An Update Evolving View of Copy Number Variations in Autoimmune Diseases

Rong-hua Song, Chao-qun Gao, Jing Zhao and Jin-an Zhang*

Department of Endocrinology and Rheumatology, Shanghai University of Medicine and Health Sciences Affiliated Zhoupu Hospital, Shanghai, China

Autoimmune diseases (AIDs) usually share possible common mechanisms, i.e., a defect in the immune tolerance exists due to diverse causes from central and peripheral tolerance mechanisms. Some genetic variations including copy number variations (CNVs) are known to link to several AIDs and are of importance in the susceptibility to AIDs and the potential therapeutic responses to medicines. As an important source of genetic variants, DNA CNVs have been shown to be very common in AIDs, implying these AIDs may possess possible common mechanisms. In addition, some CNVs are differently distributed in various diseases in different ethnic populations, suggesting that AIDs may have their own different phenotypes and different genetic and/or environmental backgrounds among diverse populations. Due to the continuous advancement in genotyping technology, such as high-throughput whole-genome sequencing method, more susceptible variants have been found. Moreover, further replication studies should be conducted to confirm the results of studies with different ethnic cohorts and independent populations. In this review, we aim to summarize the most relevant data that emerged in the past few decades on the relationship of CNVs and AIDs and gain some new insights into the issue.

Keywords: copy number variations, single-nucleotide polymorphism, autoimmune disease, autoimmune thyroid disease, systemic lupus erythematosus

INTRODUCTION

Copy number variations (CNVs), as a main type of structure variation (SV) caused by genomic rearrangement, mainly include deletion and duplication of sub-microscopic but large genomic segments ranging from 1 kb to 3 Mb (Redon et al., 2006). Single-nucleotide polymorphisms (SNPs) have been recognized to be involved in many autoimmune diseases (AIDs) (Song et al., 2021a; Song et al., 2021b; Jiang et al., 2021); however, CNVs containing more nucleotide content per genome than SNPs are responsible for a large proportion of human genetic variation and show an importance in genetic diversity and evolution (Redon et al., 2006; Cleynen et al., 2016). Thus, more attention has been paid to the research of CNVs in diseases. Nowadays, the genome-wide assays for CNV study include array-based comparative genomic hybridization (aCGH), SNP genotyping microarrays, next-generation sequencing, and long-read sequencing techniques (Hehir-Kwa et al., 2018). There are several main categories in the molecular mechanisms during the process of CNV formation, DNA recombination, rearrangement, and error replication. Besides, CNVs also have several types, such as insertions, deletions, inversions, and translocations (Feuk et al., 2006; Human Genome Structural Variation Working Group et al., 2007). Numerous reports imply that CNV is one of the main genetic factors underlying human diseases, including AIDs (Hauptmann et al., 1974; Tomer...
TABLE 1 | Copy number variant loci or genes related to autoimmune diseases.

| CNV-related genes or regions | Autoimmune diseases/syndromes | Populations (sample size) | CNV detection methods | Most common copies in healthy normal controls | Risk-associated CNVs (p-values) | Results | References |
|-----------------------------|--------------------------------|--------------------------|-----------------------|---------------------------------------------|-------------------------------|---------|------------|
| Beta-defensin gene          | Psoriasis                      | Dutch and German population (179 Dutch patients and 272 controls; 319 German patients and 305 controls) | High-throughput paralogue ratio test (PRT) | 40% controls were four copies | Higher genomic copy number (p = 0.01 for Dutch, p = 7.8E–5 for German) | Consistent | Hollox et al. (2008) |
| BMP8A                      | AS                             | Han Chinese population (1,064 patients and 2,174 controls) | TaqMan real-time polymerase chain reaction (PCR) | Two copies | No significant association | – | Shahba et al. (2018) |
| C3 and C5                  | BD                             | Han Chinese population (1,064 patients and 2,174 controls) | Real-time PCR | Two copies of C3 and C5 | More than two copies of C3 (p = 5.5E–3) and C5 (p = 1.1E–8) | – | Xu et al. (2015) |
| C4 and its two isotypes, C4A and C4B | SLE | 1,241 European Americans (Yang et al. 2007) and Brazilian (427 patients and 301 controls) | TaqI southern blots; real-time PCR (Pereira et al. 2019) | Four copies of C4 genes (majority) | Lower copy number of C4 and C4A (p = 0.00002; Yang et al. 2007); low total copy number of C4 (p < 0.001), C4A (p < 0.001), and C4B (p = 0.03) | Consistent | Hauptmann et al. (1974), Yang et al. (2007), and Pereira et al. (2019) |
|                            | BD                             | 221 Caucasians (North American) | TaqMan-based real-time PCR and Southern blotting | Not reported | Higher copy number of C4B associated with hypertension and effective response to statin therapy in childhood-onset SLE patients (p = 0.016) and higher diastolic blood pressure (p = 0.015) | – | Mulvihill et al. (2019) |
| CD                          | Belgian population (770 patients and 345 controls) | Array comparative genomic hybridization | Not reported | Lower C4L (p = 7.68E–3) and higher C4S copies (p = 6.29E–3) | – | Cleynen et al. (2016) |
| BD                          | Han Chinese population (905 patients and 1,238 controls) | Real-time PCR | Four copies of C4 genes, 2 copies of C4A genes | More than two copies of C4A (p = 1.65E–7) | – | Hou et al. (2013) |
| T1DM                        | American population (cohort 1: 150 patients and 57 controls; cohort 2: 110 patients) | TaqMan quantitative PCR | Four copies of C4 genes; two copies of C4A gene | Fewer copies of C4A (p = 1.78E–6) and HERV-K [C4] (p = 4.59E−7) | – | Mason et al. (2014) |
| GD                          | Chinese population (624 patients and 160 healthy individuals) | Quantitative real-time polymerase chain reaction | Four copies of C4 genes; two copies of C4A and C4B genes | Four copies of C4 (p = 0.001); copies of C4A (p = 0.008) and C4B (p = 2.42E−5) in GD | – | Liu et al. (2011) |
| CCL3L1                      | SLE                            | Caucasians (San Antonio), 1,084 subjects (469 cases of SLE and 615 matched controls) | 59-RACE and reverse transcription-PCR (RT-PCR) | Two copies | Lower than or greater than two copies (p = 0.032) | – | Mamtani et al. (2006) |
| RA                          | Caucasian (1,136 patients and 1,470 controls; McKinney et al.2008), Tunisians and French (100 French patients and 200 controls; 166 Tunisian patients and 102 controls; Ben Kliani et al.2016), United Kingdom population | Reverse transcriptase (RT)-PCR (McKinney et al. 2008), droplet digital PCR (ddPCR) (Ben Kliani et al. 2016), PRT methodology (Carpenter et al. 2011) | Two copies | Higher than two in the New Zealand cohort (p = 0.009) but not the United Kingdom cohort, no association in the French study, a protective effect of five copies in the Tunisian population (p value not significant) | – | McKinney et al. (2008), Ben Kliani et al. (2016), and Carpenter et al. (2011) |

(Continued on following page)
| CNV-related genes or regions | Autoimmune diseases/ syndromes | Populations (sample size) | CNV detection methods | Most common copies in healthy normal controls | Risk-associated CNVs (p-values) | Results | References |
|----------------------------|---------------------------------|--------------------------|-----------------------|-----------------------------------------------|-------------------------------|---------|------------|
| CD and psoriasis           | United Kingdom (657 CD patients and 202 psoriasis patients, and 276 controls) | PRT methodology          | Not reported          | No association                               | Reported (Ben Kilani et al. 2016), no association (Carpenter et al. 2011) |          | Carpenter et al. (2011) |
| AS                        | Algerian (81 patients and 119 controls) | Digital droplet PCR (ddPCR) | Two copies            | No association                               | –                             |          | Dahmani et al. (2019) |
| T1DM                      | Caucasian population (252 patients and 1,470 controls; McKinney et al. 2008) and 2,000 patients and 3,000 controls (Wellcome Trust Case Control Consortium et al. 2010) | Reverse transcriptase (RT)-PCR (McKinney et al. 2008) and the Agilent Comparative Genomic Hybridization (CGH) platform (Wellcome Trust Case Control Consortium et al. 2010) | Two copies                        | A copy number higher than 2 (p = 0.064) in the Caucasian population (McKinney et al. 2008); no association in the study (Wellcome Trust Case Control Consortium et al. 2010) | Consistent McKinney et al. (2008) and Wellcome Trust Case Control Consortium et al. (2010) |          | –          |
| CD40, PTPN22, and CTLA-4   | GD (191 patients and 192 controls) | Quantitative-PCR (Q-PCR) assays | Two copies            | No copy variation in the CD40, CTLA-4, and PTPN22 gene number variation in GD | –                             |          | Huber et al. (2011) |
| CFH, CFHR1, KAA0125, UGT2B15, UGT2B17, TRH6, and CCL3L1 | GD (144 patients and 144 controls) | TaqMan quantitative polymerase chain reaction (TaqMan qPCR) | Two copies            | No association                               | –                             |          | Song et al. (2017) |
| DEFA1                      | BD (65 patients and 35 controls) | A duplex TaqMan® real-time PCR assay | Mean copy number was 6.7 | Higher copy number (p < 0.001) | –                             |          | Ahn et al. (2012) |
| DEFB4                      | BD (197 patients and 197 controls) | A novel comparative multiplex polymerase chain reaction (PCR); paralogue ratio test (PRT) | Median copy number was five | Lower copy number, but no statistical difference (p = 0.245) | –                             |          | Park et al. (2011) |
| DEFA1A3                    | CD (240 patients) | Combined real-time quantitative PCR and pyrosequencing | Ranged from 2 to 6 | No association                               | –                             |          | Jespersgaard et al. (2011) |
| DEFB103                    | AS (406 patients and 401 controls) | A multiplex fluorescence competitive polymerase chain reaction (PCR) | Mean copy number was 6.7 | Higher copy number (p < 0.001) | –                             |          | Cai et al. (2015) |
| FAS, caspase8, caspase9, and BCL2 | BD (1,014 patients and 2,076 controls) | TaqMan copy number assays and real-time PCR | Diploid 2 copy number carriers | High FAS copy number (>2) (p = 1.05E−3 in the first-stage study, p = 3.35E−8 in the replication and combined study) | –                             |          | Yu et al. (2015) |
| FCGR3A                     | SLE (846 patients with SLE and 1,420 healthy control subjects) | Custom TaqMan CNV real-time quantitative polymerase chain reaction (PCR) assays | Two copies            | A low FCGR3A copy number (<2) (p = 5.06E−4) and a high (>2) FCGR3A copy number (p = 0.003) | –                             |          | Chen et al. (2014) |

(Continued on following page)
| Autoimmune diseases/syndromes | Populations (sample size) | CNV detection methods | Most common CNVs in healthy normal controls | Risk-associated CNVs (p-values) | Results | References |
|--------------------------------|--------------------------|-----------------------|---------------------------------------------|---------------------------------|---------|------------|
| RA | Taiwanese population (948 patients with RA and 1,420 healthy control subjects) | Custom TaqMan CNV real-time quantitative polymerase chain reaction (PCR) assays | Two copies A low copy number (p = 5.83E-4) | – | Chen et al. (2014) |
| AS | Algerian (81 patients and 119 controls; Dahmani et al. 2019), Chinese population (402 patients and 399 controls; Wang et al. 2016) | Digital droplet PCR (ddPCR) (Dahmani et al. 2019) and AccuCopy™ method (Wang et al. 2016) | Two copies Less than two copies (<2) (p = 0.0001; Dahmani et al. 2019), a low copy number (p < 0.001; Wang et al. 2018) | Consistent Dahmani et al. (2019) and Wang et al. (2016) |
| FCGR3B | United Kingdom Caucasians (171 patients and 176 controls; Wilcock et al. 2008), Spanish ancestry (146 patients and 409 controls; Mamtani et al. 2010), Afro-Caribbean (134 patients and 589 controls; Molokhia et al. 2011), Taiwanese (846 patients and 1,420 controls; Chen et al. 2014), and Brazilian population (135 unrelated SLE patients and 200 healthy unrelated subjects; Barbosa et al. 2018) | qPCR (Wilcock et al. 2008), real-time PCR (Mamtani et al. 2010), paralogue ratio test (PRT) assay (Wilcock et al. 2008), and quantitative real-time PCR (Barbosa et al. 2018) | Two copies A lower (<2) copy number in United Kingdom Caucasians (p = 0.027; Wilcock et al. 2008), copy number <2 or >2 in cases of Spanish ancestry (p = 0.001 and 0.013, respectively; Mamtani et al. 2010), Afro-Caribbean (p = 0.02; Molokhia et al. 2011), Taiwanese (p = 0.0032; Chen et al. 2014), and Brazilian population (p = 1.66E-3; Barbosa et al. 2018) | Consistent Wilcock et al. (2008), Mamtani et al. (2010), Molokhia et al. (2011), Chen et al. (2014), and Barbosa et al. (2018) |
| RA | Spanish ancestry (158 patients and 409 controls; Mamtani et al. 2010), South Australia (197 patients and 162 controls; Graf et al. 2012), Taiwanese (948 patients and 1,420 controls; Chen et al. 2014), British population (480 patients; Rahbari et al. 2017), French population (Bai Kilani et al. 2019) | Real-time PCR (Mamtani et al. 2010), custom TaqMan™ CN assay (Graf et al. 2012), custom TaqMan CNV real-time quantitative polymerase chain reaction (PCR) assays (Chen et al. 2014), a PRT/REDVR approach (Rahbari et al. 2017), and droplet digital PCR (Bai Kilani et al. 2019) | Two copies No association in cases of Spanish ancestry (Mamtani et al. 2010), lower and higher copy number in South Australia (p = 0.017; Graf et al. 2012), no association in Taiwanese (Chen et al. 2014), deletion in British population (p = 2.9E-3; Rahbari et al. 2017), and without null allele (one-three copy numbers) in French population (Bai Kilani et al. 2019) | Controversial Mamtani et al. (2010), Graf et al. (2012), Chen et al. (2014), Rahbari et al. (2017), and Bai Kilani et al. (2019) |
| UC | Japanese population (752 patients and 2,062 controls) | TaqMan assay | Not reported Abnormal copies (p = 0.02) | – | Asano et al. (2013) |
| Psoriasis | Han Chinese population (343 patients and 574 controls) | TaqMan™ copy number assays | Not reported A higher copy number (p < 0.02) | – | Wu et al. (2014) |
| BD | Iran (187 patients and 178 controls) | Quantitative real-time PCR | Two copies No association | – | Black et al. (2012) |
| AS | Algerian (81 patients and 119 controls; Dahmani et al. | Digital droplet PCR (ddPCR) (Dahmani | Two copies No association in Algerian population | Controversial | (Continued on following page) |
| CNV-related genes or regions | Autoimmune diseases/syndromes | Populations (sample size) | CNV detection methods | Most common copies in healthy normal controls | Risk-associated CNVs (p-values) | Results | References |
|-----------------------------|--------------------------------|--------------------------|-----------------------|-----------------------------------------------|--------------------------------|---------|------------|
| GPC5, B9D2, and ASB11       | AITD Chinese Han population (158 patients and 181 controls) | Chromosome microarray on the Affymetrix CytoScan™ HD platform, then identified by RTPCR | Not reported | The frequency of CNV loss for GPC5, B9D2, and ASB11 genes was higher in AITD (p < 0.05) | Consistent | Lundstrom et al. (2011) and Achour et al. (2018) |
| GSTM1                       | RA Swedish (2,426 cases and 1,257 controls) and Tunisian population (165 cases and 102 controls) | TaqMan copy number assays (Lundstrom et al. 2011) and digital droplet PCR (ddPCR) (Achour et al. 2018) | 51.8% for 0 copies and 40.1% for 1 copy | No association in Swedish population (Lundstrom et al. 2011) and lack of association (Achour et al. 2018) | Consistent | – |
| HBD-2                       | CD German | Genome-wide DNA copy number profiling by array-based comparative genomic hybridization and quantitative polymerase-chain reaction analysis | Median of 4 (range 2–10) copies | The copy number distribution shifted to lower numbers (p = 0.002) | – | Fellermann et al. (2006) |
| HSP90 and its two major isoforms | SLE Han Chinese population (419 patients and 538 controls) | A custom-by-design Multiplex AccuCopy™ method | Two copies | Abnormal copies of HSP90AB1 (p = 0.02) | – | Zhang et al. (2019) |
| KIR3DL1 and KIR3DS1         | T1DM White European ancestry (6,744 cases and 5,362 controls) | A hybrid qPCR/SNP array | Two copies | No evidence of association | – | Pontikos et al. (2014) |
| LCE3B and LCE3C             | Psoriasis The Dutch population (1,039 cases and 759 controls) | Array comparative genomic hybridization and a polymerase chain reaction; TaqMan SNP genotyping assay | Not reported | Absence (p < 0.0001) | – | Bergboer et al. (2012) |
| IL17F, IL23A, IL17A, and IL23R | BD Han Chinese population (1,036 patients and 2,050 controls) | TaqMan real-time polymerase chain reaction assay | Not reported | More than two copies of IL17F (p = 4.17E−8) and IL23A (p = 2.86E−11) associated with BD and no association | – | Hou et al. (2015) |

(Continued on following page)
| CNV-related genes or regions | Autoimmune diseases/syndromes | Populations (sample size) | CNV detection methods | Most common copies in healthy normal controls | Risk-associated CNVs (p-values) | Results | References |
|-----------------------------|--------------------------------|--------------------------|-----------------------|-----------------------------------------------|-------------------------------|---------|------------|
| **IL-22 gene exon1**        | Psoriasis                      | Estonian (290 patients and 263 controls) | Quantitative RT-PCR | Not reported | between CNV of IL17A and IL23R Abnormal copies associated with psoriasis severity (p < 0.0001) | – | Prans et al. (2013) |
| **miR-143, miR-146a, miR-9-3, miR-205, miR-301a, and miR-23a** | AS                             | Chinese Han population (768 patients and 660 controls) | TaqMan PCR | Two copies | Low copy numbers of miR-143 (p = 1.126E−7), miR-146a (p = 3.716E−8), miR-9-3 (p = 2.568E−5), and miR-205 (p = 7.187E−6) and high copy numbers of miR-301a (p = 3.725E−5) and miR-23a (p = 8.033E−9) AAU+, AS+; additionally, a low copy number of miR-146a (p = 0.001) and a high copy number of miR-23a and miR-205 (p = 0.002) in AAU+, AS− | – | Yang et al. (2017) |
| **miR-23a, miR-146a, and miR-301a** | BD                             | Han Chinese population (377 patients and 2,291 controls) | TaqMan PCR | Two copies | No association | – | Hou et al. (2016) |
| **NCF1**                    | RA                             | The middle and southern parts of Sweden (494 patients and 480 controls) | A multiplex qPCR assay | Two copies | RA less likely to have an increased copy number (p = 0.037) | – | Olsson et al. (2012) |
| **SIRPB1 and TMEM91**       | AITD                           | Chinese Han population (15 patients and 15 controls) | Chromosome microarray | Not reported | The frequency of CNV gain for SIRPB1 was higher in AITD (p = 0.001) and no association of TMEM91 CNV and AITD | – | Jin et al. (2018) |
| **T-Bet, GATA-3, RORC, and FOXP3** | AS                             | Chinese Han population (676 patients with AAU, including 298 patients with AAU+, AS+; 378 patients with AAU+, AS−; and 596 unrelated healthy controls) | Real-time PCR | Two copies | A high copy number (CN) of T-bet in AAU+, AS− and AAU+, AS+ (p = 4.3E−5 and 1.2E−8, respectively), a high CN of GATA-3 in AAU+, AS+ (p = 1.8E−7), a higher frequency of CN of FOXP3 in female AAU+, AS+ and female AAU+, AS− (p = 0.005 and 0.004, respectively), and no association between RORC CNVs and AS | – | Bai et al. (2016) |
| **TBX21, GATA3, Rorc, and Foxp3** | BD                             | Han Chinese population (1,048 patients and 2,236 controls) | TaqMan real-time PCR | Two copies of these four genes | High Rorc CNV in BD (p = 8.99E−8) and low Foxp3 CNV | – | Liao et al. (2015) |

(Continued on following page)
The mechanisms underlying the involvement of CNVs in clinical phenotypes are mainly gene disruption and rearrangement (McCarron and Altshuler, 2007; Yim et al., 2010). Yim et al. (2015) correlated to several specific AIDs with tumors and chronic diseases (Jia et al., 2011; Saadati et al., 2016; Voll et al., 2017). Moreover, CNVs are very common in genomic regions encoding immune-related genes, which are closely related to the etiology of AIDs. Thus, they potentially impact polygenic autoimmunity and may lead to the imbalance of the autoimmune system and the development of some AIDs. Additionally, some common CNVs have also been reported to be correlated to several specific AIDs (Mamtani et al., 2008; Mamtani et al., 2010; Liu et al., 2011). Yim et al. (2015) reviewed studies on the clinical implications of copy number variations in autoimmune disorders in detail. However, the relationship between CNVs and the pathogenesis of AIDs has not been fully revealed. Furthermore, in recent years, as new CNVs, copy number variations; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; BD, Behcet’s disease, AS, ankylosing spondylitis (AS); pSS, primary Sjögren’s syndrome; T1DM, type 1 diabetes mellitus; AITD, autoimmune thyroid disease

| CNV-related genes or regions | Autoimmune diseases/syndromes | Populations (sample size) | CNV detection methods | Most common copies in healthy normal controls | Risk-associated CNVs (p-values) | Results | References |
|----------------------------|--------------------------------|--------------------------|-----------------------|-----------------------------------------------|---------------------------------|---------|------------|
| TLR7                       | BD                             | Chinese Han population (400 patients and 600 controls) | Real-time PCR          | One copy for male and two copies for female | (p = 1.92E–5) in female BD; A high copy number of TLR7 (p = 0.021 for males and p = 0.048 for females) | – | Fang et al. (2015) |
|                           | AS                             | Chinese Han population (649 patients and 628 controls) | AccuCopy™ method       | Not reported                                   | Lower copy number (=1), especially in males (p = 0.009 for TLR7_1 fragment and p = 0.01 for TLR7_2 fragment) | – | Wang et al. (2018) |
| GD and GO                  | Chinese population (196 controls and 484 GD patients, including 203 patients with GO) | Real-time polymerase chain reaction (PCR) | Not reported | A protective effect of lower than normal CNV for TLR7 (CNV <2 for females and CNV <1 for males) but no statistical significance and no association in GO | – | Liao et al. (2014) |
| TSHR                       | GD and GO                      | Chinese population (196 controls and 484 GD patients, including 203 patients with GO) | Real-time polymerase chain reaction (PCR) | Two copies                                      | Copy number <2 or >2 in GD, not in GO (p = 0.01) | – | Liao et al. (2014) |
| UGT2B17                    | AS                             | Newfoundland (298 patients and 299 controls) | Built-in DNA analytics aberration detection method-2 (ADM-2) algorithm | Two copies | The frequency of two copies higher in cases (p < 0.05) | – | Uddin et al. (2013) |

TABLE 1 (Continued) Copy number variant loci or genes related to autoimmune diseases.

and Davies, 2003; Iafrate et al., 2004; Mack et al., 2004; Redon et al., 2006; Yang et al., 2007; Yim et al., 2010). The mechanisms underlying the involvement of CNVs in clinical phenotypes are mainly gene disruption and rearrangement (McCarron and Altshuler, 2007; Yim et al., 2010). Further deep studies on CNVs have shed new light on human genome structure, genetic variations between individuals, and genetic pathogenic factors of human AIDs.

AIDs usually share possible common mechanisms, i.e., a defect in the immune tolerance exists due to diverse causes from central and peripheral tolerance mechanisms. Although majority of human genetic variations do not contribute to overt diseases (Tomer and Davies, 2003), some genetic variations including SNPs, nucleotide insertions/deletions, structural variations, and CNVs are known to link to several AIDs during the past few decades and are of importance in the susceptibility to AIDs and the potential therapeutic responses to medicines (Iafrate et al., 2004; Redon et al., 2006). Studies have revealed that some SNPs are related to AIDs and could be genetic mechanisms underlying the development of AIDs (Song et al., 2021a; Song et al., 2021b; Jiang et al., 2021). Structural variations including complex rearrangement of segments with sizes of thousands to millions of base pairs have been recognized as a rich source of genetic diversity. CNVs as a crucial source of genomic diversity caused by the rearrangement of genome are ubiquitously presented in human genome and may affect the susceptibility to many diseases (Iafrate et al., 2004). During the past years, thousands of gene CNVs have been reported (Redon et al., 2006). However, most studies focus on their relationship with tumors and chronic diseases (Jia et al., 2011; Saadati et al., 2016; Voll et al., 2017). Moreover, CNVs are very common in genomic regions encoding immune-related genes, which are closely related to the etiology of AIDs. Thus, they potentially impact polygenic autoimmunity and may lead to the imbalance of the autoimmune system and the development of some AIDs. Additionally, some common CNVs have also been reported to be correlated to several specific AIDs (Mamtani et al., 2008; Mamtani et al., 2010; Liu et al., 2011). Yim et al. (2015) reviewed studies on the clinical implications of copy number variations in autoimmune disorders in detail. However, the relationship between CNVs and the pathogenesis of AIDs has not been fully revealed. Furthermore, in recent years, as new
technologies develop, researches on CNVs have made new discoveries and progress. Herein, based on the emergence of numerous studies on the relationship between CNVs and AIDs in the past decades, we reviewed all the related studies and summarized their findings in order to provide new ideas for future explorations and to uncover the mechanisms underlying AIDs (Table 1).

**SYSTEMIC LUPUS ERYTHEMATOSUS**

Systemic lupus erythematosus (SLE), with a prevalence rate of eight–nine times higher in females than in males during childbearing age, is a typical systemic autoimmune inflammatory disease with a strong genetic susceptibility and is characterized by the production of autoantibodies and the existence of chronic inflammation. There is a wide range of clinical features in SLE patients, such as discoid lesions, nephritis, arthritis, and malar rash (Barbosa et al., 2018). So far, the exact genetic physiology of SLE remains an open question. Complement is well known to be involved in many immune-mediated diseases. Among them, complement component C4 is a pivotal effector of the immune system. There are two common isoforms of C4: C4A and C4B, and 95% of C4A and 54% of C4B contain an endogenous retroviral sequence in their ninth intron, HERV-K (C4) (Wouters et al., 2009). HERV-K (C4) can cause the antisense transcription of C4 as it is oriented opposite to C4 (Mack et al., 2004). According to the presence or absence of HERV-K (C4), there are two different size varieties of isotypes for both C4A and C4B: C4L (long) and C4S (short) (Mack et al., 2004; Wu et al., 2008). Hauptmann et al. (1974) first found the deficiency of C4 copy number in SLE patients. Later, Yang et al. (2007) uncovered that SLE patients had lower copy number of total C4 and C4A genes than healthy volunteers. Pereira et al. (2019) observed that the risk of developing SLE was 2.62 times higher in subjects with low total C4 copy number and 3.59 times higher in subjects with low C4A copy number. These consistent results imply that deletion or deficiency of C4 or C4 isoforms will increase the risk for SLE. The potential mechanism is like this, the decrease of C4 CNVs will cause C4 deficiency, bring the impairment of autoantigen clearance and the negative selection of auto-reactive B cells, and then favor the onset of SLE (Pereira et al., 2019). In addition, there was another study aiming at the relationship between C4 CNVs and the drug response to treatment of SLE. The study of Mulvihill et al. (2019) found that higher copy number of complement C4B and elevated serum complement levels were associated with hypertension and effective response to statin therapy in childhood-onset SLE patients.

C-C chemokine ligand 3 like-1 (CCL3L1) is a potent ligand for the HIV coreceptor, and C-C chemokine receptor 5 (CCR5) is an important factor in immune response (Gonzalez et al., 2005). Mamtani et al. (2008) found that the CNVs of CCL3L1–CCR5 were strong predictors for the overall risk of SLE and high autoantibody titers and lupus nephritis, and subjects with lupus nephritis differentially recruit leukocytes. Receptors for the Fc portion of IgG are involved in the handling and clearance of immune complex and in the regulation of B cell activation during SLE development (Niederer et al., 2010). Willcocks et al. (2008) have found that low copy number of Fc gamma receptor 3B (FCGR3B), which is correlated with protein expression and immune complex uptake, was associated with SLE, implying that the association of this gene CNVs with SLE may influence protein expression and function and further confer risk for the predisposition of AIDs. Molokhia et al. (2011) identified that low copy number of FCGR3A was associated with the risk of SLE in the Afro-Caribbean population, but not in the African ancestry population. Chen et al. (2014) further showed that low copy numbers (less than two copies) of FCGR3A or FCGR3B were significantly associated with SLE, and high copy numbers (more than two copies) of FCGR3A were also related to SLE onset in the Taiwanese population. Another team, Barbosa et al. (2018), detected CNV at whole-genome level using a case–control design and showed that increased FCGR3B/ADAM3A copy number was a protective factor against SLE development. In addition, they, for the first time, uncovered heterozygous deletions overlapping the CFHR4, CFHR5, and HLA-DPB2 genes in SLE patients. Notably, different genetic manifestations attributing to different backgrounds may present different trends of gene CNV association with diseases.

Heat shock proteins 90 (HSP90) is a pivotal modulator of multiple innate and adaptive inflammatory processes (Tamura et al., 2012). HSP90 has two major cytosolic isoforms, HSP90AA1 and HSP90AB1. Zhang et al. (2019) showed that HSP90AB1 CNV was correlated with SLE in the Chinese Han population, especially in females, implying that HSP90AB1 CNV is involved in the pathomechanism and development of SLE.

**RHEUMATOID ARTHRITIS**

Rheumatoid arthritis (RA) is characterized by a massive tissue infiltration of inflammatory cells and affects approximately 1% of the adult population worldwide. Clinically, it mainly causes the chronic inflammation of synovial joints, which will result in the progressive destruction of the cartilage and bone (Achour et al., 2018). Many lines of data have implied the association of RA with genetic variations including SNPs and CNVs of several immune-related genes (McKinney et al., 2008; Graf et al., 2012; Olsson et al., 2012).

It is intriguing whether FCGR3B CNV is involved in RA. Graf et al. (2012) found a significant association between low FCGR3B copy number and RA (Rahbari et al., 2017). Chen et al. (2014) revealed a significant association of RA with low copy number of FCGR3A, but not FCGR3B in a Chinese cohort. Then, Rahbari et al. (2017) verified that RA patients from the UK had decreased copy number of FCGR3B. More recently, Ben Kilani et al. (2019) reported that genotypes without null allele of FCGR3B gene (copy numbers range from 1 to 3) were significantly associated with RA. In addition, increased FCGR3B copy number was only found in RA, and deletion of FCGR3B may have a protective effect on RA. The discrepancies on the correlation of RA with FCGR3B CNVs
may partly be due to different genetic backgrounds, and this requires further investigation in different ethnic populations.

**INFLAMMATORY BOWEL DISEASE**

Inflammatory bowel disease (IBD) is a kind of organ-specific inflammatory disease and has two main clinical subtypes, ulcerative colitis (UC) and Crohn’s disease (CD). The occurrence of CD is 300 per 100,000 people in the population with European ancestry and increasing in other ethnic populations. CD affects the gastrointestinal tract and has such symptoms, like diarrhea, abdominal pain, and aberrant weight loss (Cleynen et al., 2016). Studies have demonstrated the associations between C4 gene and several AIDs (Hauptmann et al., 1974; Hou et al., 2013), and the team led by Cleynen et al. (2016) showed that CD cases tended to have lower C4L and higher C4S copies. They also found that serum C4 protein level was not significantly different between CD patients and controls, but CD patients with higher C4 copy number may have higher serum C4 concentration (Cleynen et al., 2016). These results suggest that more C4 copy number may lead to higher C4 expression and there may be a dose-efficiency correlation between C4 copy number and protein expression in CD patients. Asano et al. (2013) studied polymorphisms of FCGR genes in the Japanese population and found that FCGR3B copy number was related to susceptibility of UC.

Defensins are endogenous antimicrobial peptides to protect the intestinal mucosa against bacterial invasion. Fellermann et al. (2006) showed that healthy volunteers as well as UC patients have 2 to 10 copies of the human beta-defensin 2 (HBD-2) gene with the median of 4 copies. However, patients with colonic CD have lower HBD-2 copy than the controls. In addition, they also found that less than four copies of HBD-2 gene were correlated with diminished mucosal HBD-2 mRNA expression (Fellermann et al., 2006). The DEFA1A3 gene encodes alpha-defensins 1–3. Jespersgaard et al. (2011) found that a higher DEFA1A3 copy number was related to CD, especially to colonic CD.

**PSORIASIS**

Psoriasis is a serious inflammatory disease of the skin, scalp, nails, and joints and has a prevalence of about 2% in the populations of developed countries (McKinney et al., 2008). Multiple studies have identified a strong genetic component in the development of psoriasis and demonstrated the relationship between CNV of some genes and psoriasis. Wu et al. (2014) found that Chinese patients with psoriasis vulgaris had a higher copy number (more than two copies) of FCGR3B compared to controls through a case–control study. Carpenter et al. (2011) found no association between CCL3L1 copy number and psoriasis. HolloX et al. studied psoriasis in Dutch and German populations and found significant associations between higher genomic copy number for beta-defensin genes (DEFB4, SPAG11, DEFB103, DEFB104, DEFB105, DEFB106, and DEFB107) and the risk of psoriasis in both of these cohorts.

IL-22, which belongs to IL-10 cytokine family, has a significant proliferative effect on different cell lines and a role of immune regulation. Prans et al. (2013) showed that the copy number variation in exon 1 but not exon 5 of IL-22 gene was significantly correlated with the severity of psoriasis.

With the emergence of new technologies, more loci with CNVs have been identified to be associated with psoriasis. Bergboer et al. (2012) utilized a pooling approach, genome-
wide CNV analysis, and array comparative genomic hybridization to detect CNV variability in psoriasis and found that the absence of the late cornified envelope (LCE) gene cluster members LCE3B and LCE3C (LCE3C-LCE3B-del) was significantly associated with the predisposition of psoriasis in populations from Netherlands.

**BEHCET’S DISEASE**

Behcet’s disease (BD) is an immune-mediated systemic inflammatory disorder involving non-granulomatous uveitis, recurrent oral and genital ulcers, as well as skin lesions (Yang et al., 2008a). It has been verified to be associated with the HLA-B51 gene (Xu et al., 2015). Further studies have provided new insight into the pathogenesis of BD and attracted more attentions on whether complement is involved in BD. Hou et al. (2013) investigated the relationship of CNV of C4A and C4B with BD and found that the frequency of more than two copies of C4A was significantly increased in BD patients, and C4A CNV was an independent risk factor for BD. Moreover, C4A expression was significantly increased in BD patients with high C4A copy number than with low C4A copy number (Hou et al., 2013). Xu et al. (2015) found that BD patients have increased frequencies of more than two C3 copies, and C5 CNV was associated with BD. Furthermore, interleukin-17 (IL-17) and IFN-gamma expressions were upregulated in BD patients with high C3 copy number, but not in BD patients with high C5 copy number (Xu et al., 2015). The results imply that there are indeed CNVs in complement-related genes, and the CNVs in these genes may be involved in the development of BD.

There were also some studies targeting the relationship between FCGR3B CNVs and BD. Black et al. (2012) found that CNV of the FCGR3B gene was associated with the risk of BD in the Iranian population. The risk of BD was decreased by 40% in people with less than two copies of FCGR3B and by 25% in people with more than two copies of FCGR3B, although these tendencies were not statistically significant. They concluded that no association exists between high or low copy number of FCGR3B and BD or its clinical features (Black et al., 2012). Of course, further studies are need to identify this result in other populations.

Toll-like receptors (TLRs), along with RIG-I-like receptor and NOD-like receptors, belong to the family of pattern recognition receptors and contain 10 functional members in human beings, namely, TLR1–10 (Medzhitov et al., 1997). TLRs have been known to play important functional roles in several AIDs and inflammatory disorders (Chang et al., 2004; Chang et al., 2006). Fang et al. (2015) uncovered that more than 98% of people tested have two copies of all TLRs except for TLR7. In addition, they found that compared to healthy controls, male BD patients had an increased frequency of more than one copy of TLR7, and female BD patients had an increased frequency of more than two copies of this gene. This research suggested that a high TLR7 copy number may contribute to the pathogenesis of BD (Fang et al., 2015). Therefore, from this research, we included that TLRs also play a potential role in BD, and the mechanism underlying this still needs to be clarified.

Many interleukins play vital roles in BD development. Hou et al. (2015) showed that BD patients have increased frequencies of more than two copies of IL-17F and IL-23A, and after stratified by sex, the association just exists in male BD patients. IL-17F protein expression is positively correlated with its gene copy number, and higher IL-17F copies are associated with enhanced proliferation of peripheral blood mononuclear cells (PBMC) (Hou et al., 2015). This suggests that not only SNPs but also CNVs of interleukins are involved in the pathogenesis of BD. Liao et al. (2015) investigated the association of some transcript factors with BD and showed that high CNV of related orphan receptor (RORC) was associated with BD susceptibility, and low Foxp3 CNV was correlated with female BD. In addition, individuals with high RORC copy number seem to have relatively high mRNA levels of RORC, IL-1β, and IL-6, but not Foxp3 (Liao et al., 2015).

The disturbed apoptosis has been reported to be involved in BD development. Yu et al. (2015) investigated whether CNVs of apoptosis-related genes, including FAS, caspase8, caspase3, and BCL2, were associated with BD in the Chinese population and showed that BD patients had an increased frequency of high FAS copy number, and BD patients with more than two copies of FAS had an increased mRNA expression of FAS in anti-CD3/CD28 antibody-stimulated CD4+ T cells. Their results provided important evidence that high FAS copy number is involved in the pathogenesis of BD (Yu et al., 2015).

It is well-known that BD may be triggered by infectious agents in some genetically susceptible people. DEFB4 CNV can affect the level of human beta-defensin 2, which is an inducible antimicrobial peptide. Park et al. (2011) found that DEFB4 copy number was lower in BD samples than in controls without statistical significance, and DEFB4 copy number was not associated with the clinical characteristics of BD. This suggests that DEFB4 CNVs confer no risk for the susceptibility of BD (Park et al., 2011). In 2012, Ahn et al. (2012) found that 31.1% of samples had five copies of DEFA1 with a mean of 5.4 ± 0.2. Although the distribution of DEFA1 copy number is not different between BD patients and the controls, high DEFA1 copy number is related to the intestinal involvement in BD, suggesting that a high DEFA1 copy number may be associated with the development of intestinal involvement in BD (Ahn et al., 2012). Hitherto, the genes related to infectious agents may be involved in BD through changing the variation of copy number, and further researches are needed to be carried out to identify this.

There was another study that investigated the relationship between microRNA CNVs and BD, like miR-23a, miR-146a, and miR-301a. As a result, no association of CNVs of the above-mentioned miRNAs was observed in BD patients (Hou et al., 2016). However, whether other microRNA CNV is associated with BD still needs further studies to explore and clarify.

**ANKYLOSING SPONDYLITIS**

Ankylosing spondylitis (AS) is an inflammatory AID causing spondyloarthritides of the spine and sacroiliac joints and prevalent
mainly in men with a ratio of 10:1 at the age of 20–30 years old in respect to women (Chimenti et al., 2021). Because the exact pathology of AS is still unclear, there are incoming data about the relationship between CNVs of these genes and AS, including CCL3L1, FCGR3A, FCGR3B, TLR7, UGT2B17, BMP8A, and so on. Wang et al. (2016) found that AS patients had low copies (≤3) of FCGR3A and FCGR3B in the Chinese population, implying that a lower copy number of these two genes confers risk for the susceptibility of AS. The study of Dahmani et al. (2019) found that the proportion of AS patients with less than two copies of FCGR3A was higher in the Algerian population and that less than two copies of FCGR3A was only associated with HLA-B27-negative AS patients, suggesting that FCGR3A deletion has an independent effect on AS regarding HLA-B27 status. Their results also showed that CCL3L1 and FCGR3B CNVs may not be involved in the predisposition of AS in the Algerian population (Dahmani et al., 2019). Wang et al. (2018) found that one copy of TLR7 was related to AS in the Chinese population after Bonferroni correction and adjustment of age and sex, and less than one copy of TLR7 confers risk for AS susceptibility in male patients, but is a protective factor in female AS patients. Uddin et al. (2013) conducted a genome-wide CNV analysis and found that UGT2B17 copy number was increased in a large AS multiplex family. The UGT2B17 gene encodes an enzyme that metabolizes steroid hormones such as testosterone and selected xenobiotics (Xue et al., 2008). UGT2B17 copy number has been shown to be related to bone mineral density and involved in the pathogenesis of osteoporosis (Yang et al., 2008b). It is known that AS in patients is often accompanied with osteoporosis (Vosse et al., 2009). This may, to some extent, explain the underlying mechanism that gain in UGT2B17 copy number could increase the risk for AS. Bone morphogenic protein 8A (BMP8A) plays multiple functions in the formation of a bone. Shahba et al. (2018) reported that the expression of BMP8A in PBMCs is decreased in AS patients, and BMP8A CNVs do not influence its transcription in PBMCs and are not associated with AS susceptibility in the Iranian population. Cai et al. (2015) found that the copy number of defensing-related gene DEFB103 was in the range of two to six in both AS patients and controls, and it was not associated with AS. More studies in different populations are needed to further identify the relationship between these gene CNVs and BD.

CD4+ T cells play pivotal roles in many AIDs, but whether CNVs of transcription factor genes in CD4+ T cells are involved in AS remains poorly defined. Bai et al. (2016) investigated whether CNV of transcription factor genes in CD4+ T cells including T-bet, GATA binding protein 3 (GATA-3), RORC, and fork-head box protein 3 (FOXP3) are associated with acute anterior uveitis (AAU) in the presence or absence of AS. They found that a higher T-bet copy number is more common in AAU+, AS+ and AAU+, AS− cases compared with healthy controls. Additionally, the frequency of AAU+, AS+ patients with high GATA-3 copy is higher, and the proportion of female AAU+, AS+ patients with high FOXP3 copy number is also higher than that of other populations, but the copy number of RORC is not correlated with AAU+, AS+ or AAU+, AS− patients (Bai et al., 2016).

People are also interested in the relationship between CNVs of various microRNAs (miRNAs). Yang et al. (2017) studied the association between CNVs of miRNAs and AS and found that the frequencies of AAU+, AS+ patients with low copy numbers of miR-143, miR-146a, miR-9-3, and miR-205 as well as high copy numbers of miR-301a and miR-23a all increased, and the frequencies of patients with AAU+, AS− with low copy number of miR-146a and high copy numbers of miR-23a and miR-205 are significantly different. In addition, they found that miR-9-3 mRNA expression is significantly decreased in AAU+, AS+ patients and positively correlated with its copy number (Yang et al., 2017).

**PRIMARY SJOGREN’S SYNDROME**

Primary Sjögren’s syndrome (pSS) is characterized by the presence of circulating autoantibody (anti-Ro/SSA and anti-La/SSB), as well as the involvement of the exocrine glands (salivary and lacrimal gland), joint, and muscle (Nossent et al., 2012; Haldorsen et al., 2013). There were few studies on the issue of FCGR3B CNVs and pSS. Mantani et al. (2010) showed that the median FCGR3B gene copy is two in the cohort of Spanish ancestry. The risk of pSS would increase if people carry less or more than two copies of FCGR3B (Mantani et al., 2010). Nossent et al. (2012) conducted a case–control study and found that less than two copies of FCGR3B can confer risk for pSS in the Australian population, and low FCGR3B copy number is associated with the levels of rheumatoid factor (RF) titers and serum IgG, but not with anti-Ro ± La autoantibodies. They further identified that FCGR3B CNV is a genetic susceptibility factor for pSS (Liao et al., 2015). However, Haldorsen et al. (2013) showed no association of FCGR3B CNV with pSS in the Norwegian and Switzerland populations. To clarify, these controversial results need more studies in more populations with different ethnicities and regions.

**TYPE 1 DIABETES MELLITUS**

Type 1 diabetes mellitus (T1DM) is characterized by β cell destruction in the pancreas and the production of antibodies against β cells, with a high prevalence of 1 in 350 teenagers in the UK (Bluestone et al., 2010). There is a series of symptoms in T1DM, such as polydipsia, polyuria, polyphagia, and weight loss. C4 is a gene of the highly variable complement pathway situated ~500 kb from DRB1 and DQB1 and strongly associated with diverse AIDs (Hauptmann et al., 1974; Hou et al., 2013; Cleynen et al., 2016), so some scientists also carried out numerous researches to uncover whether C4 is associated with T1DM development. Kingery et al. (2012) found that higher C4A copy number tends to be correlated with the protection of residual β-cell function in new-onset T1DM patients, while lower C4B copy number is related to the end of disease remission at 9 months post diagnosis. Mason et al. (2014) explored the relationship between C4 CNV and T1DM and found that individuals with T1DM have significantly fewer...
copies of HERV-K (C4), one notable component of C4. About the relationship between CCL3L1, people also did a lot of work. McKinney et al. (2008) revealed an association between CCL3L1 CNVs and T1DM in the Caucasian population from New Zealand, but the association was not statistically significant with P of 0.064. Then, the Wellcome Trust Case Control Consortium found no association between CCL3L1 CNV and T1DM (Wellcome Trust Case Control Consortium et al., 2010). These work are consistent and implies that CCL3L1 CNVs may be not associated with T1DM. FCGR3B CNVs are involved in the pathogenesis of several AIDs, such as SLE and RA, because its role in the clearance of immune complexes is impaired in these disease settings (Willcocks et al., 2008; Graf et al., 2012). Almal and Padh (2015) found that FCGR3B copy number in the Indian population varies significantly from zero to two per diploid genome in other populations, which helps us to understand the potential role of FCGR3B CNV and its association with AIDs in the Indian population.

Killer immunoglobulin-like receptors (KIRs) reside on the surface of natural killer cells to bind to their corresponding human leukocyte antigen (HLA) class I ligands. It is noted that KIRs are vital candidates for HLA-associated AIDs, including T1DM. Although Pontikos et al. (2014) did not find a relation of KIR3DL1/3DS1 copy number to T1DM in the white European population, Grayson et al. (2010) utilized a more powerful genome-wide CNV analysis and found 39 CNVs either enriched or depleted in T1DM patients, including a deletion on chromosome 6p21, near an HLA-DQ allele. Their results indicated that both enrichment and depletion of these genes are high risk factors for developing T1DM, and genetic variants such as CNVs may contribute to the development of islet autoimmunity in T1DM (Grayson et al., 2010).

AUTOIMMUNE THYROID DISEASE

Autoimmune thyroid disease (AITD), which mainly includes Graves’ disease (GD), Hashimoto’s thyroiditis (HT), and Graves’ ophthalmopathy (GO), is a kind of organ-specific AID with a prevalence of 5% of the overall population (Jin et al., 2018). GD is characterized by hyperthyroidism caused by positive autoantibodies against thyroid-stimulating hormone receptors (TSHR), and HT is often characterized by positive anti-thyroid peroxidase antibody (TPOAb), anti-thyroglobulin antibody (TgAb), and hypothyroidism. There have been many studies focusing upon the relationship between the CNVs of immune-related genes and the development of AITD, and lots of interesting results have been reported. The two earliest studies on CNVs and AITD were both published in 2011. One study aimed to explore the association between CNVs of immune regulatory genes and AITD and found no CNVs of CD40 and CTLA4 genes in GD cases and few PTPN22 CNVs in two GD individuals (Huber et al., 2011). Liu et al. (2011) found that CNVs of C4, C4A, and C4B contribute to the predisposition of GD, but not GO. Liao et al. (2014) revealed that TSHR CNVs harbor the etiology of GD, but not GO. Besides, they also observed that only female GD patients have fewer TLR7 copies, and there is no significant association between sex and TLR7 CNVs (Liao et al., 2014). GD is a disease predominantly in females (Manji et al., 2006); therefore, they believed that TLR7 CNVs affect the pathogenesis of female GD due to the gender-dependent immune response (Liao et al., 2014). In 2017, we conducted microarray to explore the profile of genes with CNVs in GD and found some genes with copy number gain. In addition, seven of these genes including CFH, CFHR1, KIAA0125, UGT2B15, UGT2B17, TRY6, and CCL3L1 were chosen to further validate these findings in an expanded cohort. The results showed no correlation between CNVs of these genes and GD (Song et al., 2017). Jin et al. (2018) assessed CNVs of two immune-related genes SIRPB1 and TMEM91 in AITD and found that the distributions of SIRPB1 copy number were different between AID patients and the controls, implying SIRPB1 is a risk factor for AITD. Guan et al. (2020) showed that the distribution of copy numbers of cell growth-related genes glypican-5 (GPC5), B9 domain-containing 2 (B9D2), as well as ankyrin repeat and suppressor of cytokine signaling (SOCS) box-containing protein 11 (ASB11) is different in AITD patients and the controls, and GPC5 CNVs are risk factors for AITD. However, they did not find any association between their CNVs and the occurrence of AITD (Guan et al., 2020). The different relationship between CNVs of these genes and different sub-types of AITD implies the diverse genetic mechanisms underlying AITD. Overall, researchers have found that CNVs of several thyroid-susceptible genes are correlated with the development of AITD. Studies on the correlation between CNVs and AITD susceptibility inevitably deepen our understanding of the pathogenetic mechanism of AITD and further promote molecular diagnosis and therapies of AITD. These studies were mainly done in Chinese population; in the future, we will need further studies in more populations to identify these results.

FUTURE OUTLOOK

To further gain new and deep insights on the genetic mechanism of AIDs, we reviewed the association between different AIDs and CNVs of some genes with potential pivotal roles in the development of AIDs. This review provides an update evolving the view of copy number variations in AIDs. For the first, several CNVs are very common in diverse AIDs, implying these AIDs may potentially possess a similar genetic pathomechanism. Therefore, more association studies should be done on some other diseases when a certain link is identified between some CNVs and a specific AID. For the second, some CNVs are differently distributed in various diseases in different ethnic populations, suggesting that AIDs have their own different phenotypes and different genetic and/or environmental backgrounds among diverse populations. Herein, more researches aiming to uncover the relationship between environmental factors and diseases and the influences of environmental elements on immunity should be encouraged. For the third, with the continuous advancement in genotyping technology such as the high-throughput whole-genome sequencing method, more susceptible variants will be found.
Thus, further replication studies should be conducted to confirm the results of studies with different ethnic cohorts and independent populations. For that, CNVs may be an important pathogenesis of AIDs; CNVs will also become an effective way to study the molecular mechanism of AIDs; and we can find molecular markers for genetic diagnosis or judgment of prognosis of this kind of disease. At the same time, it opens a new page for the research of AIDs and is becoming a new research hotspot. We believe that genetic diagnosis or judgment of prognosis based on CNVs will cover more AID spectrum and benefit a wider population. It is believed that with the high-throughput genome-wide CNV scanning platform and the new development of statistical calculation method, GWAS based on CNVs, a new genetic susceptibility marker, will become a powerful tool to study the genetic susceptibility of AIDs, just like the traditional GWAS based on SNPs and their haplotypes. These two complementary genetic markers will help us to understand the molecular mechanism, identify susceptible genes, and understand the relationship between genetic variations and disease phenotype of complex diseases, such as AIDs, which is of great significance. Simultaneously, to our hope, more functional experiments and more replication studies should be done and collected, and an entire autoimmune CNVs database should be set up, which can be searched easily and help us to understand the pathogenesis of AIDs much better. GWAS has already pointed toward genetic susceptibility loci and potential mechanisms of pathogenicity. Chromosomal microarrays have added little further information. It therefore seems unlikely that whole-genome sequencing alone will answer the necessary questions. Rather, genomic DNA approaches will likely need to be combined with other measures, such as RNA sequencing and/or proteomics to solve many of the remaining questions at hand.

Although CNVs describe the pathogenesis of AIDs from a new perspective, it is still early to explain the occurrence and development of complex diseases only by CNVs at the genomic level because the molecular mechanism of complex diseases at the chromosomal level is not completely clear. Due to the existence of multiple mechanisms of CNVs and the different effects of CNVs on molecular phenotype and gene expression, therefore, the interpretation of clinical significance and genetic mode of CNVs must be done more carefully, and it should be based on the comprehensive assessment of genomic variation.

**AUTHOR CONTRIBUTIONS**

R-HS designed the study. C-QG and JZ extracted the data. R-HS analyzed the data and wrote the first draft of the report. J-AZ revised the manuscript. All authors contributed to the article and approved the submitted version.

**FUNDING**

The present work has received funding from the National Natural Science Foundation of China (Grant No. 81800696 and 81873636), the Shanghai University of Medicine and Health Sciences hundreds of Talented Teachers Project (No. B3-0200-20-311008-30), the Science and Technology Development Fund of Pudong New District Minsheng Scientific Research (Medical and Health) Project (No. PKJ2018-Y39). The grant number of the Talent Youth Cultivation Plan of Pudong New District is No. PWQr2020-11, then the grant number of the Shanghai Medical Key Specialty is No. ZK2019C09.

**ACKNOWLEDGMENTS**

We thank all authors who took the original studies here.

**REFERENCES**

Achour, Y., Ben Kilani, M. S., Ben Hamad, M., Marzouk, S., Mahfoudh, N., Bahloul, Z., et al. (2018). Measurement of Absolute Copy Number Variation of Glutathione S-Transferase M1 Gene by Digital Droplet PCR and Association Analysis in Tunisian Rheumatoid Arthritis Population. *J. Clin. Lab. Anal.* 32 (3), e22300. doi:10.1002/jcla.22300

Ahn, J. K., Cha, H.-S., Lee, J., Jeon, C. H., and Koh, E.-M. (2012). Correlation of DEFA1 Gene Copy Number Variation with Intestinal Involvement in Behcet’s Disease. *J. Korean Med. Sci.* 27 (1), 107–109. doi:10.3346/jkms.2012.27.1.107

Almal, S. H., and Padh, H. (2015). Frequency Distribution of Autoimmunity associated FCGR3B Gene Copy Number in Indian Population. *Int. J. Immunogenet.* 42 (1), 26–30. doi:10.1111/j.12165

Asano, K., Matsumoto, T., Umeno, J., Hirano, A., Esaki, M., Hosono, N., et al. (2013). Impact of Allele Copy Number of Polymorphisms in FCGR3A and FCGR3B Genes on Susceptibility to Ulcerative Colitis. *Inflamm. Bowel Dis.* 19 (10), 2061–2068. doi:10.1097/MIB.0b013e318298118e

Bai, L., Liu, Y., Hou, S., Liao, D., Kijlstra, A., and Yang, P. (2016). Association of T-Bet, GATA-3, RORC, and FOXP3 Copy Number Variations with Acute Uveitis with or without Ankylosing Spondylitis in Chinese Han. *Invest. Ophthalmol. Vis. Sci.* 57 (4), 1847–1852. doi:10.1167/iovs.15-17960

Barbosa, F. B., Simioni, M., Wiel, C. E. V., Torres, F. R., Molck, M. C., Bonilla, M. M., et al. (2018). Copy Number Variation in the Susceptibility to Systemic Lupus Erythematosus. *PLoS One* 13 (11), e0206683. doi:10.1371/journal.pone.0206683

Ben Kilani, M. S., Achour, Y., Perea, J., Cornelis, F., Bardin, T., Chaudru, V., et al. (2016). Characterization of Copy Number Variants for CCL3L1 Gene in Rheumatoid Arthritis for French Trios Families and Tunisian Cases and Controls. *Clin. Rheumatol.* 35 (8), 1917–1922. doi:10.1007/s10067-015-3156-y

Ben Kilani, M. S., Cornèliss, F., Olasoro, R., Chaudru, V., and Petit-Teixeira, E. (2019). Investigation of Candidate Gene Copy Number Identifies FCGR3B as a Potential Biomarker for Rheumatoid Arthritis. *Clin. Exp. Rheumatol.* 37 (6), 923–928.

Bergboer, J. G. M., Umičević-Mirkov, M., Fransen, J., den Heijer, M., Franke, B., van Riel, P. L. C. M., et al. (2012). A Replication Study of the Association between Rheumatoid Arthritis and Deletion of the Late Corni Gene LCE3B and LCE3C. *PLoS One* 7 (2), e32045. doi:10.1371/journal.pone.0032045

Black, R., Lester, S., Dunstan, E., Shahram, F., Nadji, A., Bayat, N., et al. (2012). Fc- Gamma Receptor 3B Gene Copy Number Variation Is Not a Risk Factor for Behçet’s Disease. *Int. J. Rheumatol.* 2012, 167096. doi:10.1155/2012/167096

Blackburn, A. C., Matthaei, K. I., Lim, C., Taylor, M. C., Cappello, J. Y., Hayes, J. D., et al. (2006). Deficiency of Glutathione Transferase Zeta Causes Oxidative

Frontiers in Genetics | www.frontiersin.org 13 January 2022 | Volume 12 | Article 794348
Mammani, M., Rovin, B., Brey, R., Camargo, J. F., Kulkarni, H., Herrera, M., et al. (2008). CCL3L1 Gene-Containing Segmental Duplications and Polymorphisms in CCR5 Affect Risk of Systemic Lupus Erythematosus. Ann. Rheum. Dis. 67 (8), 1076–1083. doi:10.1136/ard.2007.078048

Mammani, M., Anaya, J.-M., He, W., and Ahuja, S. K. (2010). Association of Copy Number Variation in the FCGR3B Gene with Risk of Autoimmune Diseases. Genes Immun. 11 (2), 155–160. doi:10.1038/genes.2009.71

Manji, N., Carr-Smith, J. D., Boelkaert, A., Allahabadi, A., Armitage, M., Chatterjee, V. K., et al. (2006). Influences of Age, Gender, Smoking, and Family History on Autoimmune Thyroid Disease Phenotype. J. Clin. Endocrinol. Metab. 91 (12), 4873–4880. doi:10.1210/jc.2006-1402

Mason, M. J., Speake, C., Gersuk, V. H., Nguyen, Q. A., O’Brien, K. K., Odegard, J. M., et al. (2014). Low HERV-K(C4) Copy Number Is Associated with Type 1 Diabetes. Diabetes 63 (5), 1789–1795. doi:10.2337/db13-1382

McCarroll, S. A., and Altshuler, D. M. (2007). Copy-number Variation and Association Studies of Human Disease. Nat. Genet. 39 (7 Suppl. 1), S37–S42. doi:10.1038/ng2080

McKinney, C., Merriman, M. E., Chapman, P. T., Gow, P. J., Harrison, A. S., Highton, J., et al. (2008). Evidence for an Influence of Chemokine Ligand 3-like 1 (CCL3L1) Gene Copy Number on Susceptibility to Rheumatoid Arthritis. Ann. Rheum. Dis. 67 (3), 409–413. doi:10.1136/ard.2007.075028

Medzhitov, R., Preston-Hurlburt, P., and Janeway, C. A., Jr. (1997). A Human Homologue of the Drosophila Toll Protein Signals Activation of Adaptive Immunity. Nature 388 (6640), 394–397. doi:10.1038/41131

Moholkia, M., Facchini, M., Petretto, E., Patrick, A. L., McKeigue, P., Roberts, A. L., et al. (2011). FCGR3B Copy Number Variation Is Associated with Systemic Lupus Erythematosus Risk in Afro-Caribbeans. Rheumatology 50 (7), 1206–1210. doi:10.1093/rheumatology/keq456

Mulvihill, E., Ardin, S., Thompson, S. D., Zhou, B., Yu, G. R., King, E., et al. (2019). Elevated Serum Complement Levels and Higher Gene Copy Number of Complement C4B Are Associated with Hypertension and Effective Response to Statin Therapy in Childhood-Onset Systemic Lupus Erythematosus (SLE). Lupus Sci. Med. 6 (1), e000333. doi:10.1177/20551166190000333

Niederer, H. A., Clatworthy, M. R., Willcocks, L. C., and Smith, K. G. C. (2010). Inclusion of ALK5HS as a Candidate Gene for the Susceptibility of Autoimmune Thyroid Disease. Adv. Med. Sci. 66 (2), 351–358. doi:10.1016/adsms.2011.07.006

Song, R.-h., Liu, X.-r., Gao, C.-q., Du, P., and Zhang, J.-a. (2021). METTL3 Gene Polymorphisms Contribute to Susceptibility to Autoimmune Thyroid Disease. Endocrine 72 (2), 495–504. doi:10.1002/endo.2020-02503-1

Tamura, Y., Torigoe, T., Kotoshi, G., Hirotaka, K., and Sato, N. (2012). New Paradigm for Intrinsic Function of Heat Shock Proteins as Endogenous Ligands in Inflammation and Innate Immunity. Curr. Mol. Med. 12 (9), 1198–1206. doi:10.2174/15665241283036710

Tomer, Y., and Davies, T. F. (2003). Searching for the Autoimmune Thyroid Disease Susceptibility Genes: from Gene Mapping to Gene Function. Endocr. Rev. 24 (5), 694–717. doi:10.1210/er.2002-0030

Uddin, M., Maksymowych, W. P., Imman, R., Gladman, D., Munn, A., Yazdani, R., et al. (2013). UGT2B17 Copy Number Gain in a Large Ankylosing Spondylitis Multiplex Family. BMC Genet. 14, 67. doi:10.1186/1471-2156-14-67

Voll, S. L., Boot, E., Butcher, N. J., Cooper, S., Heung, T., Chow, E. W. C., et al. (2017). Obesity in Adults with 22q11.2 Deletion Syndrome. Genet. Med. 19 (2), 204–208. doi:10.1038/gim.2016.98

Vosse, D., Landewe, R., van der Heijde, D., van der Linden, S., van Staa, T.-P., and Geusens, P. (2009). Ankylosing Spondylitis and the Risk of Fracture: Results from a Large Primary Care-Based Nested Case-Control Study. Ann. Rheum. Dis. 68 (12), 1839–1842. doi:10.1136/ard.2008.100503

Wang, L., Yang, X., Cai, G., Xin, L., Xia, Q., Zhang, X., et al. (2016). Association Study of Copy Number Variants in FCGR3A and FCGR3B Gene with Risk of Ankylosing Spondylitis in a Chinese Population. Rheumatol. Int. 36 (3), 437–442. doi:10.1002/rheu.00296-015-3384-0

Wang, M., Xu, S., Zhang, X., Chen, M., Han, R., Hu, X., et al. (2018). Association of TLR7 Gene Copy Number Variations with Ankylosing Spondylitis in a Chinese Population: a Case Control Study. Clin. Exp. Rheumatol. 36 (5), 814–819.

Wellcome Trust Case Control ConsortiumCoddock, N., Hurles, M. E., Cardin, N., Pearson, R. D., Plagnol, V., et al. (2010). Genome-wide Association Study of CNVs in 16,000 Cases of Eight Common Diseases and 3,000 Shared Controls. Nature 464 (7289), 713–720. doi:10.1038/nature08979

Willcocks, L. C., Lyons, P. A., Clatworthy, M. R., Robinson, J. I., Ya, W., Newland, S. A., et al. (2008). Copy Number of FCGR3B, Which Is Associated with Systemic Lupus Erythematosus, Correlates with Protein Expression and Immune Complex Uptake. J. Exp. Med. 205 (7), 1573–1582. doi:10.1084/jem.20072413

Wouters, D., van Schouwenburg, P., van der Horst, A., de Boer, M., Schooneman, D., Kuipers, T. W., et al. (2009). High-throughput Analysis of the C4 Polymorphism by a Combination of MLPA and Isotype-specific ELISA’s. Mol. Immunol. 46, 592–600. doi:10.1016/j.molimm.2008.07.028

Wu, Y. L., Yang, Y., Chung, E. K., Zhou, B., Kitzmiller, K. J., Savelli, S. L., et al. (2008). Phenotypes, Genotypes and Disease Susceptibility Associated with Gene Copy Number Variations: Complement C4 CNVs in European American Healthy Subjects and Those with Systemic Lupus Erythematosus. CytoGenet. Genome Res. 123, 131–141. doi:10.1159/000184700

Wu, Y., Zhang, Z., Tao, L., Chen, G., Liu, F., Wang, T., et al. (2014). A High Copy Number of FCGR3B Is Associated with Psoriasis Vulgaris in Han Chinese. Dermatology 229 (2), 70–75. doi:10.1159/000360160

Xu, D., Hou, S., Zhang, J., Jiang, Y., Kijistra, A., and Yang, P. (2015). Copy Number Variations and Gene Polymorphisms of Component Compounds in Ocular Behcet’s Disease and Vogt-Koyanagi-Harada Syndrome. Sci. Rep. 5, 12989. doi:10.1038/srep12989

Xue, Y., Sun, D., Daly, A., Yang, F., Zhou, X., Zhao, M., et al. (2008). Adaptive Evolution of UGT2B17 Copy-Number Variation. Am. J. Hum. Genet. 83 (3), 337–346. doi:10.1086/ajhg.2008.008
Yang, Y., Chung, E. K., Wu, Y. L., Savelli, S. L., Nagaraja, H. N., Zhou, B., et al. (2007). Gene Copy-Number Variation and Associated Polymorphisms of Complement Component C4 in Human Systemic Lupus Erythematosus (SLE): Low Copy Number Is a Risk Factor for and High Copy Number Is a Protective Factor against SLE Susceptibility in European Americans. *Am. J. Hum. Genet.* 80 (6), 1037–1054. doi:10.1086/518257

Yang, P., Fang, W., Meng, Q., Ren, Y., Xing, L., and Kijlstra, A. (2008). Clinical Features of Chinese Patients with Behçet’s Disease. *Ophthalmology* 115, 312–318. doi:10.1016/j.ophtha.2007.04.056

Yang, T.-L., Chen, X.-D., Guo, Y., Lei, S.-F., Wang, J.-T., Zhou, Q., et al. (2008). Genome-wide Copy-Number-Variation Study Identified a Susceptibility Gene, UGT2B17, for Osteoporosis. *Am. J. Hum. Genet.* 83 (6), 663–674. doi:10.1016/j.ajhg.2008.10.006

Yang, L., Du, L., Yue, Y., Huang, Y., Zhou, Q., Cao, S., et al. (2017). miRNA Copy Number Variants Confer Susceptibility to Acute Anterior Uveitis with or without Ankylosing Spondylitis. *Invest. Ophthalmol. Vis. Sci.* 58 (4), 1991–2001. doi:10.1167/iovs.16-21047

Yim, S.-H., Kim, T.-M., Hu, H.-J., Kim, J.-H., Kim, B.-J., Lee, J.-Y., et al. (2010). Copy Number Variations in East-Asian Population and Their Evolutionary and Functional Implications. *Hum. Mol. Genet.* 19, 1001–1008. doi:10.1093/hmg/ddp564

Yim, S.-H., Jung, S.-H., Chung, B., and Chung, Y.-J. (2015). Clinical Implications of Copy Number Variations in Autoimmune Disorders. *Korean J. Intern. Med.* 30 (3), 294–304. doi:10.3904/kjim.2015.30.3.294

Yu, H., Luo, L., Wu, L., Zheng, M., Zhang, L., Liu, Y., et al. (2015). FASGene Copy Numbers Are Associated with Susceptibility to Behçet Disease and VKH Syndrome in Han Chinese. *Hum. Mutat.* 36 (11), 1064–1069. doi:10.1002/humu.22829

Zhang, M., Gu, Y., Huang, S., Lou, Q., Xie, Q., Xu, Z., et al. (2019). Copy Number Variations and Polymorphisms in HSP90AB1 and Risk of Systemic Lupus Erythematosus and Efficacy of Glucocorticoids. *J. Cel Mol. Med.* 23 (8), 5340–5348. doi:10.1111/jcmm.14410

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher’s Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Song, Gao, Zhao and Zhang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.