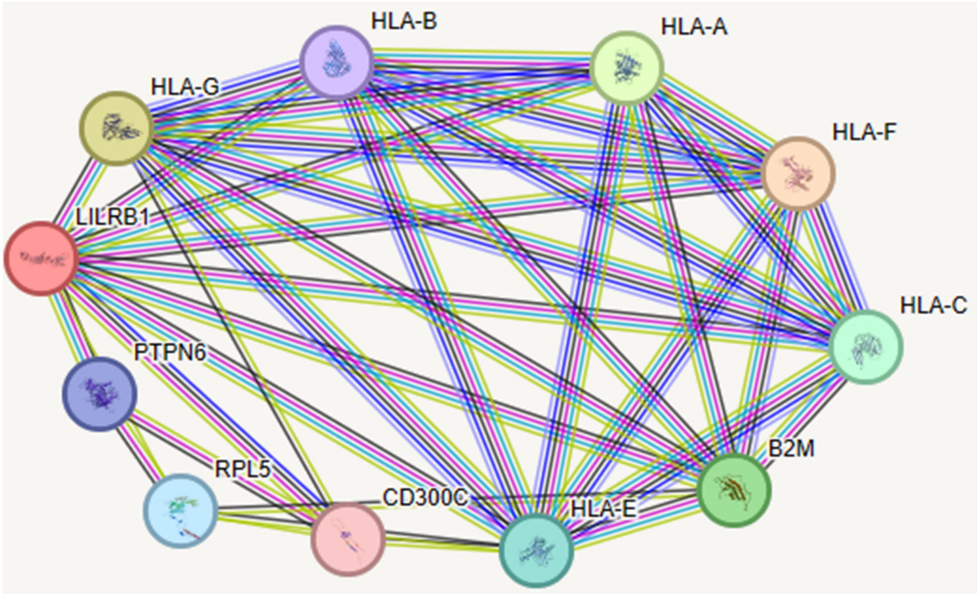

Fig 8.String search result of HLA related genes

The main advantage of Network Meta-analysis is to make up for the shortcomings of

traditional Meta-analysis, and to study the effect relationship between any two in the body of evidence. The results of the comparison with placebo by Network Meta-analysis in this study were similar to those of traditional Meta-analysis, both suggesting that HLA-related genes are highly related to BP, but it depends on the specific genes of different ethnic groups.

As we all know, BP is an autoimmune disease, and its main pathogenic mechanism is the production of autoantibodies against hemidesmosomes at the dermal-epidermal junction. A series of reasons, including the production of this antibody and the activation of the subepidermal complement system, lead to the formation of blisters. But this is only what we know about BP from the perspective of the immune system, but it is far from enough to understand the disease. For example, some people suffer from pemphigoid, but different people have different tolerances for drug treatment and different effects of drugs. If we can study clearly all the changes in genetic material related to BP, such as gene mutations, etc. In this way, not only can the patient's genes be detected in a targeted manner to determine the patient's tolerance to the drug and the possible efficacy of the drug. We can also detect an individual's DNA sequence to determine whether he or she will develop pemphigoid in the future, or predict the probability of developing pemphigoid, so that we can give people early warning and prepare in advance.

Therefore, the meta-analysis of this study can more comprehensively review the genetic research on BP over the years. Compared with previous meta-analyses, the advantages of this study are: (1) The search is more comprehensive, including all RCTs comparing 7 GLP-1 RAs with placebo and 5 traditional hypoglycemic drugs. (2) During the analysis process, subgroups were studied according to the course of treatment to make the analysis more detailed. (3) Introduce Network Meta-analysis when there are multiple interventions, lack of direct comparative evidence, and traditional Meta-analysis cannot be performed. Simultaneous evaluation and risk ranking of multiple interventions with the help of indirect comparison technology is of great significance to guide clinicians in individualized drug administration.

However, this analysis is still based on the research level, and it is not possible to analyze each study based on the individual level. Furthermore, the included RCTs were not short-term, small-sample studies reporting DSAE as the primary outcome measure. Different RCTs may have inconsistent criteria for judging outcome events, so there are inevitable biases, and the research results still need to be further explored and supplemented.

In summary, the results of this study suggest that the gene highly related to BP is DRB1*10. And DQB1* 0301 is also the main related gene of BP. However, large prospective studies are still needed to determine whether other homogeneous families or alleles are also associated with BP, and whether the association is strong. Genes that are positively or negatively related to BP are also targets that can be studied. Whether related genes are inconsistent among different races and regions is also an experiment that can be studied. As a new evidence-based evaluation method, network

meta-analysis can provide new ideas for other related research. Research on related genes can also provide a certain molecular basis for clinical treatment.

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