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Genetics of Multiple Sclerosis: An Overview and New Directions

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The contribution of genetic inheritance in multiple sclerosis was established early on. Although multiple sclerosis is not a Mendelian disease, its incidence and prevalence is higher in family members of affected individuals compared with the general population. Throughout the last decade, several small studies failed to identify any robust genetic associations besides the classic associations in the major histocompatibility complex region. During the past few years, genome-wide association studies (GWAS) have revolutionized the genetics of multiple sclerosis, uncovering more than 200 implicated genetic loci. Here, we describe these main findings and discuss the new avenues that these discoveries lay open.

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS), resulting in progressive neurodegeneration and neurological disability (Bansil et al. 1995). MS most commonly affects young adults, especially women. From the early characterization years of the disease, it was apparent that there are both genetic and environmental influences (Sadovnick et al. 1997; Sawcer et al. 2014). For more than 30 years, studies on genetics of MS have unraveled a significant piece of the puzzle that is MS. Genetic studies provide an important piece toward understanding the yet elusive etiology of this complex disease.

MULTIPLE SCLEROSIS'S HERITABILITY

The role of genetic contribution to MS emerged from both twin and familial clustering studies (Sawcer et al. 2014). Monozygotic or identical twins were shown to exhibit significantly higher clinical concordance rate (25%–30%) than dizygotic or fraternal twins (3%–7%), a difference that potentially contributes to the low penetrance of this disease (Dyment et al. 1997), that is, the low likelihood that any particular genotype will manifest in MS. Family history of MS has been reported in 15%–20% of MS patients, much higher than the prevalence in the general population (Compston and Coles 2002). The lifetime risk of MS in first-degree relatives of MS index cases is estimated at 3% (4% for siblings, 2% for parents, 2% for children), or threefold greater than the age-adjusted risk for second-degree and third-degree relatives (1%) and 10- to 30-fold greater than the age-adjusted risk in the general population (0.1%–0.3%) (Compston and Coles 2002; Sawcer et al.

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2014). The risk of MS is markedly higher if both parents have MS and the risk of half-siblings is lower than that of full siblings, whereas the risk for step-siblings of MS index cases and for individuals adopted by families with MS are similar to the general population. Thus, the familial recurrence risk of MS increases in proportion to the amount of genetic sharing with the affected family member but not in a linear relationship. A meta-analysis of more than 500 studies reported a recurrence risk for monozygotic twins of 18.2% and 2.7% for siblings, and a sibling relative risk (λs) of 16.8 (O'Gorman et al. 2013). More recently, studies on large national registries allowed more accurate heritability estimates in MS. An Italian large-scale study of up to 50 million individuals ascertained 216 twin pairs and calculate a heritability estimate of 0.48 (95% confidence interval [CI], 0.06–0.86), whereas the environmental contribution was 0.29 (95% CI, 0–0.60) for shared and 0.23 (95% CI, 0.12–0.39) for unique (individual-specific) environmental factors (Ristori et al. 2006). A national registry study of ~15 million individuals in Sweden reported 28,396 registered patients with MS (Westerlind et al. 2014b). The investigators estimated a sibling recurrence risk ($\lambda s = 7.1$; 95% CI, 6.42–7.86) and they reported a heritability estimate of 0.64 (95% CI, 0.28–0.77) based on 348 proband twins with MS. This estimate was refined further by adding information on siblings and half-siblings to 0.64 (95% CI, 0.36–0.76). Interestingly, they could not find any shared environmental component (0.01 with 05% CI, 0–0.18; the individual-specific environmental component was 0.35 with 95% CI, 0.24–0.51). Despite the national level of these studies and their large sample size, it is obvious that studies of heritability based on twin studies are not free of methodological limitations, whereas wide CIs imply luck of ability to refine heritability estimated even at the national level (Hawkes and Macgregor 2009; Fagnani et al. 2014; Westerlind et al. 2014a).

CANDIDATE GENE ASSOCIATIONS

The strong evidence of heritable component in MS from the early population studies motivated the identification of the genetic culprits. This first era of genetic association studies was plagued by many small studies that were underpowered to identify any true associations. The MSgene database has a historical archive of >700 genetic studies in MS (see msgene.org). Despite the wide lack of corroboration in genetic studies of MS, there were few true associations that were uncovered. The human leukocyte antigen (HLA) gene cluster on chromosome 6p21 had been mostly consistently identified as the strongest genetic locus for MS from candidate gene association studies and genome-linkage approaches using microsatellite markers (Hollenbach and Oksenberg 2015). HLA genes encode polymorphic cell surface glycoproteins that are involved in immune regulation via recognition of either intracellular nonself (class I) or extracellular proteins (class II) (Shiina et al. 2009). The HLA genes reside within the highly polymorphic major histocompatibility complex (MHC) region that has been associated with MS susceptibility for some time. This signal was initially described as being part of the HLA class I genes (Bertrams et al. 1972; Naito et al. 1972; Jersild et al. 1973; Winchester et al. 1975); however, it was later refined to the class II region (HLA-DR2) (Compston et al. 1976; Haines et al. 1998). Further developments in molecular techniques allowed the localization of the HLA-DR2 locus to two separate molecular allotypes, HLA-DR*15 and HLA-DR*16, whereas the MS signal was further refined to HLA-DRB1*15 (Olerup and Hillert 1991; Barcellos et al. 2002) and later on to HLA-DRB1*15:01 (Barcellos et al. 2002; Hollenbach and Oksenberg 2015).

GENOME-WIDE STUDIES AND IDENTIFICATION OF COMMON VARIANTS

The striking absence of replicated genetic associations (Ioannidis et al. 2001), despite the overwhelming number of studies, highlighted a fundamental problem of the genetic model assumed in genetics of common diseases. The scientific community was extremely successful in identifying the causal variants of several rare diseases by leveraging familial designs. This suc-

cess was never evident in common diseases, even when larger scale linkage studies were performed. In MS, linkage studies failed to identify any genetic associations (Ebers et al. 1996; Modin et al. 2003; Haghighi et al. 2006; Willer et al. 2007; Dyment et al. 2008). It became evident that common diseases with a heritable component have different genetic architecture compared with Mendelian diseases. The theory of common disease–common variant (CDCV) was proposed to address these issues (Reich and Lander 2001). CDCV states that common diseases in a population are caused by several small common genetic variations, that is, with high allele frequency in the population. In the case of MS, this implies that there could be hundreds of common variants that each of them will have a small effect toward causing the disease. The evidence accumulated from familial studies via segregation analysis also suggested that MS has one locus with moderate effect (HLA-DRB1*15:01) and many loci with small effects (O'Gorman et al. 2013).

To accommodate the study of the CDCV hypothesis, several technological advancements had to converge to allow for the agnostic investigation of the whole genome. Chip arrays were developed that could simultaneously genotype hundreds of thousands genetic positions, whereas hypercomputing systems provided the necessary computing power to run millions of associations. Genome-wide association studies (GWAS) were introduced in the mid-2000s, and this new study design enabled the hypothesis-free interrogation of the genome. Two main aspects of GWAS studies were challenging. The investigation of hundreds of thousands of genetic variants would lead to an increase rate of false positive results while using the nominal level of statistical significance (p-value < 0.05). Thus, the concept of genome-wide levels of significance was introduced, with a p-value of 5×10^{-8} being the most widely used threshold. Finally, the requirement for large samples to increase the power to identify small effects necessitated a culture of collaboration in the scientific community.

The first GWAS in MS subjects was published in 2007 and was performed by the International Multiple Sclerosis Genetics Consortium (IMSGC), using 931 family trios and a replication cohort of 2322 MS subjects and 2987 controls (International Multiple Sclerosis Genetics Consortium et al. 2007). This first GWAS identified the first-ever genome-wide association in MS, outside the MHC region, rs12722489, which lies in the first intron of IL2RA (odds ratio [OR] = 1.25, p-value = 2.96×10^{-8}). The IL2RA gene encodes the α chain of the interleukin-2 receptor, which plays a role in several immune-related pathways (Liao et al. 2011). Interestingly, IL2RA is the target of the MS-approved drug daclizumab (Bielekova et al. 2004). In the following years, several more GWAS and follow-up studies increased the number of genome-wide associated MS variants to more than 40 (Wellcome Trust Case Control Consortium et al. 2007; Aulchenko et al. 2008; Comabella et al. 2008; Australia and New Zealand Multiple Sclerosis Genetics 2009; Baranzini et al. 2009; De Jager et al. 2009c; Jakkula et al. 2010; Nischwitz et al. 2010; Sanna et al. 2010; International Multiple Sclerosis Genetics Consortium et al. 2011, 2013b; Patsopoulos et al. 2011; Martinelli-Boneschi et al. 2012; Matesanz et al. 2012; Andlauer et al. 2016). In parallel with advancements in the MS-genetics, many genome-wide variants were discovered in several other autoimmune diseases (Stahl et al. 2010; Trynka et al. 2011; Jostins et al. 2012). A striking realization was that several of these were common across several autoimmune diseases. For example, the TAGAP gene locus has been associated with MS susceptibility; the same direction of effect is present in type I diabetes and rheumatoid arthritis, and the opposite effect occurs in celiac disease (Patsopoulos et al. 2011). This pleiotropic nature of genetic variants was leveraged in designing the ImmunoChip (IC), an array that aimed to fine-map 186 genomic regions associated with at least one autoimmune disease (Parkes et al. 2013). The IC enabled a low-cost interrogation of several autoimmune diseases at a large scale (Trynka et al. 2011; Eyre et al. 2012; Jostins et al. 2012; Liu et al. 2012, 2013; Mayes et al. 2014). In MS, the IC study analyzed 14,498 subjects with MS and 24,091 healthy controls to identify 110 genome-wide variants

(International Multiple Sclerosis Genetics Consortium et al. 2013a).

Several of the largest studies were meta-analyses of case control studies that were genotyped with different arrays (De Jager et al. 2009c; Patsopoulos et al. 2011). These meta-analyses of GWAS were facilitated by advancements in the fields of population and statistical genetics that enabled the completion of the haplotypic structure of reference populations (International HapMap Consortium 2005) and the parallel development of statistical algorithms and programs that could leverage these references to impute single nucleotide polymorphisms (SNPs) in GWASs (Marchini and Howie 2010).

In a similar fashion, the complex structure of the HLA genes was captured by creating reference panels, including SNPs, HLA alleles, and corresponding amino acids (Jia et al. 2013). These HLA-specific reference panels, coupled with advanced imputation algorithms, allowed the in-depth investigation of the MHC region in MS (Patsopoulos et al. 2013). The refinement of the HLA-DRB1*15:01-HLA-DQA1*06:02 was possible, proving that HLA-DRB1*15:01 is the driving allele in these European ancestry populations. HLA-DRB1 was proven to have multiple independent associations with MS (*03:01, *13:03, *04:04, *04:01, and *14:01), with four amino-acid changes (positions 71, 74, 57, and 86), capturing most of them (Patsopoulos et al. 2013). All of these amino-acid positions reside in the peptide-binding groove of the HLA-DR molecule, thus affecting binding and recognition of antigens. The nature of HLA associations in MS is even more complex with interacting HLA alleles. Small studies suggested the presence of HLA interactions (Lincoln et al. 2009) and larger genetic studies have verified their existence at genome-wide levels (Moutsianas et al. 2015). The role of these interactions is rather elusive; however, it seems to be a more extensive mechanism since interactions with MHC with non-MHC regions have been reported (Galarza-Munoz et al. 2017).

Currently, the largest genetic study in MS has analyzed 47,351 cases and 68,284 healthy controls, and has identified 233 genome-wide loci associated with MS susceptibility (Patsopoulos and International Multiple Sclerosis Genetics Consortium 2016). Two hundred of these loci reside in the autosomal non-MHC genome, and explain ~20% of the MS genetics. The effect size of these loci is relatively small, ranging from ORs of 1.05 to 1.2, as expected according to the CVCD hypothesis. This study has also identified the first-ever chromosome X variant in MS. The associated variant, rs2807267, is within an enhancer peak area specific for T cells and resides downstream from the RNA U6 small nuclear 320 pseudogene (RNU6-320P). RNU6-320P is a component of the U6 small nuclear ribonucleoprotein (snRNP), which is part of the spliceosome and is responsible for the splicing of introns from pre-messenger RNA (pre-mRNA) (Fortner et al. 1994). This finding opens up a new era of exploring the role of sex chromosomes in MS.

The discovery of genetic associations with disease susceptibility is not the desired end goal in MS genetics. The identification of the causal genes and their functional consequences is necessary to uncover affected mechanisms and pathways. Unfortunately, several limitations have not allowed the same rate of progress in causal gene mapping as the discovery of the genetic culprits. The vast majority of MS-associated variants fall within either intronic or intragenic regions (Patsopoulos and International Multiple Sclerosis Genetics Consortium 2016). Just recently, we have started to understand that this part of the genome is involved in regulatory mechanisms (Encode Project Consortium 2012; Roadmap Epigenomics Consortium et al. 2015). Several of the MS risk variants are within regions that are promoters or enhancers of nearby genes (Maurano et al. 2012). The few successful functional studies following GWAS findings have suggested that the identified genetic variants could alter splicing of exons that lead to different isoforms. More specifically, GWAS variants lead to alternate splicing of IL7R, IL2R, and TNFRSF1A, creating soluble forms of these genes that could inhibit downstream signaling (Gregory et al. 2007, 2012; Maier et al. 2009). Other variants could change the expression of nearby genes (De Jager et al. 2009a; Raj et al. 2014). Functional studies of MS variants still

have a way to go; however, advances in RNA-seq and other high-throughput technologies are paving the way toward the creation of MS-specific genomic maps. These genomic maps can allow the parallel functional characterization of MS variants in a cell-specific and environment-aware way.

Despite the lack of functional characterization of the hundreds MS risk variants and their small effect sizes, we can gain invaluable knowledge by studying them together. Enrichment methods that take into account all the identified variants can prioritize the affected tissues and cells (Hu et al. 2011; Maurano et al. 2012; Slowikowski et al. 2014; Pers et al. 2015). These methods leverage extensive expression, or other -omic maps and allow the relative ranking of affected cells or tissues. In MS, enrichment methods strongly implicate several different immune system cells, for example, regulatory T cells and B cells, whereas CNS tissues have no sign of being implicated (Patsopoulos and International Multiple Sclerosis Genetics Consortium 2016). A possible explanation is that the majority of the genetic MS variants alter regulation of immune-related genes. Furthermore, the lack of enrichment in brain tissues does not exclude the possibility that a handful of these genetic variants could directly affect neuronal tissue or supporting cell types. What we can state with certainty is that the ensemble of the MS-associated variants acts via immune system cells and related mechanisms. This is on par with GWAS discoveries in other autoimmune diseases that affect systems other than the CNS (Hu et al. 2011; Farh et al. 2015). Pathway analyses of the GWAS variants also point to the same realization (International Multiple Sclerosis Genetics Consortium et al. 2011, 2013a). Immune system-related and signaling pathways are strongly implicated, as well as T- and B-cell differentiation and cross-immune cell communication pathways (Patsopoulos and International Multiple Sclerosis Genetics Consortium 2016).

RARE VARIANTS

The success of GWAS to identify common variants led to the discovery of low-frequency variants. An open question is whether there are monogenic forms of the disease that are caused by rare variants that have a very strong effect. One study performed exome sequencing in MS subjects from 43 families with four or more affected individuals, and reported a rare variant in the CYP27B1 gene that caused complete loss of gene function in one individual (Ramagopalan et al. 2011). A large-scale replication study (Ban et al. 2013) and a targeted sequencing study (Barizzone et al. 2013) both failed to replicate this finding. Another study based on familial data suggested that the mutation p.Arg415Gln in NR1H3 causes a severe and progressive Mendelian form of the disease (Wang et al. 2016). No corroboration was feasible in a study of 32,852 MS cases and 36,538 controls (International Multiple Sclerosis Genetics Consortium 2016). Additionally, an investigation using the Exome Aggregation Consortium (ExAC) reported several individuals carrying this mutation with no reported MS or related disease (Minikel and MacArthur 2016). To date, there is no evidence of monogenic forms of MS; however, detailed investigations using whole-genome sequencing methods have not yet been performed. Any associations with rare variation in MS are yet to be proven.

SUBPHENOTYPES AND POPULATION HETEROGENEITY

Although the discovery of MS susceptibility loci has been very successful, with more than 200 genome-wide so far, this success has not been translated into subphenotypes of the disease. No association was identified with primary progressive MS or the MS Severity Score (MSSS) in any of the published studies (Jensen et al. 2010; International Multiple Sclerosis Genetics Consortium 2011; George et al. 2016), whereas some reports exist for magnetic resonance imaging (MRI) measurements that need further replication to be considered robust (Gourraud et al. 2013; Matsushita et al. 2015). On the contrary, studies on laboratory measurements have been successful. A study has identified a genome-wide association for the extent of intrathecal immunoglobulin G (IgG) in MS (Buck

et al. 2013). The associated variants were located in the immunoglobulin heavy chain (IGHC) locus on chromosome 14q32.33, which was also implicated by an independent study (Delgado-Garcia et al. 2015). Furthermore, a third study identified two novel associations within the MHC region and IgG index (Goris et al. 2015).

The majority of GWAS in any disease or trait are performed on European ancestry populations. Evidence from other diseases suggests that genetic susceptibility could be different in diverse populations. In MS, for example, it is established that HLA associations on the island of Sardinia are different that the ones from mainland Italy (Marrosu et al. 1998). Unfortunately, GWAS on non-European populations in MS have not been performed on the same scale as those done on European ancestry populations. Genetic studies in African-American MS subjects have so far uncovered a shared genetic background with the European populations (Johnson et al. 2010; Isobe et al. 2013, 2015), although the studied sample size has yet to reach the point where distinct genetic associations can be uncovered. A small study in MS subjects from India also suggested shared genetic risk with European populations (Pandit et al. 2011), whereas a study in Ashkenazi Jews pointed toward HLA-A*68:02 and HLA-B*38:01-HLA-C*12:03 haplotypes (Khankhanian et al. 2015).

CROSS-DISEASE ASSOCIATIONS

MS has increased comorbidity with other inflammatory diseases (Nielsen et al. 2008), with a common denominator of the attack of tissues by the immune system. It is well established that family members of individuals with MS are at increased risk for other autoimmune diseases and there is mounting evidence for a shared genetic background (Cotsapas et al. 2011). Several genes implicated in autoimmune diseases are pleiotropic, that is, are associated with more than one disease (Wagner and Zhang 2011). About a third of the MS-associated genetic variants have been reported at genome-wide levels in at least one other autoimmune disease (Patsopoulos et al. 2011). Empirical proof of the existence of extended genetic background across autoimmune diseases has been the success of the IC studies. The low cost of this autoimmune-targeted array allowed the genotyping and analysis of almost 10-fold more samples than traditional GWAS arrays, thus enabling early discovery of many genetic variants in MS and other diseases.

The genetic overlap of autoimmune diseases concurs with the role of the immune system deregulation, and an important question is whether genetics can explain the involvement of the CNS in MS. Few studies comparing MS with other neurological diseases have been performed. A comparison with amyotrophic lateral sclerosis found no shared association (Goris et al. 2014), neither did a study contrasting schizophrenia (Andreassen et al. 2015). A larger effort comparing 23 diseases affecting the brain, including MS, found evidence of overlap between other neurological diseases but not MS (Anttila et al. 2016).

GENETIC RISK SCORE TO PREDICT DISEASE SUSCEPTIBILITY

The polygenic architecture of MS with hundreds of causal genetic variants with small effects implied that no single variant could be used to predict disease susceptibility. The concept of aggregated risk score was introduced to take into account the complex genetic predisposition (Wray et al. 2007). Several disease associated genetic variants can be aggregated into a genetic risk score (GRS), in an unweighted or weighted fashion. Unweighted GRS is a simple summation of the copies of risk alleles in one's genome. Weighted GRS (wGRS) adjusts the risk alleles by multiplying with the effect size of each variant. One of the first wGRS studies in MS incorporated 19 MS risk loci and had an area-under-the-curve (AUC) of 0.70 to predict MS status in an independent case-control data set (De Jager et al. 2009b). The AUC could be improved by adding gender information to 0.74; however, the wGRS could not predict conversion of a clinically isolated syndrome to MS. Another implementation of wGRS in 1213 independent MS families (810 sporadic and 403 multicase families found a higher correlation in multicase fam-

ilies compared with sporadic (Gourraud et al. 2011). This study also failed to observe any ability of the wGRS to predict case-control status. A study using a wGRS of 110 variants in 842 Belgian MS patients and 321 controls observed a correlation even in extremes subphenotypes, for example, oligoclonal band-negative and primary progressive MS (Hilven et al. 2015). Moreover, they reported an association between high non-HLA wGRS and increased relapse rate and shorter relapse-free intervals after disease onset.

Several other studies identified associations between wGRS and subphenotypes and clinical course (Harbo et al. 2014; Pan et al. 2016), thus suggesting that the clinical utility of GRS might increase as more detailed clinical information is incorporated.

ENVIRONMENT AND GENETICS

MS has a strong environmental component. Several factors have been implicated with few having high levels of corroborating evidence. An interesting question is whether environment and genetics interact to cause MS. Unfortunately, the study of environment and common diseases is plagued by many problems, such as selection bias, confounding, and reverse causation. Mendelian randomization (MR) has been proposed to overcome these issues and provide a robust framework to resolve environmental exposure (Smith and Ebrahim 2003). MR is derived from Mendel's law of independent assortment (Monaghan and Corcos 1984), which states that the inheritance of genetic variants is independent. MR in a way is similar to an intention-to-treat analysis in randomized clinical trials (RCTs) (Davey Smith and Ebrahim 2005). The genetic "exposure" is randomly assigned to be present in one group and absent in the other, as does the intervention in RCTs. Thus, an unbiased estimate of the effect of the genetic exposure's effect on the final outcome can be derived (Davey Smith and Ebrahim 2005). MR has just recently started to get traction in MS genetics. A study of 25-hydroxyvitamin D (25OHD) reported a twofold increase in the odds of MS (Mokry et al. 2015) that was corroborated by another independent MR study (Rhead et al. 2016). Finally, another MR study suggested that increased body mass index (BMI) influences MS susceptibility and 1 standard deviation increase in BMI (kg/m^2) is associated with an OR of 1.41 (95% CI, 1.20–1.66) to be susceptible to MS.

CONCLUDING REMARKS

Genetics of MS have come a long way in the last few years. Hundreds of susceptibility loci have been identified, which can explain about half of the disease's heritability. Progress in secondary phenotypes has not been on par so far, but deep phenotyping efforts and context-aware analyses are encouraging for many important discoveries to come. New methods to explore the functional implications of the identified genetic variants and their interaction with environmental changes will lead to a new chapter of MS genetics.

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