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DATABASES

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UVEOGENE: An SNP database for investigations on genetic factors associated with uveitis and their relationship with other systemic autoimmune diseases

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Abstract

Uveitis is an intraocular inflammatory disease which can lead to serious visual impairment. Genetic factors have been shown to be involved in its development. However, few databases have focused on the information of associations between single nucleotide polymorphisms (SNPs) and uveitis. To discover the exact genetic background of uveitis, we developed an SNP database specific for uveitis, "UVEOGENE," which includes 370 genes and 918 SNPs covering 14 uveitis entities and 40 populations from 286 PubMed English-language papers. Stratification analyses by gender, HLA status, and different clinical features were also extracted from the publications. As a result, 371 associations were judged as "statistically significant." These associations were also shared with Global Variome shared Leiden Open Variation Database (LOVD) (https://databases.lovd.nl/shared/genes). Based on these associations, we investigated the genetic relationship among three widely studied uveitis entities including Behcet's disease (BD), Vogt–Koyanagi–Harada (VKH) disease, and acute anterior uveitis (AAU). Furthermore, "UVEOGENE" can be used as a reliable and informative resource to identify similarities as well as differences in the genetic susceptibility among uveitis and other autoimmune diseases. UVEOGENE is freely accessible at http://www.uvogene.com.

KEYWORDS
autoimmune disease, database, immune system pathways, single nucleotide polymorphism, uveitis

1 | INTRODUCTION

Uveitis is an intraocular inflammation leading to blindness worldwide (Suttorp-Schulten & Rothova, 1996). Although the inflammation can be caused by a variety of factors (infections, systemic diseases, organ-specific autoimmune processes, trauma, and primary or secondary ocular neoplasms) (Denniston et al., 2012; Dick et al., 1999; Islam et al., 1994; Kerr, Raveney, Copland, Dick, & Nicholson, 2008; Mandelcorn, 2013), the exact pathogenesis of the disease remains unclear. Accumulating evidence indicates that genetic factors are involved in the pathogenesis of a number of uveitis entities (Du, Kijlstra, & Yang, 2016). To date, large efforts have been made on the study of the genetic background of uveitis.

With the advantage of next-generation sequencing (NGS) technologies (Burillo-Sanz et al., 2017; Kirino et al., 2013), many associations between single nucleotide polymorphisms (SNPs) have been identified as susceptibility factors for a number of diseases. To date, several databases of SNPs have been constructed, based on published data for a variety of diseases, such as PESNPdb (Tuteja, Cheng, Papadakis, & Bejerano, 2012) for Pre-eclampsia (http://bejerano.stanford.edu/pesnpdb) and RAvariome (Nagai & Imanishi, 2013) for rheumatoid arthritis (RA) (http://hinv.jp/hinv/rav/).

To the best of our knowledge, though some existing publicly available variant databases provide variant associated with different disease (such as LOVD: http://grenada.lumc.nl/LSDB_list/lsdbs and ClinVar: http://www.ncbi.nlm.nih.gov/clinvar), there is no variant database that specifically addresses uveitis-related genes and SNPs. We therefore found it necessary to construct a specific database for uveitis, thereby facilitating the research on genetic mechanisms involved in uveitis.

For this purpose, we constructed the first SNP database for uveitis, "UVEOGENE." In this database, we provide a reliable set of comprehensive genetic associations for researchers focused on uveitis and other immune-driven disease. All data of associations are publicly available from the website. Furthermore, 371 associations were judged as significant associations. These "significant associations" were submitted to "Global Variome shared LOVD" following its specific standard. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and the construction of networks were also performed on three widely studied uveitis entities to identify their similarities and differences. Additionally, comparing genetic risk variants involved in Behcet's disease (BD) and Vogt–Koyanagi–Harada (VKH) with those in RA from the RAvariome database was performed to investigate similarities as well as differences in the susceptibilities between uveitis and RA.

2 | METHODS

2.1 | Data sources

We collected 289 English-language original articles ranging from January 2001 to March 2018 from the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed). The studies included had to meet the following criteria: (i) case-control study; (ii) evaluation of the association between SNPs and uveitis entities; (iii) detailed genotype or allele data should be available; (iv) exclusion of data from meta-analysis. Hardy–Weinberg equilibrium (HWE) was not evaluated for each included study by the Chi-squared test, because some studies did not provide the number genotypes in the cases and controls (mainly in genome-wide association studies [GWASs]).

The basic information of SNPs (gene ID, RefSNP Alleles, Functional Consequences, Global Minor allele frequency, SNP chromosome position, DNA change, and description of gene) were collected with reference to the PubMed database. We manually extracted the data from these papers (method, related disease, population, the number of allele/genotype in the cases and controls, PubMed Unique Identifier). Not only statistically significant but also statistically not significant association results, stratification analyses by the gender of subjects, different uveitis entities, and clinical features were extracted manually from the full manuscript text, tables, and supplementary data. To avoid problems concerning bias between candidate gene and GWASs, we re-evaluated the associations by using two separate significance levels as mentioned in the RAvariome database. For GWASs, if the corresponding *P*-value was <5.0E-08, the result of the statistical analysis was judged as significant evidence of a strong association, and a *P*-value between 1.0E-05 and 5.0E-08 was judged as significant evidence of a moderate association. In order to investigate the similarities and differences in the genetic susceptibility between BD, VKH disease, and RA, the result of the statistical analysis was judged as significant evidence of association in this study, if the corresponding *P*-value was <1.0E-05. For selected SNPs, associations were judged as "significant" following Bonferroni correction for multiple comparisons when the *P*-value was <0.05."

In addition, the sharing of data following specific standards will facilitate the research focusing on the relationships of genetic background in the different systemic diseases which seem to have similar clinical features. Thus, we also shared the data of these "significant associations" with "Global Variome shared LOVD" which is a platform storing gene sequence variation associated with different human diseases and phenotypes (Fokkema et al., 2011). The "significant associations" were submitted to Global Variome shared LOVD according to the LOVD system (currently version 3.0, build 12) (Vihinen, den Dunnen, Dalgleish, & Cotton, 2012).

2.2 | Meta-analysis on the association of rs1800629 with BD

In previous studies, no strong association was found between rs1800629 and the susceptibility to BD except in one study that had a $P = 0.01$ (Ahmad et al., 2003; Arayssi et al., 2008; Ates, Dalyan, Hatemi, Hamuryudan, & Topal-Sarikaya, 2010; Bonyadi et al., 2009; Chang et al., 2007; Dilek et al., 2009; Duymaz-Tozkir, Gul, Uyar, Ozbek, & Saruhan-Direskeneli, 2003; Kamoun, Chelbi, Houman, Lacheb, & Hamzaoui, 2007; Lee, Kim, Lee, Park, & Song, 2003; Park, Kim, Nam, Bang, & Lee, 2006; Radouane et al., 2012), due to small sample size and the fact that only a single ethnic population was included. Based on the exact content of SNPs in this database, we describe an example of a meta-analysis of rs1800629 to test the utility of this database with our GWAS study on BD (unpublished data) in a Chinese population. Genome-wide genotyping in this study was performed using the HumanOmniZhongHua-8 BeadChip (Illumina). The GWAS included 1,000 cases with BD and 4,000 normal controls which were recruited from the First Affiliated Hospital of Chongqing Medical University (Chongqing, China) and the First Affiliated Hospital of Anhui Medical University (Hefei, China). The procedures followed the tenets of the Declaration of Helsinki. This meta-analysis was conducted according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009). HWE was evaluated for each study by the Chi-squared test (as shown in Supporting Information Table S1). The studies included in the meta-analysis used different methodologies and experimental designs which may result in heterogeneity (Kontopantelis, Springate, & Reeves, 2013). In this study, heterogeneity was measured by *Q*-test and *I*-squared statistics. A *P*-value > 0.1 of the *Q*-test and an *I*-squared < 50% indicates no significant heterogeneity in the results of the studies analyzed (Higgins, Thompson, Deeks, & Altman, 2003; Hoaglin, 2016). OR and 95% CIs were calculated to evaluate the directionality and strength of the association between the rs1800629 and susceptibility to BD. Potential publication bias occurs when studies show significant findings that may disturb the balance of findings.

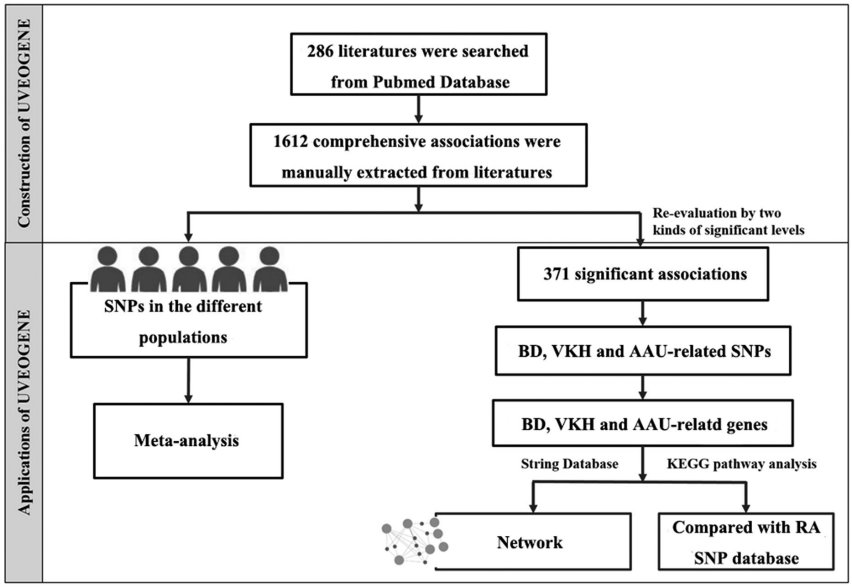

FIGURE 1 Work flow of UVEOGENE. From PubMed database, 289 literatures were collected. After integration, 1,612 associations between single nucleotide polymorphisms and uveitis were extracted from literatures. In these associations, 371 associations reached significant level for further analysis. Based on significant associations, we identified Behcet's disease (BD), Vogt–Koyanagi–Harada (VKH), and acute anterior uveitis (AAU)-related genes. Through STING database and Kyoto Encyclopedia of Genes and Genomes pathway analysis, we further investigate the relationships among three uveitis entities (BD, VKH, and AAU) as well as with rheumatoid arthritis. The data can be view and downloaded from the web database UVEOGENE

TABLE 1 Content of the UVEOGENE database

Content	Number
Diseases	14 (Behcet's disease, Vogt–Koyanagi–Harada disease, intermediate uveitis, acute anterior uveitis, Fuchs uveitis syndrome, pediatric uveitis, juvenile idiopathic arthritis, toxoplasmosis, sympathetic ophthalmia, Birdshot chorioretinopathy, multifocal choroiditis, sarcoidosis, idiopathic uveitis, and punctate inner choroidopathy)
Genes	370
SNPs	918
Populations	40
Associations	1,612
Year	January 2001 to March 2018 (289 publications)

Thus, the potential publication bias of studies was checked by Begg's funnel (Begg & Mazumdar, 1994). A funnel plot is a graph to identify the existence of publication bias. The studies with high precision will be plotted near the average creating a roughly funnel-shaped distribution. Studies deviating from this shape indicate publication bias (Egger, Davey Smith, Schneider, & Minder, 1997).

2.3 | Identification of disease-related genes and pathways in BD, VKH disease, and AAU

The data from BD, VKH disease, and acute anterior uveitis (AAU) allowed us to analyze their disease-related genes and pathways. The SNPs judged as "significant" between patients and healthy individuals were considered as disease-related SNPs. To move the related SNPs into a functional pathway, we assigned these SNPs to genes which were considered as disease-related genes through the PubMed database. In addition, KEGG pathway analysis was built by entering the disease associated genes in the KOBAS 3.0 platform (KEGG Orthology Based Annotation System; http://kobas.cbi.pku.edu.cn/index.php) using Entrez GeneIDs. KOBAS 3.0 supports the FDR correction method Q-VALUE and a corrected P-value < 0.05 was considered as statistically significant (Xie et al., 2011). Notable differences exist in the clinical features and pathogenesis of the three uveitis entities analyzed, and we therefore compared the BD associated genes and pathways with that of AAU and VKH disease. The shared and specific genes and pathways were analyzed by drawing Venn figures (http://bioinformatics.psb.ugent.be/webtools/Venn/). Additionally, we constructed a three diseases' protein–protein interactions (PPI) network by Database STRING (Szklarczyk et al., 2011) with a medium confidence score (0.400) to evaluate the interactions among these disease-related genes.

2.4 | Comparison with data from other databases focused on autoimmune disease

The genetics of a variety of diseases has been widely studied, but only a few databases focus on autoimmune disease (Burren et al., 2011). The RAvariome database for rheumatoid arthritis (RA) identified 82 RA-related genes from 102 confirmed RA SNPs which were downloaded from the website of RAvariome (Okada et al., 2014). In order to elucidate the relationships among BD, VKH, and RA at a different level, disease-related pathways of RA were also identified by using KOBAS 3.0 (The diagram of our strategy is shown in Figure 1).

3 | RESULTS AND DISCUSSIONS

3.1 | Literature search and website construction

The UVEOGENE database is based on 269 PubMed English-language articles published from January 2001 to March 2018. A total of 1,612 associations including 370 genes and 918 SNPs from 40 populations were included in the database covering 14 uveitis entities with different clinical features (Table 1). The UVEOGENE website was tested using different search engines including Microsoft® Internet Explorer, Firefox, Google Chrome, and Safari to facilitate different users. A quick search box can be found on the home page, enabling a search by

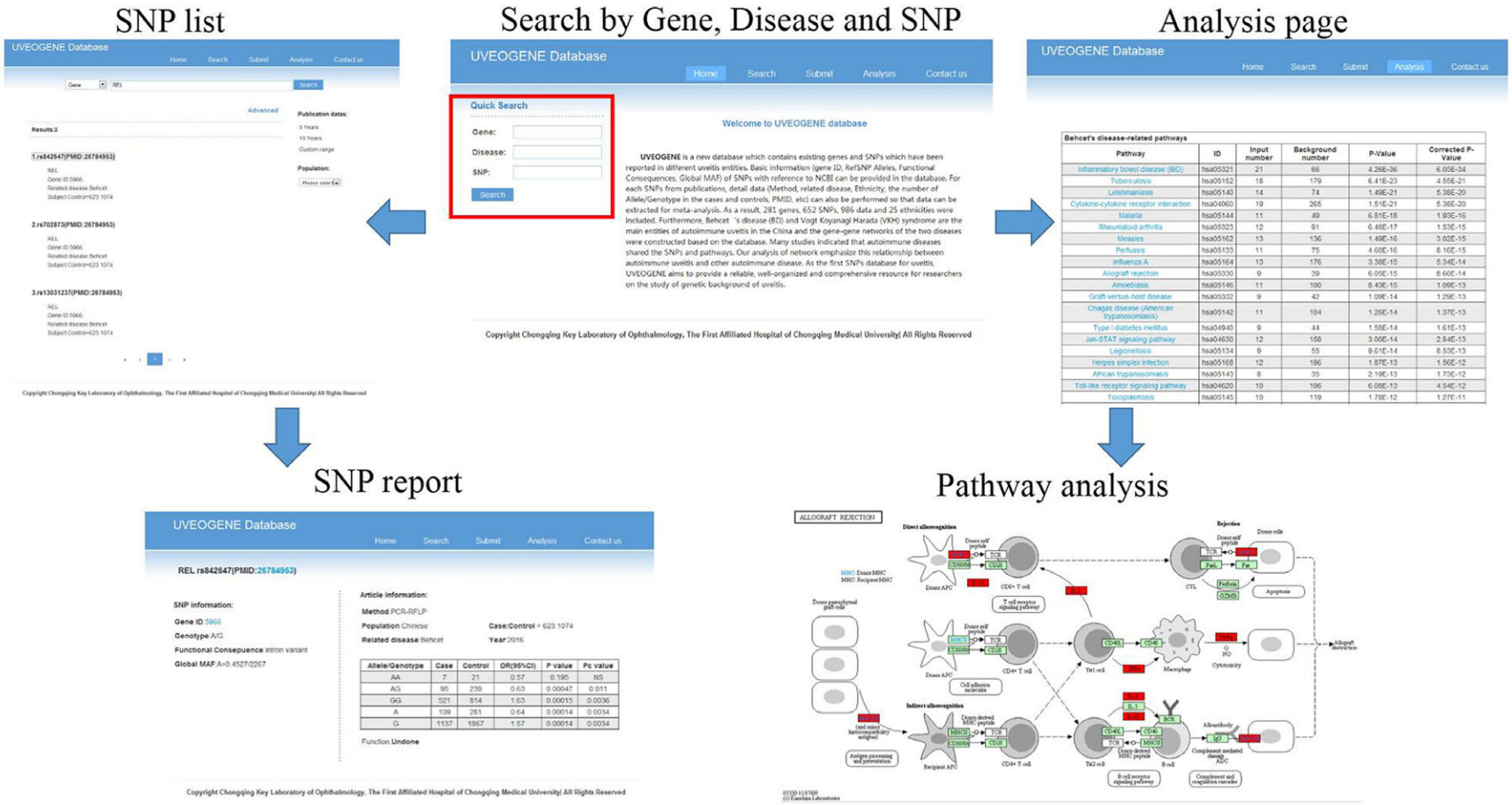

FIGURE 2 UVEOGENE web interface. In the left sidebar, a quick search box can be found on the home page, enabling a search by gene or disease or single nucleotide polymorphism (SNP). In the advanced search page, three search modules including "Gene Search," "Disease Search," and "SNP Search" were incorporated to allow users to search for different combinations. The results of search will be shown in the SNP list page. The user can get detail study information including basic information and article data for each SNP in the SNP report page. Additionally, users can access uveitis-related genes mapped in red in the pathways which are shown in the analysis pages.

TABLE 2 Meta-analysis of the association between rs1800629 and Behcet's disease (BD)

	BD		Healthy controls			Odds ratio
Study	A allele	Total	A allele	Total	Weight (%)	M–H. Fixed 95% CI
Lee et al., 2003	12 (6.38%)	188	8 (4.25%)	188	1.7	1.53 [0.61–3.84]
Duymaz-Tozkir et al., 2003	22 (11.11%)	198	32 (16.67%)	192	6.5	0.63 [0.35–1.12]
Park et al., 2006	27 (5.31%)	508	66 (9.59%)	688	11.9	0.53 [0.33–0.84]
Chang et al., 2007	13 (5.65%)	230	19 (8.33%)	228	4.0	0.66 [0.32–1.37]
Arayssi et al., 2008	7 (7.95%)	88	15 (8.33%)	180	2.0	0.95 [0.37–2.42]
Bonyadi et al., 2009	5 (4.72%)	106	18 (11.39%)	158	3.1	0.39 [0.14–1.07]
Dilek et al., 2009	22 (11.34%)	194	37 (14.56%)	254	6.4	0.75 [0.43–1.32]
Radouane et al., 2012	38 (15.83%)	240	51 (22.77%)	224	9.9	0.64 [0.40–1.02]
GWAS (Yang, unpublished)	110 (5.5%)	2,000	646 (8.08%)	8,000	54.6	0.66 [0.54–0.82]
Total (95% CI)		3,752		102,112	100.0	0.66 [0.57–0.77]
Total A allele	256		892			
Heterogeneity: $Chi^2 = 6.02$, df = 8 ($P = 0.65$); $I^2 = 0\%$						
Test for overall effect: $Z = 5.40$ ($P < 0.00001$)						

M–H. Fixed: the risk ratio was calculated by using Mantel–Haenszel method.
Weight: the reciprocal of variance within each study is used to weight each studies effect in the meta-analysis.

gene or disease or SNP (Figure 2). Three search modules including "Gene Search," "Disease Search," and "SNP Search" in the advanced search page were incorporated to allow users to search for different combinations. In the SNP information page, users are able to retrieve basic information and article data for each SNP. Additionally, users can access the signaling pathway analysis pages in a graphical view, whereby uveitis-related genes are mapped in red in the different pathways.

As mentioned in the method section, we also submitted the data of "significant associations" to "Global Variome shared LOVD" including DNA change, genomic position in the reference sequence and genome assembly (GRCh 38), frequency of variants in the cases, technique used, link to published reference, and the following anonymized clinical data: ethnic origin, gender, consanguinity, and clinical features. Every data item in "Global Variome shared LOVD" also has links to "UVEOGENE" for more detailed information of the associations.

3.2 | Study in depth on the association between rs1800629 and BD susceptibility in different ethnic populations

As mentioned above, the UVEOGENE database can be used to analyze the heterogeneity of SNPs in different populations via meta-analysis. In order to provide an example to illustrate the use of the UVEOGENE database in analyzing the association of a gene or SNP with uveitis, we selected one of the most widely investigated SNPs, "rs1800629" with BD, as an example. A total of 11 studies were found in our database. Three studies were excluded, either due to the absence of detailed information of the genotype data or due to a low HWE ($P < 0.05$). The remaining eight studies met the inclusion criteria for meta-analysis. A meta-analysis with our own unpublished GWAS study in BD was performed to accurately analyze the relationship of this SNP with BD using the data from the established UVEOGENE database. Not all BD patients included in meta-analysis were with uveitis but met International Study Group criteria. The results showed that there was no significant heterogeneity concerning these data ($Chi^2 = 6.02$, $P = 0.65$; $I^2 = 0\%$). A significant association of this SNP with BD was observed following allele frequency and Forest plot analysis (A vs. G: OR = 0.66, 95% CI 0.57–0.77, $P < 10E\text{-}05$) (Table 2, Figure 3A). No publication bias for the association between rs1800629 and BD susceptibility was identified by the Begg's funnel plot (Figure 3B).

3.3 | Disease-related genes for BD, AAU, and VKH disease

It seems unlikely that one single particular SNP can dominate the pathogenesis of multifactorial diseases. To investigate this, we assigned the SNPs judged as "significant" to genes to illustrate their potential effect. According to the assignment of the level of statistical significance as mentioned in the methods section, 1,241 associations were classified as statistically non-significant, and 371 associations were judged as "significant" (Supporting Information Table S2). Among these associations, we found that BD is the most commonly investigated uveitis entity. Additionally, the associations between 28 SNPs and BD were confirmed in different ethnic populations (Supporting Information Table S3).

After assigning SNPs judged as "significant" to genes, we identified 105 BD-related genes according to 203 disease-related SNPs. A total of 23 VKH-related genes were demonstrated according to 28 disease-related SNPs. A total of 16 AAU-related genes were based on 17 disease-related SNPs. We then used the proteins encoded by these genes to construct an interaction network. This analysis showed that most of these genes were enriched in one network (Figure 4). We further identified two genes including TRAF5 and IL23R (Figure 5A) that were shared by three uveitis entities. Despite the fact that these diseases may share an association with a certain gene, the association often does not involve the same SNP. Different SNPs within a gene may

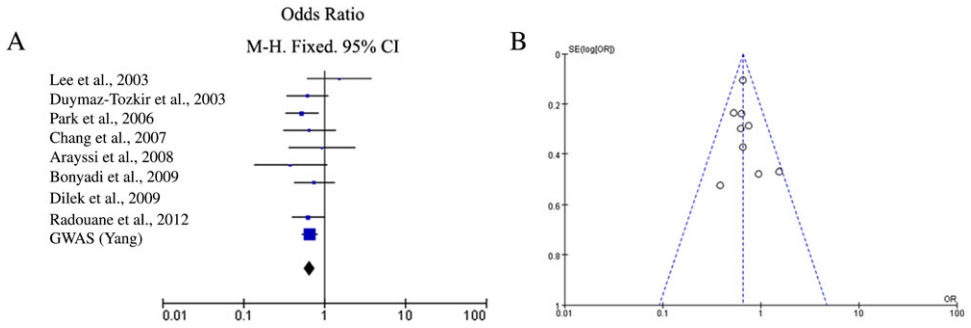

FIGURE 3 Association between rs1800629 and Behcet's disease (BD) susceptibility in different ethnic populations. (A) Forest plot of allele comparison of rs3746444 for overall comparison (G vs. A). (B) No publication bias for the association between rs1800629 and BD susceptibility was identified by the Begg's funnel plot

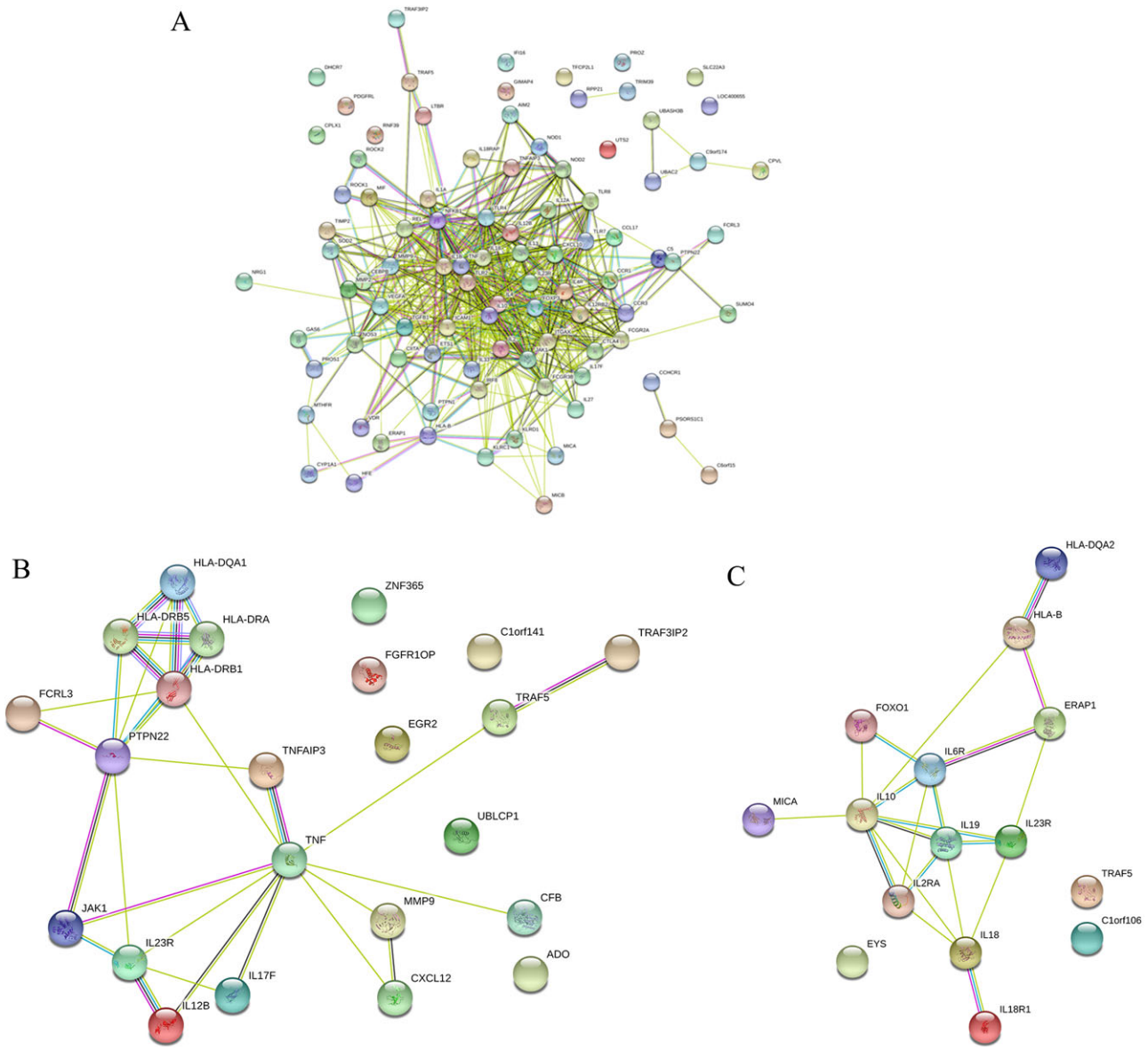

FIGURE 4 The networks of Behcet's disease (BD), Vogt–Koyanagi–Harada (VKH) disease, and acute anterior uveitis (AAU). (A) Ninety six BD-related genes were mapped in the network of BD. There were 74 of 93 genes enriched in one network (93 nodes and 623 edges). (B) Twenty two VKH disease-related genes were mapped in the network of VKH disease. Only four genes were not enriched in the same network (22 nodes and 60 edges). (C) Fifteen five AAU-related gene were mapped in the network of AAU. There were three genes were not enriched in the same network (15 nodes and 42 edges)

TABLE 3 Similarities and differences among Behcet's disease (BD), Vogt–Koyanagi–Harada (VKH) disease, and acute anterior uveitis (AAU) concerning disease-related genes and pathways

Disease	Number of genes	Genes	Number of pathways	Pathway ID
AAU, BD, VKH	2	TRAF5, IL23R	35	hsa04621, hsa04060, hsa05145, hsa04640, hsa05330, hsa04672, hsa04940, hsa04064, hsa05321, hsa04514, hsa05140, hsa05134, hsa05310, hsa05322, hsa05144, hsa05133, hsa05166, hsa05332, hsa05416, hsa05203, hsa04630, hsa05152, hsa05200, hsa05320, hsa04145, hsa05142, hsa04668, hsa05164, hsa05150, hsa04612, hsa05146, hsa05169, hsa05168, hsa05143, hsa05323
BD, VKH	9	PTPN22, IL17F, TNFAIP3, TRAF3IP2, TNF, IL12B, MMP9, JAK1, FCRL3	8	hsa05219, hsa05162, hsa04380, hsa05205, hsa04622, hsa04620, hsa05161, hsa05160
AAU, BD	5	ERAP1, IL10, MICA, IL18, HLA-B	10	hsa04933, hsa04931, hsa01521, hsa05132, hsa04151, hsa04066, hsa04660, hsa04623, hsa04650, hsa04068
BD	88	VDR, TLR7, SUMO4, MMP2, MIR196A1, TLR4, ETS1, IFI16, ROCK1, IL13, GIMAP4, TFCP2L1, CXCL10, IL4, HLA-H, NOD2, IL12A, ROCK2, LOC400655, CIITA RPP21, HLA-L, TRIM39, MIR146A, IL4R, NOD1, MTHFR, IL27, UBASH3B, REL, HLA-F-AS1, CPLX1, IL12RB2,ITGB2, FCGR2A, PDGFRL, KLRD1, CCR3, TLR2, FOXP3, DHCR7, PROZ, PROS1, NOS3, PSORS1C1, MICB, MIR499A, IL33, IL18RAP, RNF39, IL37, CCL17, UTS2, MIF, TGFB1, SOD2, PTPN1, NFKB1, AIM2, IRF8, C5, CEBPB, IL1A, TIMP2, CPVL, VEGF, MIR182, ITGAX, CCHCR1, GAS6, IL1B, ICAM1, SLC22A3, CYP1A1, LOC100129342, NRG1, CTLA4, UBAC2, FCGR3B, TLR8, HCG17, CCR1, IL2, HCG22, C6orf15, KLRC1, CCDC180	23	hsa04810, hsa04921, hsa04062, hsa04071, hsa04024, hsa05130, hsa04664, hsa04022, hsa05120, hsa04610, hsa05206, hsa05020, hsa04350, hsa04915, hsa04611, hsa05211, hsa04932, hsa05202, hsa05131, hsa04010, hsa04920, hsa05212, hsa04670
VKH	12	CFB, UBLCP1, HLA-DQA1, CXCL12, C1orf141, HLA-DRA, FGFR1OP, ADO, EGR2, HLA-DRB1, HLA-DRB5, ZNF365	3	hsa00430, hsa05014, hsa04930
AAU	9	EYS, IL6R, IL19, INAVA, FOXO1, IL18R1, HLA-DRB3, HLA-DQA2, IL2RA	6	hsa05222, hsa05215, hsa04211, hsa04922, hsa04213, hsa04144

The detailed name of the pathway can be found in the Supporting Information Tables S4–S7 according to the pathway ID.

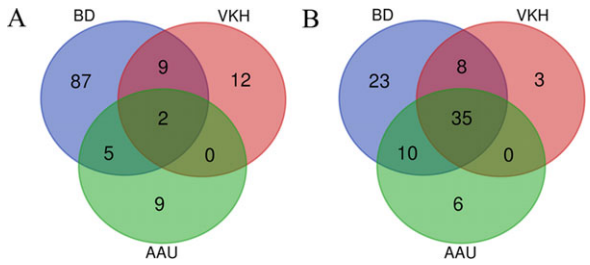

FIGURE 5 Comparison between Behcet's disease, Vogt–Koyanagi–Harada (VKH) disease, and acute anterior uveitis in the level of gene and pathway. (A) Specific and shared diseased-related genes among three uveitis entities. (B) Specific and shared diseased-related pathways among three uveitis entities

have different biological functions such as protein expression level or functional activity. The biological function of many of the SNPs covered in the UVEOGENE database are not yet clear and further functional studies are needed to address this issue.

3.4 | Pathway analysis in BD, VKH disease, and AAU

We further carried out a study to investigate whether there were pathways specific for a certain uveitis entity and whether they shared common pathways. A total of 76 BD-related pathways, 46 VKH-related pathways, and 51 AAU-related pathways were identified using a corrected *P*-values of <0.05 through KEGG pathway analysis (Supporting Information Tables S3–S5). Of these pathways, 35 pathways were shared by three uveitis entities (Figure 5B), and only two genes were shared by all three tested entities. The shared genes and pathways might be involved in the pathogenesis of uveitis in general, and the specific genes and pathways might account for the differences observed between the three uveitis entities investigated (Table 3).

Focal adhesion and VEGF signaling pathways were included in the BD-specific pathways which are in agreement with the development of vasculitis that is so characteristic for BD (Yang et al., 2005). One of the VKH disease-specific pathways involves the regulation of taurine and hypotaurine metabolism. However, no study reported the pathway was involved in the VKH disease and have effect on melanosomes. The relation of this pathway with VKH is unclear and deserves further study. A limitation of this analysis is the fact that the use of relatively selective genotype platforms (immunochip) by different immune disease and lack of data between MHC and uveitis studies may facilitate the detection of similar (immune gene) SNPs which may bias pathway enrichment analysis.

3.5 | Similarities and differences between BD, VKH disease, and RA-related pathways

To investigate differences and overlap concerning disease-related pathways we compared BD, VKH, and RA groups using KEGG pathway

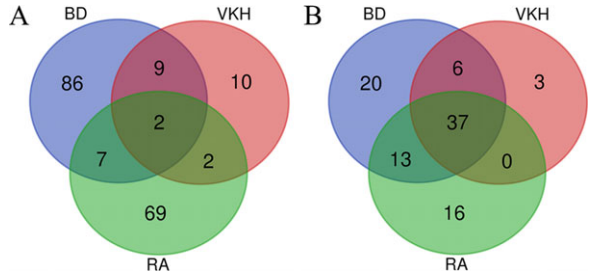

FIGURE 6 Comparison between Behcet's disease (BD), Vogt–Koyanagi–Harada (VKH) disease, and rheumatoid arthritis (RA) in the level of gene and pathway. (A) Specific and shared diseased-related genes between BD, VKH disease, and RA. (B) Specific and shared diseased-related pathways between BD, VKH disease, and RA

analysis (Supporting Information Table S6). Of the 95 tested pathways, 37 were shared by these three diseases (Figure 6B), 20 were specific for BD, 3 were specific for VKH, and 16 for RA. The open access database UVEOGENE is not only useful for researchers in the field of uveitis, but may also be of interest for other immune driven disease researchers.

4 | CONCLUSIONS

The UVEOGENE website contains 1,612 genetic associations of 370 genes and 918 SNPs covering 14 uveitis entities and 40 ethnic populations. The database contains data from several studies and can be used for meta-analysis. According to two kinds of statistical significance level, 371 associations were judged as "significant." Based on these associations, we identified 105 BD-related genes, 23 VKH-related genes and 16 AAU-related genes. We showed that 76, 46, and 51 pathways were found to be involved in BD, VKH disease, and AAU, respectively. Comparing our database with a database on RA, revealed similarities as well as differences in the genetic susceptibility to uveitis as compared with another autoimmune disease such as RA.

4.1 | Future prospects

The number of variants discovered underlying uveitis is expected to keep increasing owing to the sequencing technology. Continuous efforts will be made to (i) collect the latest SNPs data related to uveitis, (ii) share the new "significant associations between SNPs and uveitis" with "Global Variome shared LOVD," (iii) add other genetic markers such as gene copy number variants and HLA subtypes. Ultimately, we hope that the efforts of "UVEOGENE" and its functional analysis of the data will be beneficial to our better understanding of the complex pathogenesis of uveitis.

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CONFLICT OF INTEREST

All authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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