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Genes associated with multiple sclerosis: fifteen and counting

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Abstract

Evaluation of: The International Multiple Sclerosis Genetics Conssortium (IMSGC). IL12A, MPHOSPH9/CDK2AP1 and RGS1 are novel multiple sclerosis susceptibility loci. *Genes. Immun.* 11(5), 397-405 (2010).

Multiple sclerosis develops in genetically susceptible populations as a result of enviromental exposures, and discovering these genetic and/or environmental factors will provide fundamental new insights into the pathogenesis, diagnosis and treatment of this disabling disease. With the introduction of genome-wide association studies, number of genes associated with MS has grown rapidly. In all of them the classic MS risk locus HLA-DRB1 stood out with remarkably strong statistical significance, but they also identified altogether 12 other loci and/or genes associated with MS. However all of these alleles have a very modest odds ratio and they explain ~3% of the variance in MS risk. Recently The International Multiple Sclerosis Genetics Consortium provided evidence for three new loci that show significant association at a genome-wide level: RGS1, IL12A and MPHOSPH9/CDK2AP1. In this article we will review the three new susceptibility loci and implication of genome-wide association studies in MS on clinical practice.

Key words: multiple sclerosis, genetics, genome-wide association studies, RGS1, IL12A, MPHOSPH9/CDK2AP1

MS seems unlikley to result from a single causative event; instead it seems to develop in genetically susceptible populations as a result of enviromental exposures. Discovering these genetic and/or environmental factors will provide fundamental new insights into the pathogenesis, diagnosis and treatment of MS. Genetics of complex disorders like MS is a difficult target to study. The earliest attempts consisted of a large number of studies mainly based on patient and control collections with small number of samples, and numerous weak associations were reported in the literature. Some of the identified genes have been verified by better-powered genetic association studies, but most have never been replicated in a follow-up . Things have significantly changed in the field of MS, as well as in other complex disorders with the introduction of genome-wide association studies. This indirect approach uses a set of sequence variants, single nucleotide polymorphisms (SNPs), in the genome that serve as genetic markers to detect association between a particular genomic region and the disease, whether or not the markers themselves have functional effects. (1) The main problem in the beginning was the reprlicability of the results. However, it became apparent that many true susceptibility genes in complex disorders have effect sizes so small that association significance, in order to be powerful enough, should have been based on significantly larger sample sets. (2) When The International HapMap Project determined the common patterns of DNA sequence variation in the human genome, it provided researchers tools that allowed the indirect association approach to be applied readily to the whole genome for scans of disease risk factors. (3) However it has been shown that most common variants individually or in combination confer relatively small increments in risk (1.1–1.5-fold) and explain only a small proportion of heritability. (4) The questions arise as to why so much of the heritability is apparently unexplained by initial genome wide association analysis. There are several possible explanations: a) much larger numbers of

variants of smaller effect are yet to be found; b) rarer variants are poorly detected by available genotyping arrays that focus on variants present in 5% or more of the population; c) structural variants are poorly captured by existing arrays; d) low power to detect gene–gene interactions; e) inadequate accounting for shared environment among relatives. (5) The modest size of genetic effects detected so far confirms the multifactorial etiology of these conditions and suggests that complex diseases like MS will require substantially greater research effort to detect additional genetic influences. (5)

Familial aggregation is one of cardinal epidemiological features of multiple sclerosis suggesting that factors influencing disease onset and disease course may be in part inherited. (6) This is supported by twin studies (7), candidate gene population association (8) and linkage studies. (9) In an effort to decipher the genetic component of MS pathogenesis many candidate genes have been investigated, but, to date, the only region of the genome that has clearly and consistently shown evidence of association with the disease is the major histocompatibility complex (MHC) on chromosome 6p21, where, in Northern Europeans, association with the *DR15* human leukocyte antigen (HLA) haplotype (*DRB1*1501-DQB1*0602*) is a constant finding. (10) It is believed that in addition to the *HLA* region, 20–100 common genetic variants might be sufficient to account for the genetic risk in MS.

There are several published genome wide association studies in MS to date and in all of them the classic MS risk locus HLA-DRB1 stood out with remarkably strong statistical significance. (11,12,13) The International Multiple Sclerosis Genetics Consortium undertook a large-scale genome-wide association scan aimed at identifying alleles associated with MS. Beside the already known HLA locus, the authors identified alleles of IL2RA and IL7RA as heritable risk factors for MS. (11) Following this, several more loci were identified and replicated in

independent cohorts or through meta-analysis studies. (14,15) Genome-wide association studies identified altogether 12 loci and/or genes associated with MS to date, however all of these alleles have a very modest odds ratio (16) and they explain ~3% of the variance in MS risk. (17) These results statistically demonstrate a polygenic component to MS susceptibility and suggest that the risk alleles identified to date represent just the tip of an iceberg of risk variants likely to include hundreds of modest effects and possibly thousands of very small effects.

Summary of methods and results

Recently, De Jager and colleagues reported the results of a meta-analysis of genome-wide association studies that included 2624 MS subjects and 7220 control subjects. (15) The replication phase of this study was performed in an independent set of 2214 MS subjects and 2116 controls, and the combined analysis led to the validation of three new loci that met genome-wide significance. Furthermore, this analysis highlighted seven loci with suggestive evidence of association to MS: CXCR4 (rs882300, combined P value $1.37x10^{-7}$), IL12A (rs4680534, P value $5.58x10^{-6}$), MPHOSPH9/CDK2AP1 (rs1790100,P value $7.21x10^{-7}$), OLIG3/TNFAIP3 (rs9321619, P value $1.71x10^{-5}$), PTGER4 (rs6896969, P value $2.40x10^{-7}$), RGS1(rs2760524, P value $9.77x10^{-6}$) and ZMIZ1 (rs1250540, P value $1.59x10^{-6}$). Based on this paper, the International Multiple Sclerosis Genetics Consortium attempted to validate these seven putative MS susceptibility loci by genotyping the implicated polymorphisms in new samples and then combining the results with those of the published meta-analysis and its replication effort. (18)

This study involved 8085 MS patients and 7777 healthy controls from USA, UK, Germany, Italy, Sweden and Finland, and all patients were of self reported European ancestry. SNP

genotyping was performed at each center using different platforms (Sequenom iPLEX Gold or TaqMan (7900 Sequence Detection System)). One of the drawbacks of the study was that not all of the SNPs were successfully genotyped in each sample collection, however authors took into account the differences in the number of cases and controls across the polymorphisms when they analyzed the data. This may also explain why some of the studied loci did not reach statistically significant association. The results of this meta-analysis of the replication samples exhibited following odds ratios for seven investigated loci: RGS1 0.87 (0.81–0.92), IL12A 1.11 (1.05–1.16), MPHOSPH9/CDK2AP1 1.10 (1.04–1.16), ZMIZ1 1.05 (0.99–1.11), OLIG3/TNFAIP3 0.94 (0.90–0.99), PTGER4 0.94 (0.88–1.00) and CXCR4 0.91 (0.87–0.96) showing evidence of association at a genome-wide level of significance (P value < $5x10^{-8}$) in three loci: RGS1 (rs2760524, joint P value $3.55x10^{-9}$), IL12A (rs4680534, joint P value $3.08x10^{-8}$) and MPHOSPH9/CDK2AP1 (rs1790100, joint P value $3.96x10^{-8}$).

The second part of the study explored the possible functional consequences of the seven polymorphisms by performing a quantitative trait analysis that correlates genotyping data with gene expression data. Only one of the seven SNPs, rs1790100 in the MPHOSPH9/CDK2AP1 locus, showed evidence of association in 'cis': the risk associated allele correlates with lower CDK2AP1 RNA expression in the samples from the HapMap phase II study. (19) Given this result, authors analyzed CDK2AP1 gene expression in another publicly available data set, the 'mRNAby-SNP-browser'.(20) In this data set, two of the SNPs associated with the level of CDK2AP1 RNA expression were in strong linkage disequilibrium with rs1790100. Authors further explored these in vitro observations using ex vivo RNA data obtained from peripheral blood mononuclear cells (PBMCs) in 255 relapsing–remitting MS and clinically isolated syndrome (CIS) subjects. As there was no difference between treatment naïve patients and

patients treated with interfernos or glatiramer acetate, all data were pooled together, and results showed reduced CDK2AP1 expression in the presence of the rs1790100G susceptibility allele. MS subjects who are homozygous for the risk ('G') allele have a substantial reduction of the CDK2AP1 expression profile compared with the other two genotype classes.

Discussion

This study provided us with three new genes associated with MS susceptibility.
RGS1gene encodes a member of the regulator of G-protein signaling family. This protein is located on the cytosolic side of the plasma membrane and contains a conserved, 120 amino acid motif called the RGS domain. The protein attenuates the signalling activity of G-proteins by binding to activated, GTP-bound G alpha subunits and acting as a GTPase activating protein (GAP), increasing the rate of conversion of the GTP to GDP. The major cells of RGS1 expression are T and B lymphocytes, natural killer (NK) cells, dendritic cells, and monocytes. (21) Studies of RGS1 knockout mice revealed a role for RGS1 in the control of B lymphocyte migration induced by chemokines (22). RGS1 regulates B cell homing to lymph nodes and motility within the lymph node microenvironment. Another recent study reported enrichment of both RGS1 and RGS16 in regulatory $CD4^+$ T cells and activated T cells compared with naïve T lymphocytes (23). These studies suggest that RGS1 may play a major role in the chemokine-mediated homing of lymphocytes to secondary lymphoid organs as well as their localization within these spaces during the immune response. Therefore it can be speculated that that

alterations in RGS1 function mediated by allelic variants could impact the migratory capability of B cells and possibly alter their recruitment to the central nervous system.

It is interesting to observe that genetic variants in RGS1 have recently been observed to be associated with CD and diabetes type 1, and therefore it is possible that the polymorphisms in the RGS1 locus are tagging SNPs for a common causative inflammatory disease variant that remains to be discovered. (24,25)

The second gene reported is IL12A which encodes a subunit of a cytokine that acts on T and natural killer cells, and has a broad array of biological activities. This cytokine is required for the T-cell-independent induction of interferon (IFN)-gamma, and is important for the differentiation of both Th1 and Th2 cells. IL-12, which is produced principally by monocytes and dendritic cells, is one of the major mediators of immune response that is critical for the differentiation of Th1 cells. (26) Similarly toRGS1, IL12A has been associated with type 1 diabetes, celiac disease, rheumatoid arthritis and primary billiary cirrhosis, again suggesting that the autoimmune diseases, despite many differences, share a number of genetic risk factors. (25,27,28) However the study discussed in this manuscript showed that the effect of the rs4680534C allele seems to be different in MS and celiac disease: the risk allele for MS seems to be protective in CD and vice versa.

The third polymorphism is located in intron 12 of the MPHOSPH9 gene on chromosome 12q24.31. This region has not been previously identified as a susceptibility locus for inflammatory diseases, and little is known about it. However this polymorphism strongly correlated with the expression of the neighboring CDK2AP1 gene. The protein encoded by this gene is a specific CDK2-associated protein, which is thought to negatively regulate CDK2 activity by sequestering monomeric CDK2, and targeting CDK2 for proteolysis and has the

regulatory role in DNA replication during S phase of the cell cycle. *CDK2AP1* was initially identified as a cancer-related gene by using hamster oral cancer model, but in addition to its role as a cell cycle regulatory molecule through two important cellular partners: CDK2 and DNA polymerase-alpha/primase, CDK2AP1 has a role in TGF-β induced growth arrest, cisplatin induced genotoxicity, and cellular apoptosis. (29) The MS susceptibility allele rs1790100G is associated with a lower expression of CDK2AP1, suggesting that there may be a reduced inhibition of DNA replication and proliferation mediated by p12DOC-1 in subjects with the risk allele.

Five-year view

The question arises whether the identification of these allelic variants is clinically meaningful. For each patient, the identification of a single polymorphism that is common in the general population, but has a small effect is not clinically significant. However, because there are many MS susceptibility loci with common alleles, the aggregate risk could be meaningful when estimating the probability that an individual will develop MS. The results from whole-genome association studies in MS have not yet been fully implemented in a clinical setting. The only attempt to do this was by De Jager and colleagues who used a weighted genetic risk score (wGRS) that combines weighted odds ratios from 16 loci (nine of the SNPs were located in validated MS susceptibility loci that were reported to exceed genome-wide significance ($p<5\times10^{-8}$) in the meta-analysis or in previous publications; and seven of the SNPs were strongly suggestive of association with MS in the meta-analysis ($p<10^{-4}$ in the final joint analysis) that have been associated with MS for prediction of a diagnosis of MS. (30) The inclusion of 16

susceptibility alleles into a wGRS modestly predicted MS risk, showed consistent discriminatory ability in independent samples, and was enhanced by the inclusion of non-genetic risk factors into the algorithm (smoking, EBV antibodies status). However, the wGRS didn't seem to be correlated with the conversion of CIS to MS. Others are arguing that using genetic information from genome-wide association studies will be futile, in other words, given that none of the high-frequency associated alleles is sufficient to cause MS or obligatory for the development of MS, very few people can have their probability of developing MS accurately predicted from genetic testing. (31)

On the other hand genome-wide association studies have provided us with only ~3% of the variance in MS risk. There are several possible approaches to address this problem. The aggregate role of low-frequency rare functional gene variants in MS has not been properly evaluated. These uncommon variants with relatively large effects might account for part of the unexplained heritability in MS. To establish the associations with rare variants it is necessary to perform direct mapping and rare variants within a sample must first be identified. Sequencing of candidate genes or entire genomes is the optimal way to identify rare variants. There is emerging interest in association studies of rare variants and it is hypothesized that rare variants are more likely to be functional than common variants. (32) The advancement in this field enabled the launch of the 1,000 Genomes Project, which will sequence at least 1,000 genomes from 10 different ethnic backgrounds. The project's goals include providing a detailed catalog of human variants to facilitate the identification of disease causing ones. (33)

Another possible approach is genomwe-wide copy number variation (CNV) analysis. Genomic structural variations are important source of genetic variation. (34) It has recently been recognized that structural genomic variants are a common cause of genetic variation in humans,

and such variants have been reported to substantially increase the risk of a number of multifactorial diseases. (35) For example it has been shown that the overall load of CNVs is greater in individuals with schizophrenia than controls and that there is association between schizophrenia and a number of specific rare CNVs (<1% population frequency). (36) This remains to be investigated in MS.

Key issues

- Discovering genetic and/or environmental factors will provide fundamental new insights into the pathogenesis, diagnosis and treatment of MS.
- Genome-wide association studies have been successful in discovering susceptibility loci for MS and other inflammatory diseases.
- Unlike *HLA DRB1*1501*, most of the genetic risk factors identified so far have only a slight effect on susceptibility to MS (with odds ratios that range from 1.1 to 1.2); however, the risk alleles in these loci are common in people of European ancestry, with allele frequencies of 0·1–0·9.
- Genome wide association studies identified altogether 12 loci and/or genes associated with MS which exceed genome-wide significance ($p<5\times10^{-8}$).
- The International Multiple Sclerosis Genetics Consortium provided evidence for three new loci that show evidence of association at a genome-wide level of significance: RGS1 (rs2760524, joint P value $3.55x10^{-9}$), IL12A (rs4680534, joint P value $3.08x10^{-8}$) and MPHOSPH9/CDK2AP1 (rs1790100, joint P value $3.96x10^{-8}$).

- MS patients, in the presence of the rs1790100G susceptibility allele (who are homozygous for the risk "G" allele) have a substantial reduction of the CDK2AP1 expression profile compared with the other two genotype classes.
- Genome-wide association studies have provided us with only ~3% of the variance in MS risk.
- Future studies which will detect low-frequency rare functional gene variants or perform genome-wide CNV analyses will probably give us more insight into genetic basis of MS.

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Tables

Table 1. MS genes that show evidence of association at a genome-wide level of significance.

IL7R
IL2R
CLEC16a
CD58
EVI5
TYK2
GPC5
RGS1
TNFRSF1A
IRF8
CD226
CD40
RGS1
IL12A
MPHOSPH9/CDK2AP1