INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system resulting in disability. At present MS is detected in nearly each world population, but more frequently in northern regions [1]. According to the data of 2007, 380,000 MS patients resided in 28 European countries; for their treatment and maintenance 12.5 billion Euros has been spent annually [2]. MS is one of the most socially essential neurological problems because the majority of MS patients are young people, who are socially and professionally active [3].

The early data on potential genetic predisposition to MS were obtained from epidemiologic studies, which revealed different incidence of MS in various ethnic groups residing on the same territory. MS is more frequently observed in the families with MS patients than in the whole population [4]. However, the disease transmission within the family is not Mendelian [5]. The recurrence risk of MS for relatives of MS patients is 20–50 times higher than on average in the population [6], and a systematic decrease in this value depending on the relative genetic distance to the proband is also observed [7, 8]. Such mode of inheritance is characteristic for polygenic diseases, which arise from the combined contributions of multiple independent or interacting polymorphic genes [9].

The studies on MS etiology have led to a suggestion that both hereditary predisposition and environmental factors are required for the disease development. The number of hypothetic mechanisms has been suggested, according to which infectious agents (such as viruses and bacteria) and other environmental factors could affect the risk of MS development. Although family studies in the individual groups (sibs, half-sibs, adopted children, spouses, etc.) showed that environmental factors are less important than genetics at the family level [10, 11], it is commonly accepted at present that MS, like the majority of other common diseases, depends on genetic and environmental factors, which are in programmed or random interaction with each other [12]. The complexity of these interactions does not permit to predict MS development unequivocally basing on a single trait. However, even identification of the limited contribution of any individual gene in MS development or progression can facilitate the understanding of the biological nature of the disease and reveal new possibilities for its prevention or treatment.

SEARCH FOR GENES RESPONSIBLE FOR MS DEVELOPMENT

Since recently the search for genes responsible for MS development has been conducted using two main approaches: (1) analysis of association of the individual “candidate genes” with the disease and (2) analysis of the wide spectrum of chromosomal loci (whole genome screen) linkage with the disease in families with several MS patients. In the last two years, a new method, which borrowed the best approaches of the previous studies, genome-wide association screening (GWAS), which is based on the modern high-throughput DNA analysis, has been developed. This review describes replicated (validated) results for individual genes and DNA loci located on the majority of chromosomes obtained using these three strategies as well as data on association of MS with allelic combinations of various genes.

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Abstract—Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. The observed type of heredity associated with MS is characteristic of polygenic diseases, which arises from a joint contribution of a number of independently acting or interacting polymorphic genes. Recently to identify the genes responsible for genetic predisposition to MS two main approaches have been applied: (1) analysis of association of individual “candidate genes” with the disease and (2) analysis of the wide spectrum of chromosomal loci (whole genome screen) linkage with the disease in families with several MS patients. In the last two years, a new method, which borrowed the best approaches of the previous studies, genome-wide association screening (GWAS), which is based on the modern high-throughput DNA analysis, has been developed. This review describes replicated (validated) results for individual genes and DNA loci located on the majority of chromosomes obtained using these three strategies as well as data on association of MS with allelic combinations of various genes.

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genome to the gene”. In contrast the “candidate gene” approach suggests a potential involvement of the gene in the pathogenesis of the diseases based on the nature of the disease and the function of the gene product (the pathway “from the phenotype to the gene”), and then test this suggestion.

Analysis of the association of candidate genes with MS is conducted by comparison of the allele distribution in the particular genetic polymorphic region in representative samples of unrelated patients as well as in unrelated healthy individuals (“case–control” matched by gender, age and ethnicity. The allelic variants examined could be localized in any DNA segment, including coding sequences (exons), non-synonymous substitutions in which change the structure of the final protein molecule, as well as introns and promoter regions, in which transcription regulation sites are often located, and other DNA regions. However, apart from a direct association of the examined locus and hereditary pathology, this association could result from linkage disequilibrium between the marker locus and the disease locus if these loci are located in the vicinity to each other. In addition, the observed association may be an artifact in a heterogeneous population. Therefore, to obtain correct results with the “case–control” method, it is important to use a homogenous population or family based material, when the control group is formed using the same alleles of the healthy parents, which are not transferred to affected offspring [13].

Under the conception of the autoimmune nature of MS (see reviews [14, 15]) the first suggestion on the involvement of HLA genes in the formation of genetic predisposition to this disease, which is based on the primary role of HLA molecules of the major histocompatibility complex (MHC) in the immune response, was experimentally supported in the early 1970s by analysis of association of HLA class I and II genes with MS. Some studies have shown that the associations with HLA class I genes are independent from these of HLA class II genes; however, the presence of strong linkage disequilibrium in HLA region hinders interpretation of these results. It is beyond the scope of this review to describe in detail the 35-year history confirming a major role of these genes in the MS development. This information is described in the reviews of 2008 [16, 17] and summarized at the website www.acceleratedcure.org. Essentially, the association of MS with HLA genes, which are localized on chromosome 6p21.3, was revealed almost in each population (the results of more than 215 studies). In the majority of these studies, the alleles of genes located in regions DR, DP, or DQ HLA class II as well as their extended haplotype were associated with MS. For example, Caucasoids, including Russians, are characterized by a stable association of the disease with the DR15 haplotype (DRB1*1501, DQA1*0102, and DQB1*0602) (except Sardinia residents, which are characterized by MS association with DR3 and DR4).

In other ethnic groups, the association was observed with other DRB1 gene alleles, for example DR3 and DR4 in the MS patients in the Northern Africa, DR4 combined with DR15 in the population of Canary Islands. Some studies reported a decrease of the risk of MS development in DR1 or DR8 carriers.

The presence of the DRB1*1501 allele can explain 20 to 60% MS cases in Caucasoids [18], while association with HLA class II genes is the strongest observed so far (typically, the odds ratio value is close to 3). However, the contribution of these genes to the MS development is lower than in other autoimmune diseases, e.g., insulin dependent diabetes mellitus. In any case, the presence of DR15 haplotype is not considered the fatal prerequisite for MS development, while its absence is not responsible for immunity to this disease.

In contrast to HLA genes, hundreds of studies aimed at detecting the contribution of other candidate genes in the MS development have not all presented unequivocal evidence. Table 1 gives a list of genes for which an association with MS has been observed in more than two independent studies and mostly in different populations. Such confirmation of the association in independent samples of MS patients and control groups (validation or replication) owing to the danger of the false-positive associations is considered at present as an important condition for the approval of the role of any gene/allele as a risk factor of the disease. As seen from Table 1, such genes were observed on the majority of chromosomes. However, often the results are contradictory since the associations have been observed only in the small number of the studies carried out for the given gene, the total number of which could reach several dozens. The gene IL-7RA encoding alpha-chain of interleukin-7 receptor located on chromosome 5p13 represents an important exception. For this gene, in five out of six published studies, the most comprehensive of which were performed in 2007–2008 for various ethnic groups, non-synonymous base pair substitution has been revealed in exon 6, the more common allele of which highly significantly increased the risk of MS development [38].

Table 1 also shows that for some genes located on chromosomes 1 (SH2D2A, FAS ligand), 6 (CD24), 7 (TAC1, PAI-1), 10 (IL-2RA (CD25)), 11 (UCP2), and 17 (RANTES (CCL5), CCL3 (MIP-1 alpha, SCYA3)), in all or nearly all studies an association with MS was observed, although for each of these genes the total number of publications does not exceed four. Many of the genes listed in Table 1 are in some way involved in the inflammatory process. They encode either various pro- or anti-inflammatory cytokines and their receptors, or antigens against which the immune response could be developed (e.g., proteins located on myelin envelope, myelin basic protein, MBP, and myelin oligodendrocyte glycoprotein, MOG). Note that the contribution of each of the associated with MS genes is modest (for example, for IL-7RA...