ABSTRACT

The common neurodegenerative disorder of the central nervous system is multiple sclerosis (MS). It progresses with autoimmune inflammation and demyelination. Molecular basis study of MS pathogenesis is a significant element of field research, leading to new prevention and treatment strategies by defining the genetic association, epigenetic, and environmental risks factor of MS that could provide a predictive method for estimating human predisposition to MS. From a genetic perspective, MS is a complex disorder due to the combination of genetic and non-genetic factors. The main histocompatibility complex (MHC) is the only universal genetic site associated with MS, and it has been approved for many years. The most common risk for MS in most populations is human leukocyte antigen (HLA) at 6p21. Before the advent of genome-wide association studies (GWASs) encouraging finding new susceptibility loci, other genetic factors in the MS remained uncommon. In this literature review, we summarized details, including references, abstracts, and full text of journal articles. These details were selected and obtained from virtual databases such as Medline and PubMed. Using the keywords and health descriptors in MS, GWAS, IL7R and HLA genes for published data from 2007 until 2019. So, the purpose of this research was to perform an analysis of recent progress in identifying genetic factors and gene polymorphism that affect the risk of MS and how these results explain the disease pathogenesis.

Keywords: Multiple sclerosis; genome-wide association studies; genetic association; major histocompatibility complex; human leukocyte antigen.
1. INTRODUCTION

Multiple sclerosis (MS) is one of the most common neurologic diseases in young adults. The average age at diagnosis is between 20 and 40 years [1]. MS is a chronic inflammatory condition with an autoimmune reaction due to the deposition of plaques and myelin sheath degradation. Clinically, MS has episodes of the variable magnitude of remission and relapse in several years marked by focal disorganization of the nerves, trunk, periventricular region, spinal cord, and cerebellum. The clinical events are unclear and depend upon where the demyelination degree occurs [2]. MS’s best-known form is relapsing-remitting MS (RRMS) known for its acute attacks and followed by remission periods. There were several theories suggested for MS, but their etiology remains unclear. Scientists advocate a complex mix of environmental and genetic factors to foster autoimmune origins (Fig. 1) [3,4].

Many studies showing family aggregation, high concordance rates among twins, and an increased risk between relatives of patients with MS are supporting the contribution of genetics to MS. People with MS are 5-26% likely to have one or more relatives affected [5-7]. A study in populations worldwide has shown that MS is considered a genetic determinant for major histocompatibility complex (MHC) genes located on the short arm of human chromosome 6. In the MHC region, essential molecules involved in immune responses are coded by human leukocyte antigen (HLA) genes. The strongest MS association with class II alleles occurs among the three classes of HLA genes [8]. According to the International Multiple Sclerosis Genetics Consortium (IMSGC), MS has many genes coding immunologically important molecules. These genes are involved in cytokine pathways, co-stimulants, signal transduction, and inter-relations with environmental risk factors (CBLB, GPR 65, MALT1, RGS1, STAT3, TAGAP, TYK2) [9].

The epidemiologic studies of ethnicity, geography, family aggregation, and, more recently genome-wide association studies (GWAS) are evidence of genetics’s significance. In individuals with an affected family member, the risk of disease increases approximately in relation to the number of genetic details exchanged between a relative and the individual affected [10].

Fig. 1. Schematic diagram of the complex pathogenesis of multiple sclerosis [3]
Geographical latitude is another significant factor for MS' environmental risks and high-risk countries have been found to be mainly in North America/Europe, whereas low-risk areas are near the Equator [11]. There is a significant prevalence of MS in various geographical areas, of which the Middle East is low-risk zones [12]. In Saudi Arabia, MS prevalence has increased substantially but remains much lower than in western and other neighboring countries such as Kuwait, Qatar and the United Arab States [13,14]. In Saudi Arabia, the first multicenter MS registry in the Kingdom was launched for 2015–2018 to define the current epidemiology, disease dynamics and clinical features of MS. The data show that MS is higher in Kingdom, worrying and warrants urgent public health action [15]. Therefore, further studies are recommended to define risk factors linked to increased Saudi prevalence.

The new genomic experiments that have been arriving in recent decades have confirmed that genetic factors are associated with MS. Genetics studies are an essential element for understanding this complex disease's still unknown etiology. The purpose of this research was to perform an analysis of recent progress in identifying genetic factors and gene polymorphism that affect the risk of MS and how these results explain the disease pathogenesis.

2. STUDY DESIGN

Details, including references, abstracts and full text of journal articles, were selected and obtained from virtual databases such as Medline and PubMed. Keywords and health descriptors in MS, GWAS, IL7R and HLA genes have been used.

2.1 Genetic Risk in Multiple Sclerosis

MS is not recognized as a heredity disease. Genetic factors are indeed considered to contribute to the risk of MS. For all MS phenotypes, the prevalence of family MS is 20% [16]. The fact that the familial MS is identified as first- to third-grade relative to MS is reinforced further. The general population is approximately at risk of MS of 0.2 %. The first-grade relative has an estimated 3% -5%, and 15–25% higher relative MS risk than the background population [17–19]. Among families, the risk of recurrence is increasing with the proportion of gender sharing. For example, in monozygotic twins, the risk of age adjustment is 35% compared to 6% in dizygotic twins and 3% in siblings. The heritability of MS is polygenic and includes polymorphisms in several genes, each linked to a slight increase in disease risk. Polymorphisms express the higher risk of MS between class I of HLA and HLA class II [20,21]. Also, the risk of adoptive relatives is not increased. Also, the sex of the family member affected, and the parenting effect also influences the risk of MS [16].

When both parents have MS and the risk of half-siblings is smaller than that of whole-siblings, MS risks are greatly increased, while the risk of MS step-siblings and those recognized by families with MS is close to that of the overall population. The probability of family MS incidence risk thus increases proportionally to the amount of sharing genes with the family member concerned, but not in a linear relationship [22].

The relative risk of disease among families of the individuals affected by the disease in the overall population can be calculated to indicate relatives' risk of MS. This is defined as λs. If the risk for MS patients' relatives was not raised, then the λs ratio would be 1. The ratio increases as patient families are more at risk of disease. The λs ratio is around 15–40 for MS, which is a moderately important family impact on the risk of MS [23]. Therefore, it is important to note that the λs ratio higher than 1 is unavoidably indicative of a genetic trigger for the function concerned. Similar environmental factors are therefore shared between families, which could explain such family aggregation [24].

In a large-scale Italian analysis of up to 50 million individuals, 216 twin pairs were found in the MS. It measured a heritability estimation of 0.48 (CI 95%, 0.06 to 0.86), while the environmental contribution was 0.29 (CI 95%, 0–0.60), for a shared and 0.23 (95%CI, 0.12–0.39) for unique (individual-specific) environmental factors [25]. More recently, over 500 studies have shown that the probability of recurrence of monozygotic twins for siblings is 18.2% and 2.7% and the risk of siblings (λs) was 16.8% [26]. A national study reported 28,396 registered MS patients with a total number of ~15 million in Sweden. They reported that on 348 proband twins with MS a recurrence probability of the sibling (λs = 7.1; 95% CI, 6.42–7.86) and recorded a heritability estimate of 0.64(95% CI, 0.28–0.77) [27]. By incorporating details on siblings and half-siblings, this estimate was further refined. Interestingly, no shared environmental aspect could be found [28–30].
2.1.1 Genetic factors associated with multiple sclerosis

MS genes have long been pursued and many approaches have been successfully applied to this issue. Many studies have used a candidate gene approach for decades, whereby genes associated with MS have been selected based on assumed MS pathogenesis. Genetically susceptible factors contributing to increased susceptibility to MS are known to exist, with the region for human leukocyte antigen (HLA)-DRB1 presenting the highest risk [9,31]. Besides HLA, interleukin 2 receptor alpha (IL2RA) and interleukin 7 receptor (IL7R) are two genes that are more consistently associated with the risk of MS [32,33].

2.1.1.1 Human leukocyte antigen (HLA)

The MHC occupies a chromosome 6 region of 7.6 Mb and contains over 400 genes and pseudogenes. HLA genes are the primary components of the cell surface-encoding immune system. Molecules in class I of HLA-A, -B and -C present CD8+ cytotoxic T cells with foreign molecules [34].

For the first time, HLA protein polymorphisms between MS and healthy controls compared MS inheritance with particular genetic variations. The early studies have shown that certain surface cell proteins, which occur in peripheral blood mononuclear cell membranes, were more prevalent in MS patients than healthy controls. HLA-A3 was identified as the first such antigens [35,36], followed by HLA-B7 and then HLA-DRw2 [37].

The genetic loci HLA-DRB1 might perform a significant part in the HLA-DQA1*0102-DQB1*0602-DRB1*1501-DRB5*0101 haplotype, which gave a significant association with MS. Polymorphisms in HLA genes account for 20–60% of the genetic predisposition to MS, which suggests a potential role for genetic factors other than HLA in developing diseases [38].

2.1.1.2 Non-HLA genes

After 35 years of the first HLA analysis in MS, combined studies identified the first non-HLA genetic risk factors for MS: IL2RA and IL7R variants for cytokine receptor genes. [32,33].

Several studies have revealed that the genetic link between MS susceptible and IL-7R gene polymorphisms was first discovered [39,40]. IL17R gene, at the 5p13 region, is second only to MHC polymorphisms in affecting risk for MS [33,41,42]. This gene was correlated in various ways with the control of the immune response and 32 multiple sclerosis. In 34 autoreactive T cells from memory T cell pool patients with MS, the alpha chains of the IL-7 have an important role [43]. Meta-analysis indicated the relation between IL7R T244I polymorphism and MS susceptibility [44]. Another meta-analysis conducted at the same time supported this finding. Subgroup evaluation showed a significant European association, but no Asian association was found [45]. Interestingly, one study found that IL7R may influence the progressive course of the disease [46]. In addition, in MS-patients, the IL-7R in certain subsets of T cells is typically larger than average [47]. Surprisingly, an elevated IL-7R expression was found in MS patients with a distinct protective polymorphism [48]. Although this is surprising (high IL-7R is supposed to improve autoimmunity), it is also associated with more Tregs and recent thymic emigrants compared to other MS patients whose representation of these subpopulations is relatively depressed [48–50].

The IL2RA gene was shown to be associated with many autoimmune diseases in the 10p15.33 region. Earlier studies indicate a strong correlation with an increased risk for MS between the t allele of polymorphic IL2RA rs2104286 and the C alleles of IL2RA rs127224 [33]. But there was a poor correlation in another research. Before the onset of the disease, genetic variations in IL2RA may be involved in MS. The meta-analysis demonstrated increased susceptibility to MS-associated with IL2RA rs2104286 and rs127224 89 and showed an effect on IL2RA expression, which modulates the lymphocytes’ role [51,52].

2.2 Genome-Wide Association Studies (GWass) Data for Multiple Sclerosis

Gene-wide association research was used during the 1990s-2000s to analyze the MS legacy in families as well as to identify genome regions that deviate from independent separation. More than 30 studies in families with many MS patients have shown a relatively stable distribution of genomes with several hundred highly polymorphic microsatellites [53].

Genome-wide association studies (GWAS) have helped classify genetic regions of interest for many common complex diseases and features [54]. GWAS has been the most popular tool in
recent decades to search for new genes correlated with MS predisposition. GWAS is a powerful instrument to examine human polygenic disease genetic architecture and is focused on comparisons of all frequencies of single nucleotide polymorphisms (SNPs). The research is conducted using micro-arrays or advanced techniques to simultaneously genotyping thousands or millions of SNPs in several tens of SNPs thousands to several million per genome [55–57].

The first published MS-GWAS was performed by the International Multiple Sclerosis Genetics Consortium (IMSGC) using trio families (an affected individual and both their parents) from the UK and the USA [58]. The IMSGC and WTCCC2’s MS GWAS identified 52 loci that were definitively associated with MS susceptibility (Fig. 2).

In recent years, there have been studies of numerous GWASs involving thousands of MS patients with large numbers of normal controls. Most of these studies have been fairly powered and have found more than 50 risk loci that affect the sensitivity to MS in humans [59,60]. The most recent study of 23 previously identified genetic variants associated with MS was confirmed by a massive multinational GWAS. Their vulnerability to MS included 29 new genetic variants [9].

In 2007, 1540 parent-affected relative trios were investigated in the first MS GWAS and two outside the MHC were identified, which included the IL-2RA and the IL-7RAs, respectively [62]. Several GWAS had taken place before August 2011 and reported that HLA DRB*1501 is most closely associated with MS and at least 14 other regions associated with multi-gene disease [63,64]. In addition, meta-analyses with these data were performed by adding regions to the list of associations [65,66].

The International Multiple Sclerosis Genetics Consortium and the Wellcome Trust Case Control Consortium 2 have developed a seminal analysis in August 2011 by the Nature Group. In 9772 cases and 17376 controls, a total of 465,434 SNPs were analyzed, and a list of non-HLA candidate genes associated with MS was submitted after a refined study. [9].

The IMSGC recorded 11 statistically independent effects in the MHC region in 2013 using GWAS-SNP data (5091 cases/9595 checks): six HLA-DRB1s and one HLA-DPB1s alloy in the centromeric class II area in the locus, one HLA-A and two HLA-Bs in the telomeric class I area, and one in Class III between the MHC class I polypeptide B (MICBs) and the leukocyte-specific transcript 1 (LST1) [67].

Fig. 2. Multiple sclerosis (MS) genomic regions of interest identified by genome-wide association study (GWAS) [57,61]
2.2.1 GWAS studies and different mechanism of MS

2.2.1.1 Coagulation mechanism

The role of coagulation cascade in neuroinflammation and neurodegenerative diseases was studied recently, and the impact of new suggestions on the interaction of hemostasis, inflammation, and the immune system was considered [68]. In MS development, the function of the CD40 path is the most general topic of B cells' role in neuroinflammation and is a major therapeutic objective in the MS field at present [69]. The possible relationships between urokinase (PLAU) and signal essential for B cell pathogenicity, such as CD40, suggest new study lines and pave the way for new therapeutic objectives to be implemented [70].

MetaCore (version 6.35 builds 69300, 2018) was used by Starza et al. and the network connectivity resulting from feeding the MS GWAS data to MetaCore was analyzed. The over-connectedness of both networks was remarkable: 958 connections versus 561, which was predicted by chance; z-score = 17.39; p-values < 0.00001. Also, CD40 coding genes, plasminogen, and PLAU have been shared between both networks and have shown an integral connection between the coagulation cascade and the major pathogens [71].

2.2.1.2 Neuronal mechanism

MS has inflammation, demyelination, deficient remyelination and severe neural injuries that contribute to continuous and progressive impairment. MS is usually diagnosed between the ages of 20 and 40 and is almost three times higher in women than in men [72,73]. It is still not clear if MS has a different etiology between patients. MS is believed to be occurring in people with genetically predisposed potential causes or at least environmental contributions [74]. One hypothesis involves a still unknown CNS infection that causes auto-reactivity of T-cells by a molecular simulation mechanism [75]. GWAS has been linked to many genetic variants or SNPs outside the HLA region because of its larger size than the initial genetic mapping studies [9,76]. Some of these MS GWAS studies are available publicly as GWAS summary statistics, summarizing the SNP level p values of the particular population or subpopulation [77]. A MS GWAS research was conducted in 2009 by the Genetic Multiple Sclerosis Association (GMSA), and an MS GWA study by the IMSGC was conducted in 2011. Two MS GWAS datasets were released separately and conjecturally. These two GWA studies record genome-wide SNPs, but these variants are mainly found in non-coding regions with unknown functions and, therefore, difficult for biological interpretation [9,76].

T cells have been central in MS disease, primarily because of the EAE animal experimental model, but also because the HLA II genes are strongly genetically linked [78]. The use of animal models also deals with molecular events and cell interactions that underlie neural damage in MS. An experimental autoimmune encephalomyelitis (EAE) is a MS animal model with pathological, histological, and clinical symptoms consistent with the human disorder. EAE actually encompasses several models that are believed to mimic different aspects of MS. It is induced by immunization with myelin components or passive transfer of encephalitogenic T-cells in some animal species and strains [79].

2.2.1.3 Immune-related mechanism

The genetic overlap of autoimmune disorders is a position for the deregulation of the immune system, and a significant question is genes may explain whether CNS involved in MS. Few studies have been conducted which compare MS with other neurological conditions. A comparison with amyotrophic lateral sclerosis found no shared association [80]. The immune system's function is further enhanced by overlapping with other diseases. Other autoimmune disorders, primarily Celiac disease, Crohn's disease, Primary Bile cirrhosis, type 1 diabetes and rheumatoid arthritis, share almost half of MS risk genes [81].

Thus, the latest understanding of MS genetics leads to new insights into disease pathogenesis and indicates that the immune system and, in particular, lymphocyte differentiation and growth play an important role. Cytokines (e.g., IL12A, IL12B) and cytokine (e. g., IL7R, IL2RA, IL22RA), co-stimulatory molecules (e.g., CD58, CD40, CD80, CD86) and signal transducer molecules (e.g. TYK2, STAT3) inside interaction regions involved with GWAS are selected [9,82].

For years, epidemiological studies have shown patients' increased susceptibility with one autoimmune disorder to having another
autoimmune disease [83,84]. Also, most autoimmune diseases display a significant connection to the HLA region, although this highly-related region’s exact causal genes for any particular disease cannot yet be established [85]. Results from GWAS have further added to the concept of a shared genetic background for autoimmune diseases. In addition to IL2RA, CLEC16A and CD226, several other genes have been identified that show evidence for an overlapping association with different autoimmune diseases [86].

The latest review of GWAS data on 7 common autoimmune disorders (including MS), ‘gene networks of diseases,’ reveals a complex autoimmunity architecture with shared genes as well as specific autoimmune disease susceptibility genes [87].

### 2.3 Genetic Polymorphisms Studies and MS in the Worldwide Population

It is not clear that polymorphisms in genes that encode cytokine and its receptors are susceptible or resistant to various infectious or autoimmune diseases and to variables in clinical disease, like MS [2]. The data on the independence of MS susceptibility in the world populations were summarized in Table 1.

Three major results were observed by Marigorta et al. first, genes associated with complex diseases have smaller than the average genome-wide level differentiation between humans. Second, there is an extensive association between variations between European and East Asian genetic differentiation between these populations in the replicability of related diseases. In comparison with African populations, strongly replicated genes show an increase in the high-frequency allele in the European and Asian populations [88].

In 931 family trios using DNA microarray technology, the first GWAS found that IL2RA and I7RA alleles, as inherited as risk factors for MS, have been identified and evaluated for the determination of common DNA related sequence variants. Replication data were used to estimate the overall significances and consequences of the associations between alleles and risks of MS by another 609 family trios, 2322 cases and 789 control [58].

The majority of GWASs have demonstrated a highly significant relationship between MS and the MHC region, the genetic management of immune response being the most important function. HLA-DRB1 class II was the most significant signal [66], [89–92]. In general, the HLA-DRB1*15:01 risks alleles on this SNP tag. HLA class II is the only MS-associated locus in many studies [93]; in others, there was an increase in the number of significantly associated loci [64,92,94].

Three SNPs in the most well-powered GWAS to date were associated with MS at the genome-wide significance either in women (rs1800693 in TNFRSF1A) or in men (rs2293370 in TIMMDC1 and rs13333054 downstream IRF8) [92].

In Slovak patients, correlations were also identified between the variants HLA-DRB1*1501 and MS susceptibility. The first reported that genotypes of HLA-DRB1 and -DQB1 are genetic markers associated with impairment in patients with MS. The DRB1*15/15 genotypes, as opposed to the DQB1*03/03 genotypes, have been described as short term clinically negative prognostic factors [95]. The HLA-DRB1*15 and HLA-DRB1*14, respectively, were vulnerable and defensive alleles in another Colombian MS study [96]. Also, a subpopulation of Iranian MS patients evaluated the frequency of polymorphism (rs16375) in HLA-G. In cases with −14 bp−14 bp, the concentration of sHLA-G was shown to be significantly higher than in genotype +14/+14. Furthermore, sHLA-G was considerably higher than the average in patients [97]. Furthermore, Čierny et al. [98] first showed that a decrease in Slovak population susceptibility to MS was correlated with the Bsml genotype BB (AA). However, their results indicated that the Apal VDR gene polymorphisms Bsml and Taq1 do not act as a predictor to the disease impairment progression rate in Slovakia’s MS. Bsml was one of the significant genetic markers in the risk assessment of MS.

Polymorphism rs6887695 in IL12B has shown to increase the sensitivity to MS in Iranian’s subpopulation, which connects the GG genotype with the IL12B expression in PBMCs of MS subjects [99]. In Bulgarian MS patients, similar genders have documented IL12B polymorphisms’ sex-specific effects on genetic predisposition [100].

Following the previous findings, highly significant association results in virtually all GWAS were achieved by markers in the HLA region. Since HLA has previously been recognized as the region of MS susceptibility, this will focus on the
non-HLA genes found to have recently become MS susceptible genes through GWAS.

The cohort of 206 Spanish and French patients with relapsing-remitting MS, including 99 patients and 107 controls, was analyzed in 2008, with 100 K gene chips in a pooled DNA approach. There were no relapses and no changes in EDSS during the follow-up, while non-respondents had at least two relapsing-remitting MS. After individual genotyping validation, 35 SNPs showed significantly different genotype frequencies in response to the hyaluronan proteoglycan connection protein (HAPLN1) and glypican 5 Genes (GPC5), with two genes being the strongest in their responses [101].

There are very few reports of MS interaction with HLA from the Arab world. Almost all these trials have been shown to be consistent with HLA-DRB1*15:01 (DR2) or DQB1*06 (DQ1)[102–105].

MHC B-Chain-related expression (MICB) was evaluated in Iranian MS subpopulations with PBMCs in approximately one-third of the patients, relative to healthy cases, with MICB overexpression. MICB is involved in the activation of autoreactive T cells. They concluded that upregulation of MICB is associated with a serious disease and CNS degeneration of myelin [106].

An Iranian patient was tested for the correlation between HLA-DRB1 class II and MS. The higher frequency of the DRB1 01 allele was demonstrated in males relative to females. Also involved in MS progression was the DRB1*15/11 genotype. In patients with a positive MS history, the DRB1-11 and DRB1-15 alleles were considerably lower and higher in contrast. In addition, DRB1-15 was associated with lower age and higher impairment. They typically stated that there was a link between HLA DRB1 alleles and MS [107].

Yamout et al. investigated the connection between MS gene polymorphism and VDR gene, HLA-DR locus and 25OHD and Lebanese vitamin A serum levels. The frequencies A, b and t alleles were comparable in their studies between MS and controls. There was no correlation between VDRG polymorphism and M [103].

In contrast to healthy cases in an Iranian study of subjects, it was observed that MS patients were more frequent in T allele and CT genotype at rs6897932 of IL7RA [43].

2.4 Genetic Polymorphisms Studies and MS in the Saudi Arabia Population

The Gulf area was historically considered to have a low MS prevailing, but in recent years, data indicates a dramatic increase of prevalence rates of 31–55 MS per 100,000 in the number of MS cases in general in the region, including Saudi Arabia [14]. No national or regional registers in the country are still available to explain the actual disease burden and obtain precise estimates [108]. According to few reports, the Gulf region’s increased prevalence may be attributed to lifestyle changes, vitamin D deficiencies and parental consanguinity [13,109].

During 2015-2018, the Kingdom launched the first national multicenter MS registry to define the latest epidemiology, trends of disease and clinical characteristics of MS. The data indicate that MS is more widespread in the Kingdom, worrying and guarantees urgent action on public health [15].

Al Jumah et al. [8] stated that familial MS could be a risk factor. The popular association of SNPs and MS by GWAS was studied and documented. In Saudi MS people outside the MHC area, they found that SNPs Rs6498169 and 10984447 are the two most important MS linked SNPs. They suggested that the most important MS-connections in the Saudi population, even with very limited sample sizes, can be identified using a more homogeneous genetic pool [8].

The genetic predisposition of familial MS in the Saudi population was studied by Aljumaha et al. [110] Whole Exome Sequencing (WES) has been carried out in family members of several generations. For research, including poor quality reading filtrations, alignment to the reference genome (Hg19) and variant call, Life Scope software has been used. In-house, developed strategies between subjects were used for filtration of variants. Pathogenic mutations using public databases have been filtered from the SNPs and Indels. Within the family, the proofs filtered unique variants and unique mutual sequence variants in carriers and proofs. Variants with specially crafted primers were verified by Sanger sequencing. In the exome sequence, they recorded that of 11 unaffected and seven affected families of the family MS based on hg19, 10,257 variants were identified:
Table 1. Genetic polymorphisms studies and MS in the worldwide population

<table>
<thead>
<tr>
<th>References</th>
<th>Study population</th>
<th>Original samples</th>
<th>SNP</th>
<th>P value</th>
<th>Original genome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hafler et al. [33]</td>
<td>United Kingdom / United States</td>
<td>1540 family trios, 2322 cases and 5418 controls</td>
<td>rs12722489</td>
<td>2.96 x 10^{-8}</td>
<td>IL2RA</td>
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<td></td>
<td></td>
<td></td>
<td>rs2104286</td>
<td>2.16 x 10^{-7}</td>
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<td>Comabella et al. [117]</td>
<td>Spanish</td>
<td>275 cases</td>
<td>rs6897932</td>
<td>2.94 x 10^{-7}</td>
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<td>rs1327328</td>
<td>7 x 10^{-7}</td>
<td>IL7RA</td>
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<td></td>
<td></td>
<td>rs3129934</td>
<td>4.2 x 10^{-10}</td>
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<td>HLA-DRA</td>
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<td>Byun et al. [101]</td>
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<td>Glypican 5 (GPC5)</td>
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<td>De Jager et al. [66]</td>
<td>meta-analysis of GWASs for MS</td>
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<td>0.002</td>
<td>MHC class I chain-related gene A, B (MICA and MICB)</td>
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<tr>
<td>Abolfazli et al. [107]</td>
<td>Iranian MS patients</td>
<td>73 multiple sclerosis patients 40 healthy volunteers</td>
<td>-</td>
<td>0.062</td>
<td>HLA-DRB1* 11/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.033</td>
<td>DRB1 4/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
<td>DRB1 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.035</td>
<td>DRB1 16</td>
</tr>
<tr>
<td>Čierny et al. [98]</td>
<td>Slovac cases</td>
<td>270 clinically diagnosed MS patients and 303 healthy controls</td>
<td>-</td>
<td>0.014</td>
<td>VDR gene (BsmI genotype BB (AA))</td>
</tr>
<tr>
<td>Mohammadi et al., [97]</td>
<td>Iranian MS patients</td>
<td>212 patients and 210 healthy</td>
<td>rs16375</td>
<td>P&lt;0.05</td>
<td>polymorphism in HLA-G</td>
</tr>
<tr>
<td>Toro et al. [96]</td>
<td>Colombian MS patients</td>
<td>100 patients with MS 200 healthy controls</td>
<td>-</td>
<td>&lt; 0.001</td>
<td>HLA-DRB1*15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>= 0.001</td>
<td>HLA-DRB1*14</td>
</tr>
<tr>
<td>Yamout et al.,[103]</td>
<td>Lebanese</td>
<td>control 48 healthy and 51 non-MS 50 relapsing–remitting type of MS</td>
<td>rs7975232</td>
<td>0.018</td>
<td>HLA-DRB1*15 VDR polymorphisms</td>
</tr>
<tr>
<td>Javan et al. [99]</td>
<td>Iranian</td>
<td></td>
<td>rs6887695</td>
<td></td>
<td>IL12B</td>
</tr>
<tr>
<td>Taheri and Sayad, [43]</td>
<td>Iranian MS patients</td>
<td>75 control 75 MS</td>
<td>rs6897932</td>
<td>0.009</td>
<td>IL7RA</td>
</tr>
<tr>
<td>Čierny et al. [95]</td>
<td>Slovac cases</td>
<td>282 MS patients</td>
<td>-</td>
<td>0.018</td>
<td>HLA-DRB1*07 allele</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.035</td>
<td>HLA-DQB1*03 allele</td>
</tr>
<tr>
<td>Miteva et al. [100]</td>
<td>Bulgarian</td>
<td>379 control healthy 166 relapsing–remitting type of MS</td>
<td>rs6887695</td>
<td>0.007</td>
<td>IL12B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs3212227</td>
<td>0.023</td>
<td>IL12B</td>
</tr>
</tbody>
</table>
of which 1268 were found only novel, 35 variants were shared by the affected members and expected to be deleterious or harmful. Sanger sequencing confirmed mutation. Mutation. They expected ten new candidate genes in Family MS from 35 new variants [110].

The first study on the combination of HLA Class II Alleles and MS was published by Al Jumah et al. [111]. The majority were young and female patients in the sample. The research was carried out in King Abdulaziz Medical City, Riyadh, Saudi Arabia. The next-generation sequencing was used to study HLA interaction with MS. Researchers found that many HLA-DRB1 and DQB1 alleles have been related to MS. The alleles included: HLADQB1*15:01, HLADQB1*02:01, HLADQB1*06:02, HLADQB1*05:03, and the HLA-DQB1*06:03. They have shown a strong association with increased risk of MS. [111].

Though Saudi Arabia is sunny, the recent deficiency in vitamin D has become one of the major public health issues. Studies in Saudi Arabia have shown that vitamin D deficiency is particularly common among females [112]. DRB1*15:01 and DQB1*06:02 alleles in patients with lower serum vitamin D levels relative to patients with no alleles [111].

2.5 Future Directions

Since MS is a multifactorial disorder characterized by phenotype heterogeneity, multiple genes and environmental factors are involved. These factors are part of complex schemas for the non-linear interacting of genetic and non-genetic variables. While attempts are being made to identify causative genes, the findings remain unclear. The MS has proven remarkably effective with genome-wide association studies, with > 200 risk loci identified. However, as discussed in this article, the practical interpretation of these findings remains a challenge, and the near future will continue to focus on translating to an understanding of pathobiology. Several further steps are appropriate and probable in the near future, starting from the promising findings of GWAS [113].

In addition, all licensed and forthcoming medicines mainly influence the mechanism of inflammatory diseases. To date, no medications significantly accelerate the process of degenerative disease, explaining the ineffectiveness of chronic disease processes. The big breakthrough in MS will be the discovery of neurodegeneration therapies and the regeneration and reconstruction of tissues affected [114].

Even more assessment of the MS FDA's approved drugs, their drug goals, and gene results. Further evaluation of the approved drugs of the MS by the FDA, their drug goals, and gene results. Around 32 specific FDA-approved target genes have been identified by Manuel et al. [115]. They find four pharmaceutical goals for these drugs. The four genes that have been approved for MS FDA drugs include HDAC1, IL2RA, KEAP1 and RELA. MS drug target gene IL2RA, a gene present in the top IMSGC test module and the top module of dual evaluation. IL2RA is an MS ocrelizumab target gene [116].

3. CONCLUSION

After all, in the last decade, a large number of GWAS studies have uncovered the genomic of many complicated conditions and characteristic features; thus, the GWAS strategy may rightly be seen as a key element of this period, but further advancement depends heavily on the disaggregation and identification of key pathways and processes leading to functionality in the different risk variants.

4. LIMITATION OF THE STUDY

While the literature review represents a powerful method to analyze recent progress in the identification of genetic factors and genetic polymorphism that influence MS risk and how these results explain the pathogenesis of this disorder, several limitations can lead to confusion. A significant drawback is that in general, some related studies in major databases have not been published or indexed. Some related studies may not be available. Studies that are lacking or not published can lead to bias. It was less likely that negative findings would be reported or made available in electronic databases, leading to a possible over-estimation of effect sizes. In certain polymorphic genes, haplotype analysis may be more successful and provide more details than analysis of SNPs. In most primary studies, though, haplotype data is not given. In most cases, data are only categorized by race, age, and rarely by MS subtypes, sex and lifestyle. This is because the primary studies did not provide adequate details. In most cases, studies have not documented
enough details, particularly for inspection purposes, concerning recruitment methods and participant characteristics. Vitamin D, Epstein-Barr and smoking have been the key environment modulators for MS diseases in recent studies. The effects of genetic interactions may be changed by environmental exposures.

Taking all these problems into consideration and taking the limitations into consideration, it requires further individual genetic association studies to provide sufficient information on population characteristics, clinical conditions, environmental exposures, and genetic interactions.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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