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Genetics of primary progressive multiple sclerosis.

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<https://escholarship.org/uc/item/49v5331w>

Author

Cree, Bruce AC

Publication Date

2014

DOI

10.1016/b978-0-444-52001-2.00042-x

Peer reviewed

Chapter 10

Genetics of primary progressive multiple sclerosis

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INTRODUCTION

Multiple sclerosis (MS) patients can be clinically classified as having either relapsing-onset or progressive-onset disease. Compared to relapsing-onset MS, primary progressive MS (PPMS) is associated with an older age of onset, affects men as often as women, is associated with more rapid progression of disability, and does not respond to treatment with immunomodulatory or immune-suppressive medications. Given these marked clinical distinctions, genetic variance has been proposed as a potential determinant of disease course in MS. This chapter will systematically review the English-language literature on the genetics of PPMS with the goal of determining whether genetic factors are proven contributors to disease course.

PubMed search terms “primary progressive multiple sclerosis” and “genetics” were used. The language was restricted to English. The last search was performed on March 19th, 2012. All identified abstracts were reviewed for content. Only manuscripts that specifically addressed genetic risk factors for PPMS were included in the reference list. Additional manuscripts referenced by these citations were included when relevant.

FAMILY STUDIES

Familial aggregation in MS suggests a genetic contribution to the disease (Pratt et al., 1951; Millar and Allison, 1954; Sadovnick et al., 1988). Several studies examined clinical phenotypes within multiply affected family members to determine whether the disease course in MS may be genetically determined. These family-based studies do not seek to associate specific genetic variants with disease phenotypes but rather examine whether clinical phenotypes such as disease course are similar among affected family members.

A study of the clinical phenotypes of 177 non-twin sib pairs who were both affected by MS in UK families found no correlation with age of onset, presenting site, or disability (Robertson et al., 1996). However, disease course (PPMS versus relapsing-remitting MS (RRMS)) was weakly correlated ($\kappa = 0.150$, $p = 0.023$). This effect was more pronounced in same-sexed pairs ($\kappa = 0.266$, $p = 0.002$). These observations suggest that the disease course in MS is partially genetically determined. A follow-up study of the clinical phenotypes in an expanded dataset of 262 non-twin sib pairs affected by MS in the United Kingdom again found that disease course was correlated (50% overall concordance, $\kappa = 0.17$) (Chataway et al., 2001). Although 50% concordance may appear to be due to random chance, because a primary progressive onset is more rare than bout onset MS, 50% concordance indicates that disease course is not randomly distributed between affected siblings.

In support of these observations from the United Kingdom, a Scandinavian family-based study of 136 co-affected sib pairs found significant concordance between affected sibs with disease course ($\kappa = 0.28$, $p < 0.001$) and age of onset ($r = 0.23$, $p = 0.028$) (Oturai et al., 2004). The authors suggest that disease course and age of onset might be under genetic control due to sib pair concordance. In contrast to these familial associations of MS disease course, a much smaller study of 87 French sib pairs found no concordance with age of onset or disease course. However, there was a correlation in the progression index, a measure of disability accumulated over time based on the expanded disability status scale score ($r = 0.234$, $p = 0.03$) (Brassat et al., 1999).

A Dutch family-based study of 82 patients with a family history of MS and 231 patients with sporadic MS examined whether a family history of MS influenced

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various MS phenotypes, including age of onset and disease progression (Koch et al., 2008). The only phenotype that appeared to differ between familial and sporadic MS was the age of onset of PPMS patients, which was 4.69 years younger in familial cases (37.73 versus 33.04, $p=0.02$). This was interpreted as being consistent with genetic factors influencing the age of onset in PPMS. Correction for multiple comparison tests was not performed for this study. As a follow-up to this preliminary study, a population-based longitudinal cohort study from British Columbia found that familial PPMS patients ($n=84$, median age = 37.6 years) had a younger age of onset than sporadic PPMS patients ($n=327$, median age = 42.7 years; $p=0.007$) (Koch et al., 2010). Gender (52.1% women) had no influence on the age of onset. Taken together, these studies suggest that there may be a genetic basis that influences the age of onset of PPMS.

A larger European family-based study of 1083 families with two or more first-degree relatives with MS found concordance in disease course between affected siblings ($\kappa=0.12$, $p<0.001$) but, interestingly, not between parents and children ($\kappa=-0.04$, $p=0.09$) (Hensiek et al., 2007). Although interpreted as indicating a genetic influence on disease course, this observation argues more for an effect of shared sibling environment on disease course because disease course did not appear to be transmitted from parents to offspring.

Taken together, these studies show a correlation of disease course (progressive onset versus bout onset) between affected sib pairs. This indicates that either shared genetic or environmental factors, or both, in part determine which disease course an individual will experience. Perhaps the most challenging observation to the hypothesis that disease course is genetically determined is the observation that disease course was not transmitted from affected parents to offspring (Hensiek et al., 2007). Despite its relatively large size (1083 families) this study may not have had sufficient statistical power to discern transmission of weak genetic effects.

An important limitation to all of these studies is the relative scarcity of PPMS relative to relapsing-onset MS. As a consequence, all of these studies lack statistical power. Other possible confounders include: inconsistent standards for clinical ascertainment, failure to exclude MS phenocopies (see section below), uncertainty of age of onset determination, as well as potential heterogeneity within the PPMS population. Nevertheless, taken together these family studies do not convincingly argue for a genetic predetermination of disease course (progressive onset versus bout onset). Indeed, in a study of the effect of timing of birth on MS disease course, the month of birth effect, wherein MS patients are more likely to be born in May than November, was found only

in bout onset patients and not in PPMS patients, arguing for an environmental factor in bout onset MS (Sadovnick et al., 2007).

HUMAN LEUKOCYTE ANTIGENS

By far the most robust genetic determinant of MS susceptibility is genes within the major histocompatibility locus (MHC) at chromosome 6p21 (Bertrams et al., 1972; Naito et al., 1972; Sawcer et al., 2005; Hafler et al., 2007). Allelic variation at human leukocyte antigen (HLA) alleles is associated with MS risk, with the peak signal mapping to the HLA class II region. The HLA association with MS susceptibility was found across all populations (Table 10.1). Although several haplotypes have been associated with MS susceptibility in various populations, the haplotype that is most clearly associated with increased MS risk in European-descended populations is *HLA-DQB1*0602*, *HLA-DQA1*0102*, *HLA-DRB1*1501*. HLA molecules are highly polymorphic cell surface glycoproteins that have important roles in immune recognition of self and non-self antigens. The MHC is the most genetically dense region of the human genome, with thousands of recognized genes and open reading frames of unknown function encoded in this region. The potential contributions of several genes within this region to MS susceptibility are currently being elucidated. In addition to alleles of the *HLA-DRB1* gene within the class II region, alleles at the class I genes *HLA-A*, *HLA-B*, and *HLA-C* may also contribute to MS susceptibility (Fig. 10.1) (Brynedal et al., 2007; Yeo et al., 2007; De Jager et al., 2009).

Whether genetic variation at HLA contributes to the disease course in MS was first studied using a case-control study design in a French dataset consisting of 200 relapsing-onset MS patients compared to 61 patients with PPMS (Madigand et al., 1982). Using serologic typing, HLA-A1-B8 was found to be overrepresented in PPMS patients versus controls (OR = 2.23, $p=0.01$). In a subset of 18 PPMS patients and 76 RRMS patients for whom DR3 typing was performed, the HLA-A1-B8-DR3 haplotype was overrepresented in the PPMS patients (OR = 4.73, $p=0.008$). HLA-B7 was overrepresented in both PPMS and RRMS relative to controls. HLA-DR2 was overrepresented in MS patients as a whole but was not overrepresented in the subset of 18 PPMS patients who were typed for DR when compared to controls. This study suggested that haplotypic differences at HLA-A, HLA-B, and HLA-DR genes in part determine the disease course in MS.

A Dutch case-control study compared 23 patients with PPMS to 31 patients with RRMS. Relative to healthy controls, PPMS patients were more likely to carry HLA-B8 (odds ratio (OR) = 2.44, $p=0.046$) and less likely to

Table 10.1

Principal findings of studies on human leukocyte antigens (HLA) and primary progressive multiple sclerosis (PPMS)

Study	Location	PPMS (n)	Controls (n)	Gene	OR	p-value
Madigand et al. (1982)	France	61	200 RRMS	<i>A1-B8</i>	2.23	0.01
Madigand et al. (1982)	France	18	76 RRMS	<i>A1-B8-DR3</i>	4.73	0.008
Van Lambalgen et al. (1986)	Netherlands	23	31 RRMS	<i>B8</i>	7.18	0.008
Olerup et al. (1989)	Sweden	26	100 HC	<i>DRw15-DQw6</i> (<i>DRB1*1501-DQB1*0602</i>)	2.72	0.032
Olerup et al. (1989)	Sweden	26	74 RRMS	<i>DQw8, DQw9, DQw4 (DRB1*04-DQB1*08)</i>	5.1	0.0008
Olerup and Hillert (1991)	Sweden	36	250 HC	<i>DRw15 (DRB1*1501-DQB1*0602)</i>	3.27	0.001
Francis et al. (1991)	United Kingdom	19	100 HC	<i>DR2 (DRB1*1501-DQB1*0602)</i>	3.64	0.018
Hillert et al. (1992)	Norway	20	42 RRMS	<i>DRw17-DQw2 (DRB1*0301-DQB1*0201)</i>	0.25	0.02
Marrosu et al. (1993)	Sardinia	28	86 HC	<i>HLA-DQA1*0301</i>	5.47	0.0003
Weinshenker et al. (1998)	United States	12	107 RRMS	<i>DRB1*04-DQB1*08</i>	3.1	0.126
McDonnell et al. (1999)	Ireland	102	398 HC	<i>DRB1*1501</i>	3.68	< 0.0001
Marrosu et al. (2006)	Sardinia	100	835 RRMS	<i>HLA-DPB1*0301/D6S1683 + DRB1*1501</i>	2.31	0.007
Barcellos et al. (2006b)	United States and United Kingdom	87	433 HC	<i>DRB1*1501</i>	~2*	0.0004
Smestad et al. (2007)	Scandinavia	164	1281 RRMS	<i>DRB1*04</i>	NR	NS
Stankovich et al. (2009)	Australia	246	984 RRMS	<i>DRB1*1501</i>	3.88	< 0.0001
Stankovich et al. (2009)	Australia	246	984 RRMS	<i>DRB1*04</i>	0.66	0.01
Vasconcelos et al. (2009)	Brazil	33	180 HC	<i>DRB1*1501</i>	8.0	< 0.0001
Qiu et al. (2010)	Australia	41	189 HC	<i>DRB1*1501</i>	6.1	< 1 × 10 ⁻¹⁴

HC, healthy controls; NR, not reported; NS, not significant; RRMS, relapsing-remitting multiple sclerosis.

Odds ratios (OR) and *p*-values are calculated from data provided in each referenced manuscript using the chi-square immediate function in Stata 9.0 (Cary, NC) with *p*-values calculated using the Fisher exact, two-tailed hypothesis method.

*Precise OR not stated; OR estimated from figure 3 in the referenced manuscript.

Fig. 10.1. Human leukocyte antigen (HLA) genes in multiple sclerosis. (Copyright Bruce Cree.)

carry HLA-B15 (0% of PPMS and 17% of controls, $p=0.022$) (Van Lambalgen et al., 1986). HLA-B8 was also overrepresented in PPMS patients relative to RRMS patients ($OR=7.18$, $p=0.008$). RRMS patients were more likely to carry the HLA-A3, B7, DR2 haplotype than controls. This haplotype was not overrepresented in PPMS patients. Men with PPMS more often carried the HLA-B8 and B35 antigens, whereas women with RRMS more often carried the HLA-DR2 allele.

HLA alleles of *DRB*, *DQA*, and *DQB* were compared between 100 Swedish MS patients and 100 healthy controls (Olerup et al., 1989). Twenty-six patients had PPMS and 74 patients had RRMS/secondary progressive MS (SPMS) (100 total patients). *HLA-DRB*, *-DQA*, and *-DQB* alleles were typed using restriction fragment length polymorphisms (RFLPs) in each study subject rather than serologic typing. An RFLP associated with the *HLA-DRw15-DQw6* haplotype (the genetic correlate of the HLA-DR2 serotype) was present in 60% of patients and 30% of controls ($OR=1.95$, $p<0.0001$, Fisher exact). The association with the *HLA-DRw15-DQw6* haplotype was also found in PPMS patients relative to controls ($OR=2.72$, $p=0.032$). The authors also found that PPMS patients were enriched for the *DQw8*, *DQw9*, *DQw4* haplotype relative to patients with a relapsing onset ($OR=5.1$, $p=0.0008$, Fisher exact) as well as controls ($OR=3.08$, $p=0.015$). The *DQw7* haplotype was also present in 19% of RRMS and 29% of controls but was not found in PPMS subjects. The *DRw17-DQw2* haplotype (DRw17 is the equivalent of the DR3 serotype) was also overrepresented in RRMS patients ($OR=12$, $p=0.0032$). There was no difference between PPMS patients and controls for this haplotype. The authors concluded that the *DQw8*, *DQw9*, *DQw4* haplotype was associated with increased risk for PPMS, that the *DQw7* haplotype was protective for PPMS, and that the *DRw17-DQw2* haplotype was a risk factor for RRMS. Based on these observations the authors proposed that PPMS is immunogenetically distinct from RRMS. Although the authors reached this conclusion, the key finding of this paper was that the PPMS patients were indistinguishable from controls, most likely due to low power of the PPMS cohort. This paper also found that the *HLA-DRw15-DQw6* haplotype (*HLA-DRB1*1501-DQB1*0602*) was associated with MS susceptibility in both RRMS and PPMS.

In a follow-up case-control study of 179 Swedish patients and 250 controls, these investigators confirmed the association with *HLA-DRw15* (*HLA-DRB1*1501*) and MS in both PPMS and RRMS patients relative to healthy controls ($OR=3.99$, $p<0.0001$) (Olerup and Hillert, 1991). When the 36 PPMS patients were considered separately, the association with *HLA-DRw15* persisted ($OR=3.27$, $p=0.001$), as did the association in

RRMS ($OR=4.2$, $p<0.0001$). This study also found an association in RRMS patients with *HLA-DRw17-DQw2* ($OR=1.85$, $p=0.019$). This association was not found in the PPMS patients. The authors were not able to replicate their previously proposed association of PPMS with *HLA-DR4-DQw8* in this study.

A study of 200 patients and 128 unrelated controls from the Grampian region of Scotland found no differences between cases and controls for HLA-DR antigens but did find that *DQw1* was overrepresented in MS cases ($OR=2.07$, $p=0.0049$, Fisher exact). This study also found that HLA-DR2 was associated with relapsing MS but not patients with progressive MS; however, PPMS and SPMS patients were grouped together (Francis et al., 1987).

A case-control study from the United Kingdom of 19 PPMS and 52 RR/SPMS patients and 100 healthy controls found no difference in DR2 alleles between the two MS subtypes. Compared to controls, DR2 was overrepresented in both PPMS ($OR=3.64$, $p=0.018$) as well as RR/SPMS patients ($OR=3.69$, $p=0.0003$). For all MS $OR=3.68$, $p=0.0001$ (Francis et al., 1991).

A case-control study of 42 Norwegian RRMS, 20 PPMS, and 98 healthy controls using RFLP analysis of HLA haplotypes found that the *HLA-DRw15-DQw6* haplotype was over-represented in both RRMS and PPMS cases relative to controls. The authors also found that the *HLA-DRw17-DQw2* haplotype was more common in RRMS patients compared to PPMS patients ($OR=4$, $p=0.02$) (Hillert et al., 1992).

A case-control study of 116 Sardinian patients with MS and 86 unrelated healthy controls of *HLA-DQA* and *HLA-DQB* alleles found that *HLA-DQA1*0301* was overrepresented in MS cases. The MS cases were characterized as RR ($n=67$), PP ($n=28$), and "benign" ($n=21$). Relative to controls, the *HLA-DQA1*0301* allele was found more frequently in both RR and PPMS patients (Marrosu et al., 1993).

A population-based case-control study of MS patients and healthy controls in Olmsted County of MS susceptibility compared 119 MS patients with 100 healthy controls and found that the *HLA-DR15-DQ6* ($OR=3.3$, $p=0.00002$) and *HLA-DR13-DQ7* ($OR=11.1$, $p=0.004$) haplotypes were overrepresented in MS whereas the *HLA-DRI-DQ5* haplotype was under-represented ($OR=0.306$, $p=0.003$). Five of 12 PPMS patients carried the *HLA-DR4-DQ8* compared with 20 of 107 RR/SPMS patients ($OR=3.1$, $p=0.126$) (Weinshenker et al., 1998). The *HLA-DR4-DQ8* association in PPMS is in keeping with the earlier observation of Olerup et al. (1989).

A case-control study in an Irish dataset consisting of 202 RR/SPMS patients, 102 PPMS patients, and 398 healthy controls typed the alleles of *HLA-DRB1* using

polymerase chain reaction. *HLA-DRB1*15* (referred to as HLA-DRw15 or HLA-DR2, above) was overrepresented in both RR/SPMS (66.83%) and PPMS (63.73%, OR = 3.68, $p < 0.0001$) patients compared to controls (32.41%, OR = 4.22, $p < 0.0001$). *HLA-DRB1*04* was underrepresented in RRMS patients compared to controls (OR = 0.513, $p = 0.0007$). An overrepresentation of *HLA-DRB1*04* was not found in PPMS patients. Overall the distribution of *HLA-DRB1* alleles was similar comparing RR/SP MS patients to PPMS patients (McDonnell et al., 1999). This study is distinguished from its predecessors by the relatively large size of the PPMS cohort examined.

These studies share several important limitations. First, typing HLA alleles based on serologies or RFLPs is imprecise. Second, the datasets for most of these studies were very small, especially for comparisons between RRMS and PPMS. Third, appropriate corrections for multiple comparison tests were usually not performed. Fourth, no attempt for controlling for population stratification was made. Finally, replication of the proposed associations in a second independent dataset was not done. Because of these substantial limitations it is not surprising that the various associations of some HLA alleles with PPMS are inconsistent between studies and most likely are due to chance. The only finding that has at least some consistency across several, but not all, of the above studies, is the overrepresentation relative to healthy controls of the *HLA-DRB1*15* haplotype (HLA-DR2) in both relapsing-onset as well as PPMS patients.

In reviewing two large studies of HLA types and MS susceptibility (McDonnell et al., 1999; Masterman et al., 2000), Greer and Pender (2005) noted that the HLA-DR1, -DR4, -DR6, and -DR9 serologically defined HLA groups were less frequent in RR/SPMS patients and controls but that these differences were not found in PPMS patients. Greer and Pender hypothesized that these serologic subtypes were related because the HLA-DR molecules associated with these serotypes contain glutamic acid at residue 71 or 71 of the $\beta 1$ chain. These residues are important in determining the shape and charge of pocket 4 of the antigen-binding groove of the HLA-DRB1 molecule. However, not all alleles that compose the serologic subtypes of HLA-DR1, -DR4, or -DR6 contain glutamic acid at $\beta 1_{71}$ or $\beta 1_{71}$. Using an Australian case-control dataset consisting of 71 RR/SPMS, 50 PPMS, and 109 healthy controls and molecular typing of *HLA-DRB1* alleles, the authors investigated whether a glutamic acid at these residues influenced the disease course in MS. The presence of a glutamic acid residue at $\beta 1_{71}$ or $\beta 1_{71}$ was found in alleles of the serologic subgroups DR1, DR5, DR6, DR9, and DR53 (DRB4 contains a $\beta 4$ chain instead of $\beta 1$ at the HLA

molecule that is present in most DR4, DR7, and DR9 haplotypes). Glutamic acid residues at $\beta 1_{71}$ or $\beta 1_{71}$ were underrepresented in RR/SPMS patients (12.7%) relative to controls (34.9%, OR = 0.27, $p = 0.038$) and relative to PPMS patients (40%). This reported p -value is corrected for multiple comparisons. This study suggests that the presence of a glutamic acid residue $\beta 1_{71}$ or $\beta 1_{71}$ was protective from development of bout onset MS but not for PPMS. This apparent protective effect was observed in both *HLA-DRB1*1501*-positive and negative patients. *HLA-DQA1* and *-DQB1* alleles were also typed in this study and these alleles did not appear to influence the disease course. Presumably these genotypes result in differential presentation of specific antigens and account for the apparent protective effect in bout onset MS. This study is noteworthy because of its consideration of how a specifically charged amino acid residue might alter antigen presentation and thereby contribute to disease course. Although intriguing, replication of this observation in larger independent datasets has not been done.

An extended HLA haplotype may influence disease course

A population-based Sardinian case-control study of 835 RR/SPMS patients, 100 PPMS patients, and 471 ethnically matched controls compared HLA haplotypes defined by markers that span the HLA locus, *HLA-DPB1*0301* and the extended class I microsatellite marker D6S1683 (Marrosu et al., 2006). The *HLA-DPB1*0301* and 1683+ alleles were overrepresented in PPMS patients relative to bout onset patients (OR = 2.31, $p = 0.007$). In addition, carriers of *HLA-DPB1*0301* and 1683p were much less likely to have PPMS MS (OR = 0.08, $p = 0.03$), suggesting that an interaction between these alleles is present. This study also confirmed the association, in aggregate, of several *HLA-DRB1-DQB1* haplotypes previously identified with MS susceptibility in this population (DR2, DR4, and DR13) (Marrosu et al., 2001). The *HLA-DRB1* haplotypes did not influence the disease course. This study suggests that allelic interaction between a gene linked to the extended class I microsatellite maker D6S1683 and the HLA class II gene *HLA-DPB1*0301* influences the risk of PPMS. In one study, *HLA-DPB1*0301* was hypothesized to contribute to epitope spreading and disease progression in MS by preferentially restricting T-cell responses to myelin proteolipid protein epitopes (Yu et al., 1998).

Family-based HLA studies

A family-based study of 48 PPMS trio families found excessive transmission of the *HLA-DRB1*1501* allele ($p = 0.0004$). A case-control study using 87 PPMS cases

and control genotypes derived using non-transmitted allele frequencies from 433 parents also found overrepresentation of the *HLA-DRB1*1501* allele in PPMS patients (Barcellos, et al., 2006b). A study of a single family in the Faroe Islands examined HLA haplotypes among affected and unaffected individuals (Binzer et al., 2010). Three patients with early-onset severe PPMS had *DRB1*01/DRB1*15* haplotypes whereas RRMS patients had *DRB1*04/DRB1*13* or *DRB1*04/DRB1*07* haplotypes. This study is too small to draw any conclusions regarding disease course and HLA haplotype.

Recent studies of HLA in PPMS

A Scandinavian case-control study of 1281 RRMS and 164 PPMS patients investigated whether allelic variation at *HLA-DRB1* and *HLA-A* influenced clinical phenotypes in MS (Smestad et al., 2007). *HLA-DRB1*1501* was associated with a lower age of onset but allelic variation at these loci did not influence the disease course. An apparent trend associating *HLA-DRB1*04* with PPMS did not retain statistical significance after adjustment for multiple comparisons. The direction of the trend was not provided.

An Australian case-control study of 984 RRMS, 246 PPMS, and 1210 healthy controls investigated the associations between *HLA-DRB1*01*, **03*, **04*, **07*, **11*, **13*, and **15* alleles and MS susceptibility and disease course (Stankovich et al., 2009). Gene dose-dependent effects of *HLA-DRB1*15* and *HLA-DRB1*03* alleles on MS susceptibility were identified. In addition, a protective effect of *HLA-DRB1*04* was observed. Further analysis showed that this protective effect was present only in PPMS patients (OR = 0.66, $p = 0.01$) and not in RRMS patients. This observation is in contrast to the proposed effect of *HLA-DRB1*04* on increasing risk for PPMS (Olerup et al., 1989; Weinshenker et al., 1998). The direction of effect of *HLA-DRB1*04* in this study also contrasts with that reported in Sardinian MS in which this allele is associated with increased risk (Marrosu et al., 1993, 2006).

In contrast, a smaller Australian case ($n = 466$)-control ($n = 189$) study of *HLA-DRB1* allelic heterogeneity using four-digit typing found no difference in *HLA-DRB1* frequency among PPMS ($n = 41$) and bout onset patients (Wu et al., 2010). As expected, the strongest association with MS susceptibility was with the *HLA-DRB1*1501* allele for both PPMS (OR = 6.1, $p = 10^{-14}$) and for bout onset MS (OR = 4.8, $p = 10^{-14}$).

In a related paper, an apparently contradictory finding was observed when patients were stratified by early versus late-onset MS (Qiu et al., 2010). Patients with late-onset MS ($n = 73$), defined as presentation over the age of 50, were more likely to have PPMS and carry the *HLA-DRB1*0801* allele compared to patients with early-onset

MS ($n = 100$). If these traits (late-onset MS and PPMS) shared a common genotype, then *HLA-DRB1*0801* should be overrepresented in PPMS patients. That said, the numbers of *HLA-DRB1*0801* carriers were very small ($n = 9$ for late-onset MS, $n = 5$ for early-onset MS, and $n = 7$ for healthy controls), thus any inferences with respect to associations are susceptible to misinterpretation because of the small numbers in this study.

Possible influence of *HLA-DRB1*1501* on disability progression in PPMS

A Brazilian case-control study of 33 PPMS patients and 180 healthy controls sought to determine whether disease course was associated with *HLA-DRB1*1501/1503*, *HLA-DQA1*0102*, and *HLA-DQB1*0602* alleles (Vasconcelos et al., 2009). The non-parametric Mann-Whitney test, rather than survival analysis, was used to explore time to major MS disability milestones (expanded disability status scale (EDSS) 3, 6, and 8). The *HLA-DRB1*1501* allele was significantly associated with PPMS (*HLA-DRB1*1501*: OR = 8.0, $p < 0.0001$; *HLA-DQB1*0602*: OR = 4.18, $p = 0.001$). PPMS patients carrying the *HLA-DRB1*1501* allele more rapidly reached EDSS 6 compared to patients who did not carry this allele (~ 3.8 years versus ~ 6 years, $p = 0.039$). The authors concluded that *HLA-DRB1*1501* adversely influences the disease course in PPMS. Interestingly, the association of *HLA-DRB1*1501* with PPMS was found irrespective of white versus African ancestry in this dataset.

In summary, the major MS susceptibility allele, *HLA-DRB1*1501*, is overrepresented in both relapsing-onset and PPMS relative to healthy controls. A consistent effect of other HLA alleles on the disease course in MS is not supported by the literature. It is likely that all of the studies reviewed are substantially underpowered to detect modest or weak effects of genetic variants on the disease course in MS given that the largest analysis to date investigated a dataset with only 246 PPMS patients. Another limitation of any meta-analysis of published data is that varied techniques have been in use for HLA typing over the past quarter-century, making any comparison between different studies tentative at best. With the recent development of a worldwide consortium, the International Multiple Sclerosis Genetics Consortium (IMSGC) for exploration of the genetics of MS, the infrastructure may now in place for a deep exploration into the role of HLA genes in PPMS (see Conclusion, below).

Non-HLA neuroinflammatory genes

APOE

The *APOE* gene encodes a lipid carrier protein (apoE) that modulates central nervous system (CNS)

inflammation and influences repair following injury with allele-specific effects. The *APOE* $\epsilon 4$ allele is associated with less effective downregulation of inflammatory cytokines in the brain than the *APOE* $\epsilon 3$ allele and contributes to an earlier age of onset of Alzheimer disease (Lynch et al., 2003). A large number of studies have explored whether *APOE* contributes to MS susceptibility or influences the disease course.

A case-control study of 50 PPMS patients and 159 healthy controls in the United Kingdom found no association of the *APOE* $\epsilon 4$ allele and PPMS and no correlation with *APOE* $\epsilon 4$ and disease severity (Weatherby et al., 2000b). This result is consistent with a similar finding in a cohort of 370 RR/SPMS patients and 159 controls (Weatherby et al., 2000a).

A Sardinian case-control study of *APOE* and *HLA-DRB1* alleles involving 773 relapsing and 98 PPMS patients and 348 healthy controls found an interaction between *APOE* alleles, *HLA-DRB1* alleles, sex, and disease course. The *APOE* $\epsilon 4$ allele was associated with PPMS patients who did not carry the *HLA-DRB1**1501 allele (OR = 3.23, $p = 0.01$). Further analysis showed that the interaction between *APOE* and *HLA-DRB1* was only in women. When *HLA-DRB1**X (where X represents all non-1501 alleles of *HLA-DRB1*) women were considered separately from men, the *APOE* 4 genotype was associated with increased risk of PPMS (OR = 6.81, $p = 0.002$) (Cocco et al., 2005).

The *APOE* $\epsilon 4$ allele was also found to be overrepresented in PPMS patients (53.3%) relative to healthy controls (8.9%, $p < 0.0001$) or RRMS patients (24.4%, $p = 0.009$) in a Hungarian case-control study of 45 PPMS, 45 RRMS, and 45 healthy controls (Losoncz et al., 2010). Conversely, the 2 allele was underrepresented in PPMS patients (8.9%) relative to healthy controls (37.8%, $p = 0.002$) or RRMS patients (48.9%, $p < 0.0001$). In contrast to the Sardinian study, sex-specific associations were not observed. This study did not look for, and was too small to identify, interactions between *APOE* alleles and *HLA-DRB1* alleles.

A meta-analysis was performed using 17 published datasets. No association between *APOE* alleles and MS susceptibility or disease course was identified (Burwick et al., 2006). This same study also performed a pooled analysis of 4048 MS patients, including 353 PPMS patients. An association between *APOE* alleles and either PPMS or disease severity was not found. Data on *HLA-DRB1* status was not available for all MS cases and so an investigation into whether the *APOE* 4 allele was associated with PPMS patients who do not carry the *HLA-DRB1**1501 allele could not be performed in this pooled dataset. The authors acknowledged that this question remains outstanding.

CHEMOKINE (C-C MOTIF) RECEPTOR 5 (CCR5)

The chemokine receptor *CCR5* is expressed in actively demyelinating plaques (Simpson et al., 1998; Balashov et al., 1999; Sorensen et al., 1999) and its chemokine ligands macrophage inflammatory protein-1 α and -1 β (MIP-1 α , MIP-1 β) and RANTES (regulated on activation, normal T cell expressed and secreted) are elevated in the cerebrospinal fluid (CSF) of patients experiencing relapses (Miyagishi et al., 1995; Mahad et al., 2002). A 32-basepair deletion in the coding region of *CCR5* (*CCR5* $\delta 32$) abolishes *CCR5* function and may impair entry of inflammatory cells into MS lesions. However, several studies did not find an association between *CCR5* $\delta 32$ and MS susceptibility (Bennetts et al., 1997; Chataway et al., 1999; Barcellos et al., 2000; Sellebjerg et al., 2000). A German case-control study of 201 RR/SPMS and 42 PPMS patients did not find an association of the *CCR5* $\delta 32$ with disease course (Haase et al., 2002). An Irish case-control study of 331 RR/SPMS, 108 PPMS, and 230 healthy controls did not find any associations between the *CCR5* $\delta 32$ and disease course (Silversides et al., 2004).

Expression of *CCR5* in peripheral blood mononuclear cells (PBMCs) may be increased in PPMS patients (Jalonen et al., 2002). A Finnish study of 63 RR/SPMS, 26 PPMS, and 119 healthy controls found that the *CCR5* $\delta 32$ homozygous alleles were overrepresented in PPMS patients relative to controls (OR = 15.4, $p = 0.018$), although individuals homozygous for this were rare in either PPMS (3/23) patients or controls (1/118) and corrections for multiple comparisons were not implemented. Furthermore, this study did not show an association between *CCR5* expression (RNA or protein) and disease course (Pulkkinen et al., 2004).

CASPASE 8 (CASP8)

Caspase 8 is a cysteine protease that initiates apoptotic signaling via the extrinsic pathway and is differentially expressed in the peripheral immune system of MS patients (Comabella and Martin, 2007). A case ($n = 546$)-control ($n = 547$) study of *CASP8* single nucleotide polymorphisms (SNPs) found associations for the GG homozygous SNP of rs2037815 in a Spanish dataset (OR = 2.0, $p = 0.016$) (Camina-Tato et al., 2010a). The risk haplotype was significantly overrepresented in PPMS patients (28.5%) compared to RRMS patients (19.5%) and healthy controls (16.1%). Conversely, the protective haplotype was underrepresented in PPMS patients (19.2%) versus RRMS (37.6%) and healthy controls (36.2%). In a small substudy of PBMCs mRNA levels of *CASP8* were found to be no different in patients harboring the protective or risk *CASP8* haplotypes.

This suggests that these haplotypes do not influence CASP8 expression in resting cells at the mRNA level.

CYTOTOXIC T-LYMPHOCYTE-ASSOCIATED PROTEIN 4 (CTLA-4 OR CD152)

CTLA-4 is an important costimulatory molecule involved in modulating T-cell activation via binding to CD80 and CD86. The G⁴⁹ allele of CTLA-4 was associated with MS susceptibility in two Scandinavian case-control studies (Harbo et al., 1999; Ligiers et al., 1999) as well as in Olmsted County (Kantarci et al., 2003), and may influence disease severity in Japanese MS (Fukazawa et al., 1999b). However, multiple other case-control studies found no association with MS susceptibility (Masterman et al., 2000; Rasmussen et al., 2001; Bocko et al., 2003; van Veen et al., 2003a; Bonetti et al., 2004; Teutsch et al., 2004; Fukazawa et al., 2005; Lorentzen et al., 2005; Roxburgh et al., 2006). A family-based study in Canadian MS also found no association (Dyment et al., 2004); however, family-based studies with replication in French and southern European MS found an association, especially in families carrying the *HLA-DRB1*15* haplotype (Alizadeh et al., 2003). A case-control study of 330 German MS patients and 152 controls examined whether the G⁴⁹ allele of CTLA-4 contributed to MS susceptibility and the disease course. An association with MS susceptibility was not identified in this study; however, the G⁴⁹ allele of CTLA-4 was overrepresented in PPMS patients relative to controls (OR = 3.45, $p = 0.035$). This allele was also overrepresented in PPMS relative to RR/SPMS (OR = 3.00, $p = 0.044$). This study did not attempt to correct for multiple comparisons inherent in the genotype test (Maurer et al., 2002).

A Swedish case-control study of 40 PPMS patients, 300 relapsing-onset patients and 237 healthy controls considered four two-locus haplotypes (SNPs in the promoter and exon 1) of the CTLA-4 gene. A haplotype bearing the G⁴⁹ allele of CTLA-4 was overrepresented in PPMS patients relative to controls (OR = 4.4, $p = 0.0001$). This allele was also overrepresented in PPMS relative to RR/SPMS (OR = 3.20, $p = 0.0024$). This study was unable to replicate these observations in a second independent dataset of 43 PPMS, 31 RR/SPMS, and 290 controls (Masterman et al., 2002).

A case-control study found that the C-A-AT₈ allele of the -318C/T-+49A/G-AT_n haplotype of CTLA-4 conferred susceptibility to MS. This study looked for influences of CTLA-4 allelic variants on disease course, although a non-significant trend correlating PPMS with the G⁴⁹ allele was claimed (Kantarci et al., 2003).

A Northern Irish case-control study of 84 PPMS patients, 246 RRMS patients, and 158 healthy controls

investigated whether the CTLA-4 alleles influenced PPMS susceptibility. The A⁴⁹ allele of CTLA-4 was overrepresented in RRMS patients (OR = 1.36, $p = 0.038$) but not in PPMS patients. A minor allele of a 3' UTR microsatellite repeat AT₈₋₁₇ was overrepresented in both RRMS (OR = 2.44, $p = 0.037$) and PPMS patients (OR = 4.3, $p = 0.0013$) relative to controls. After correction for multiple comparisons these associations did not retain statistical significance. Linkage disequilibrium (LD) was present between the various CTLA-4 alleles assessed in this study. The A-C-A-AT₈-G allele of the -318C/T-+49A/G-AT_n-CT60 haplotype was overrepresented in RRMS patients compared to controls (9% versus 4.5%, $p < 0.05$). This is in keeping with a prior observation that suggested the C-A-AT₈ haplotype conferred susceptibility to MS (Kantarci et al., 2003). This haplotype was underrepresented in PPMS patients relative to RRMS patients (2.5% versus 9%, $p = 0.003$). In contrast, the T-A-AT₈₋₁₇-G allele of the -318C/T-+49A/G-AT_n-CT60 haplotype was overrepresented in PPMS patients relative to RRMS patients (7.8% versus 1.6%, $p < 0.003$) (Heggarty et al., 2007). The 3' UTR microsatellite repeat alleles have been reported to modulate T-cell reactivity in myasthenia gravis (Huang et al., 2000; Wang et al., 2002) and Graves' disease (Takara et al., 2003). The CT60 SNP of the CTLA-4 gene was also overrepresented in families with several members affected by MS who also had other autoimmune diseases ($p = 0.02$), suggesting that this allele could influence a predisposition for autoimmunity in families who have a genetic predisposition for MS (Barcellos et al., 2006a).

Although it is unlikely that CTLA-4 contributes substantially to MS susceptibility, it is possible that the G⁴⁹ allele of CTLA-4 influences the disease course, favoring progression from onset, because several small studies observed a similar overrepresentation of this allele in PPMS patients.

INTERLEUKIN-4 (IL4) AND IL4R

A case-control study in a Northern Irish dataset using 172 RR/SPMS patients, 95 PPMS patients, and 179 controls found that the VNTR*B2-+33 C/T*C haplotype of the IL4 gene was overrepresented in PPMS patients ($p = 0.03$) (Suppiah et al., 2005). Replication was unsuccessfully attempted in a Basque dataset consisting of 11 PPMS and 131 RR/SPMS patients. Polymorphisms in the IL4R were also examined in these datasets but associations with MS susceptibility were not found. In contrast, a Belgian, family-based analysis found significant distortion of transmission of the IL4R receptor Q551*R allele to MS patients due to under transmission of the C allele. The authors attributed the disparate findings in these studies to population-based differential

genetic effects rather than lack of statistical power due to small sample sizes and acceptance of marginally statistically significant p -values as true rather than chance associations.

A case-control study of *IL4R* variants in 341 German MS patients and 305 healthy controls found no association between *IL4R* variants and MS susceptibility. In comparing the subset of 48 PPMS patients to that of 248 RR/SPMS patients, the *Q551*R* allele was overrepresented in the PPMS patients, although after multiple comparison testing this result was no longer statistically significant. The *Q551*R* allele was overrepresented in PPMS patients relative to controls and this result retained statistical significance after multiple comparison testing ($p=0.018$). Interaction with the *HLA-DRB1*15* haplotype was not observed (Hackstein et al., 2001). The *IL4R* gene was investigated because a candidate gene analysis suggested possible linkage between *IL4R* alleles and MS susceptibility (He et al., 1998). The *IL4R Q551*R* allele is thought to affect signal transduction via the IL-4 receptor and alter immunoglobulin E (IgE) levels; altered IL4R signaling could in theory affect Th1 immune responses and thereby contribute to MS pathogenesis, although why this would be specific to PPMS is not obvious. The *IL4R Q551*R* variant has been associated with kidney allograft rejection (Hackstein et al., 1999) and asthma, indicating a functional role of this allele in immune regulation (Loza and Chang, 2007).

IL7R

Alleles of the IL7R contribute to MS susceptibility (Zhang et al., 2005; Gregory et al., 2007; Hafler et al., 2007; Lundmark et al., 2007). An Australian case-control study of 63 PPMS, 108 SPMS, 192 RRMS, and 182 healthy controls found that the promoter -504 T allele was overrepresented in PPMS patients (OR=2.2, $p=0.013$) (Booth et al., 2005). This association was replicated in another dataset of 50 PPMS patients. Using the transmission distortion test this allele was overtransmitted to patients in 18 PPMS families ($p=0.05$). This study also found that *IL7R* gene expression was relatively diminished in 6 PPMS patients compared to 6 SPMS patients along with 24 other genes assessed using microarrays. A trend was reported for the -504 C haplotype and more soluble IL7R.

In a follow-up study of *IL7R α* gene expression, mRNA from whole blood of 32 PPMS patients, 21 RRMS patients, and 42 healthy controls was isolated. *IL7R α* expression was decreased in the whole blood of PPMS patients relative to controls (McKay et al., 2008b). The level of *IL7R α* in RRMS was intermediate between controls and PPMS patients and could not be statistically differentiated from these two groups. *IL7R α* mRNA was

also isolated from PBMCs from an overlapping group of 34 PPMS patients, 20 RRMS patients, and 31 healthy controls and the level was lower in the PPMS patients. Again, statistical differentiation between RRMS and PPMS groups based on this level was not possible. When the ratio of the full length to the soluble isoform was compared both PPMS and RRMS patients produced more of the soluble form relative to controls. This observation is consistent with the association of a polymorphism within the *IL7R α* gene that increases the percentage of soluble *IL7R α* and increases risk of MS (Hafler et al., 2007). The haplotype that causes increased soluble *IL7R α* was enriched in the PPMS patients in the Australian dataset. The authors also found that neutrophil levels were higher in PPMS patients ($p=0.02$) and suggested that this might be secondary to proinflammatory, proneutrophil Th17 cells. The authors proposed that the reduction in *IL7R α* expression seen in PPMS would reduce the population of Treg cells; however, no differences in CD4+CD25^{Hi}FoxP3+ cells were observed between PPMS and controls (McKay et al., 2008a).

IL10

Tumor necrosis factor (TNF) and IL10 cytokine production was studied in lipopolysaccharide stimulated whole blood cultures of 126 Dutch family members of 50 patients with RRMS and 61 family members of 25 patients with PPMS. Members of families with low IL10 and high TNF production had a fourfold increased risk of developing RRMS compared to family members with high IL10 and low TNF. Patients of families with low IL10 and high TNF levels were eightfold more likely to develop RRMS compared to PPMS (de Jong et al., 2000).

In a follow-up Dutch case-control study of 163 RRMS, 88 PPMS, and 129 healthy controls these authors investigated whether *IL10* polymorphisms were associated with MS susceptibility and disease course. *IL10* was investigated because IL10-deficient mice have more severe experimental allergic encephalomyelitis (Bettelli et al., 1998). In addition *IL10* polymorphisms influence the mRNA expression levels of this cytokine. The *IL10* 2849A allele is associated with lower levels of *IL10* and therefore might contribute to MS susceptibility. No association between *IL10* polymorphisms in RRMS was found. However, the *IL10*-2849A allele was found to be underrepresented in MS patients (OR=0.057, $p=0.03$) and in RRMS patients (OR=0.040, $p=0.001$) relative to controls (de Jong et al., 2002).

BETA-1,6 N-ACETYL-GLUCOSAMINYLTRANSFERASE (MGAT5)

MGAT5 is a glycosylation enzyme thought to be involved in experimental autoimmune encephalomyelitis

susceptibility. A genome-wide association screen identified two SNPs in *MGAT5* that are associated with MS disease severity as measured by the multiple sclerosis severity score (MSSS) (Brynedal et al., 2010). MSSS scores were correlated with 11 *MGAT5* SNPs in 194 patients with PPMS. The rs1257169 G allele was associated with lower disease severity scores ($p=0.02$) (Esposito et al., 2011). This association did not withstand Bonferroni correction and was not the same SNP associated with disease severity in RR/SPMS that was previously reported. This study was underpowered to assess disease severity associations in PPMS.

PERFORIN 1 (*PRF1*)

A case ($n=420$)-control ($n=512$) study of *PRF1* SNPs found associations for the A SNP of rs 10999426 and G SNP for rs3758562 in a Spanish dataset (Camina-Tato et al., 2010b). Interestingly, when stratified by gender, these associations were present only in men. Three SNP haplotypes were constructed and found that two minor-risk haplotypes were associated with PPMS in men ($n=45$) but not women ($n=51$). For the AGG haplotype the OR was 97.4, corrected p value = 5×10^{-5} and for the GAA haplotype the OR was 123.3, corrected p value = 2×10^{-6} . A total of 16.6% of PPMS, 3.7% of RR/SPMS patients, and 0.2% of healthy controls carried either haplotype. Replication studies found similar associations with overall MS susceptibility in a US dataset (296 cases and 300 controls) but not an Icelandic dataset (340 cases and 424 controls). Stratification by disease course was not performed in these replication datasets. *PRF1* mRNA levels were lower in PPMS patients ($n=10$) with the risk haplotype ($p=0.014$). CD8 T cells from male patients with the risk haplotype had numerically lower, but not statistically significant, cytotoxic activity. This study suggests alleles of the *PRF1* gene linked to MS susceptibility are sexually dimorphic. Furthermore the risk haplotype is associated with decreased expression of *PRF1* and lower cytotoxic activity in PPMS patients. If replicable, the unusually high ORs for the AGG (OR=97.4) and GAA (OR=123.3) haplotypes suggest that, when present in men affected by MS, these alleles essentially determine that the disease course will be primary progressive.

TUMOR NECROSIS FACTOR α (*TNF α*)

The proinflammatory cytokine gene *TNF α* has been associated with MS susceptibility in Spanish case-control studies (Fernandez-Arquero et al., 1999; Martinez et al., 2004). A Hungarian case-control study in 45 PPMS, 45 RRMS, and 45 healthy controls found that the G>A -376 *TNF α* SNP was overrepresented in PPMS patients relative to controls (OR=5.5, p -value=0.032)

(Losoncz et al., 2009). This study did not investigate whether the G>A -376 *TNF α* allele is in LD with HLA alleles because the *TNF α* gene is also located within the HLA complex at chromosome 6p21.3. An Egyptian case (PPMS $n=36$, RRMS $n=36$)-control ($n=30$) study of the *TNF α* -376 polymorphism found associations of the G allele in both PPMS (OR=8.75, $p=0.0016$) and RRMS (OR=4.25, $p=0.0152$) patients versus healthy controls (Nada and Labib, 2011). The authors did not correctly report correct the ORs or p -values in their study. Whether this polymorphism is associated with functional changes for the *TNF α* gene is not known. As with the Hungarian dataset, the Egyptian dataset did not assess HLA alleles to control for effects of LD with known HLA alleles.

In a follow-up study to a case-control study of MS susceptibility using microsatellite markers in a Northern Irish dataset (Heggarty et al., 2003; Abdeen et al., 2006) consisting of 348 RRMS (181 were classified as benign and 167 had aggressive MS) and 136 PPMS patients, genotype-phenotype correlations were assessed for the top 12 microsatellite markers associated with MS susceptibility identified by the genome-wide screen. Five of these markers retained statistical significance in this dataset after correction for multiple comparisons. Of these five markers, two were significantly associated with PPMS versus RRMS: D3S1278 and *TNF α* . Because MS patients were classified as having either benign or aggressive MS further distinctions could be made. Alleles 213 and 215 of the microsatellite marker D3S1278 seem to distinguish bout onset MS alleles 249, 251, 267, and 269 from PPMS whereas the associations of *TNF α* distinguish benign MS from aggressive MS and PPMS but do not distinguish aggressive MS from PPMS. As such, the *TNF α* alleles may be predictors of disease severity rather than disease course.

TNF α expression may also influence the disease course. A study of cytokine expression in MS versus healthy control sera found that sFAS (serum Fas), Chemokine (C-C motif) ligand 2 (CCL2), and *TNF α* levels were higher in PPMS patients compared to controls (Hagman et al., 2011). sFAS, macrophage migration inhibitory factor (MIF), and *TNF α* levels were higher in PPMS patients compared to RRMS patients. Differences between SPMS patients and PPMS, RRMS patients, or healthy control patients were not identified. Thus differential gene expression of these cytokines may be involved in the MS disease course; however, the cross-sectional nature of this study cannot assign cause-and-effect relationships between these gene expression profiles and the disease course.

VITAMIN D RECEPTOR (*VDR*)

VDR polymorphisms have been associated with the autoimmune diseases primary biliary cirrhosis (Vogel et al.,

2002), systemic lupus erythematosus (Huang et al., 2002), type 1 diabetes (Skrabic et al., 2003), and MS (Fukazawa et al., 1999a). The *VDR* gene is located at 12q.12-14, a region of interest identified in genome-wide association screens in Sardinian and Spanish datasets (Coraddu et al., 2003; Goertsches et al., 2003). An Australian case-control study compared *VDR* RFLPs in 42 RRMS, 37 SPMS, and 26 PPMS patients with 104 sex, race, and age-matched controls (Tajouri et al., 2005). A TaqI RFLP in the ninth exon of the *VDR* gene was more overrepresented in MS patients relative to controls (OR = 2.35, $p = 0.0069$). This polymorphism alters gene transcription but does not result in an amino acid substitution (Verbeek et al., 1997). This study also claims that the *VDR* TaqI polymorphism is more prevalent in SPMS and PPMS patients than in RRMS patients, although the confidence intervals surrounding the point estimates of the ORs in these subgroups overlap.

GENES INVOLVED IN NEURODEGENERATION

α Bcrystallin (CRYAB)

A Dutch case-control study of 490 MS patients, including 94 PPMS patients and 182 healthy controls, investigated correlations between alleles of the *CRYAB* gene (α crystallin). The *CRYAB-650*C* allele was associated with a primary progressive disease course (non-significant trend), an older age of onset, a shorter time to EDSS = 6, a lower T2 lesion volume, and greater measures of brain volume loss. The impact of the *CRYAB-650*C* allele on measures of brain volume was found in both PPMS as well as RR/SPMS patients. This study is noteworthy in that it investigated the impact of genetic modifiers on magnetic resonance imaging (MRI) measures of disease in PPMS (van Veen et al., 2003b). It is remarkable that, despite extensive advances in neuroimaging and characterization of MRI findings associated with PPMS, correlations between MRI phenotypes with genotypes in PPMS have not been systematically undertaken.

Cannabinoid receptor 1 (CB1)

CB1 modulates severity in experimental allergic encephalomyelitis and may have a neuroprotective role in response to inflammation (Rossi et al., 2011). A case ($n = 143$)-control ($n = 98$) study of an AAT repeat microsatellite near the CB1 receptor gene found a putative association of the 7/8 genotype with PPMS patients ($n = 47$) versus healthy controls ($p = 0.016$) in a Spanish dataset (Ramil et al., 2010). This association did not retain statistical significance after correction for multiple comparisons.

Complement factor H

Complement factor H regulates the formation of C3 and C5 convertase enzymes and the functional Tyr402His allele has been associated with Alzheimer's dementia in individuals carrying the *APOE4* allele (Zetterberg et al., 2008). A case (PPMS $n = 53$, RRMS $n = 212$, SPMS $n = 85$)-control ($n = 86$) study of the Tyr402His allele of complement factor H found no difference in the allele frequency (Ingram et al., 2010). Serum concentrations of factor H, and the 402His allele of factor H, were higher in patients with progressive disease (SPMS and PPMS). This observation suggests that either consumption of 402Tyr, or upregulation of 402His, occurs in progressive MS patients. The possible biologic significance of this observation is not known.

Complex I mitochondrial genes

Mitochondrial genes regulate energy metabolism and are involved in several neurodegenerative diseases (Triepeles et al., 2001). A study of genes involved in mitochondrial function in 26 PPMS and 163 RR/SPMS families found associations between two- and three-marker haplotypes in the nuclear genes *NDUFS5*, *NDUFS7*, *NDUFA7* on chromosome 19p13. The exclusion of the PPMS patients did not alter the outcome and the dataset was too small to determine whether these alleles were associated with PPMS (Vyshkina et al., 2005).

Glycogen synthase kinase 3 beta (GSK3 β) and tau

The abnormal hyperphosphorylation of tau is involved in the pathogenesis of several neurodegenerative disorders, including Parkinson's disease, frontotemporal dementia, and Alzheimer's disease. *GSK3 β* encodes for a serine threonine kinase that phosphorylates a variety of nuclear and cytoplasmic proteins, including tau. Abnormally phosphorylated tau and insoluble tau were found in progressive MS (Anderson et al., 2008, 2010). To investigate whether *GSK3 β* is associated with MS, SNPs in *GSK3 β* were genotyped in an Italian case-control dataset (Galimberti et al., 2011). The GG genotype of SNP rs334558 in *GSK3 β* was overrepresented in MS cases versus controls (25.4% versus 17.7%, $p = 0.02$). This association was found in RRMS (230) patients but not in SP (64) or PP (25) patients. The small sample size of PP patients and the failure to recognize that SP patients are genetically identical to RR patients only later in the disease course make the associations suggested by this study suspect.

Kinesin family 1B (*KIF1B*)

A SNP within *KIF1B* was recently associated with MS susceptibility in datasets from the Netherlands, Sweden, and Canada (Aulchenko et al., 2008). *KIF1B* encodes a kinesin protein believed to transport mitochondria and synaptic vesicles along axonal microtubules. Furthermore, *KIF1B* plays a direct role in myelin formation by correctly localizing myelin basic protein mRNA to developing oligodendrocyte processes (Lyons et al., 2009). As such, this is the first putative MS susceptibility allele that maps to a gene potentially involved in myelin development as well as neurodegeneration. An Italian case-control study of 221 PPMS cases and 221 controls did not find that rs10492972 SNP within *KIF1B* was associated with PPMS (Martinelli-Boneschi et al., 2010). This study had statistical power of only 0.33, assuming that the relative risk for MS associated with the CC and CT versus TT allele was 1.27–1.67. Therefore this study's result could be due to the sample size rather than absence of a true association.

NAD(P)H: quinone reductase 1 (*NQO1*)

Reactive oxygen species may contribute to CNS injury and MS lesion formation (Gonsette, 2008). *NQO1* protects cells from oxidative injury by maintaining antioxidant forms of vitamin E and ubiquinone and is upregulated in MS lesions (van Horssen et al., 2006). A case ($n=231$)-control ($n=380$) study of the *NQO1*C⁶⁰⁹T functional variant found that the T allele was overrepresented in MS cases versus controls (OR = 1.45, $p=0.009$) (Stavropoulou et al., 2011). When MS cases were stratified by disease course the T allele was overrepresented in PPMS patients versus bout onset MS patients (OR = 2.98, $p=0.009$). This functional allele affects individual vulnerability to oxidative damage (Dinkova-Kostova and Talalay, 2000; Ross et al., 2000) and as such may influence MS risk. This allele is implicated in other degenerative diseases, including Alzheimer's disease (Bian et al., 2008) and Parkinson's disease (Shao et al., 2001). Whether this allele also correlates with MS disability is not known.

Prion protein (*PRP*)

A case (PPMS $n=498$)-control (healthy controls $n=600$, RRMS $n=979$) study found no association between the codon 129 polymorphism of the *PRP* gene and PPMS (Stuve et al., 2011). Despite the relatively large size of this study it is still underpowered to conclude definitely that there is no influence of the codon 129 *PRP* polymorphism on MS disease course.

Progranulin (*PGN*)

An Italian case-control study with 354 patients and 343 controls assessed whether five SNPs in *PGN*, a gene implicated in neurodegenerative diseases such as frontotemporal dementia, Alzheimer's disease, and amyotrophic lateral sclerosis, might also be associated with MS. SNP rs2879096 TT genotype trended in an association test with MS phenotype (Fenoglio et al., 2010). When stratified by disease course (PP versus RR/SP), the TT genotype was found to be associated with 16.0% of patients and 3.5% of controls (OR = 5.2, $p=0.023$). An association of the C allele of SNP rs4792938 was also found (55.3% versus 33.5%, $p=0.011$, OR 2.4). A replication analysis in 233 MS patients and 224 age-matched controls was unsuccessful with either of these SNPs. A post hoc analysis stratifying by sex found an association of the rs4792938>C allele in men with PPMS (40.7% versus 26.9%, $p=0.002$, OR = 1.87). In men, an association with the rs2879096 T allele was also found (29.2% versus 18.9%, $p=0.012$, OR = 1.77). The relatively small sample sizes, nature of the post hoc analysis, and marginal p -values in this study make the conclusion that alleles of *PGN* are associated with susceptibility for PPMS in men questionable. The result that an association was found primarily in men is somewhat reminiscent of those for the *APOE* $\epsilon 4$ allele.

GENES OF UNKNOWN FUNCTION

A Disintegrin-like and metalloproteinase domain with thrombospondin type 1 modules (*ADAMTS14*)

A genome-wide screen using microsatellite markers and pooled DNA methodology identified a region of interest at 10q22.1 (Goertsches et al., 2003). A Spanish follow-up case-control study of 192 RR/SPMS patients, 95 PPMS patients, and 285 healthy controls investigated whether SNPs within the *ADAMTS14* gene that is present at this chromosomal locus were associated with MS susceptibility. Three of eight SNPs genotyped in *ADAMTS14* were associated with both RR/SPMS and PPMS relative to controls. The CC genotype of SNP6 C/T (hCV11453336) was associated with increased risk of RR/SPMS relative to controls (OR = 2.0, $p=0.008$). Associations for PPMS and SNP2 (hCV1229671) were also claimed, although this SNP deviated from Hardy-Weinberg equilibrium and therefore is suspect. Haplotype analysis indicated that one haplotype pair conferred disease risk and two haplotype pairs conferred protection. *ADAMTS14* is an interesting candidate gene because matrix metalloproteinases play important roles in brain extracellular matrix cleavage and regulation of neuroinflammation (Parks et al., 2004).

C10orf27

Another gene located at 10q22.1 near *ADAMTS14* is *C10orf27*, a gene that encodes a 351-amino-acid protein of unknown structure or function. A Spanish case-control study of 192 RRMS, 94 PPMS, and 285 matched healthy controls investigated whether three SNPs in the *C10orf27* gene were involved in MS susceptibility (Goertsches et al., 2008). SNP rs2254174 T and TT alleles were overrepresented in PPMS (OR = 2.7, p^{corr} = 0.031). This non-synonymous variant introduces an amino acid change from arginine to glutamine at codon position 2 and could lead to functional alterations in the protein. This gene is expressed in brain, testes, and thymus. The transcript was modestly upregulated in MS brain samples (1.7-fold, p = 0.035).

Human endogenous retrovirus Fc1 (HERV-Fc1)

Recently, the SNPs near the endogenous retrovirus HERV-Fc1 were found to be associated with MS (Nexo et al., 2011). The potential relationship between SNPs at this locus and MS disease course was investigated in a case-control study (Hansen et al., 2011). The C-allele of rs391745, near the endogenous retrovirus HERV-Fc1 locus, was associated with bout onset MS (n = 1160, p = 0.003) but not PPMS (n = 140, p = 0.96) relative to healthy controls (n = 1838). The authors suggest that development of bout onset MS may be influenced by the endogenous retrovirus locus HERV-Fc1.

Table 10.2 lists non-HLA genes possibly associated with PPMS.

PHENOCOPIES

The clinical hallmark of PPMS, asymmetric progressive leg weakness with spasticity, is a symptom shared by several other disorders (Natowicz and Bejjani, 1994). Phenocopies, illnesses that appear to be PPMS but are actually due to other genetic disorders, have been reported. These phenocopies are presented here to illustrate that the clinical manifestations of PPMS are shared by several other single-gene Mendelian disorders. It is possible that understanding genetic variation within these genes might lead to understanding how allelic variation within these genes, or the biologic pathways in which they function, could contribute to the genetics of PPMS.

Adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder caused by mutation in the ALD protein (ALDP) that catabolizes very-long-chain fatty acids (Moser et al., 2007). As with other leukodystrophies onset is typically

Table 10.2

Non-human leukocyte antigens (HLA) genes possibly associated with primary progressive multiple sclerosis (PPMS)

Gene	Allele	Association
Neuroinflammatory genes		
<i>APOE</i>	ε4	PPMS risk
<i>CCR5</i>	δ32 homozygotes	PPMS risk
<i>CASP8</i>	GG homozygous	PPMS risk
	SNP of rs2037815	
<i>CTLA4</i>	G ⁴⁹	PPMS risk
<i>IL4</i>	VNTR*B2- + 33 C/ T*C haplotype	PPMS risk
<i>IL4R</i>	Q551*R	PPMS risk
<i>IL7R</i>	Promoter -504 T	PPMS risk
<i>MGAT5</i>	rs1257169 G allele	PPMS severity
<i>PRF1</i>	GAA haplotype	PPMS risk
<i>TNFα</i>	G > A -376	PPMS risk
<i>VDR</i>	Taq1 RFLP in the ninth exon	PPMS risk
Neurodegenerative genes		
<i>CRYAB</i>	-650*C	PPMS risk
<i>CB1</i>	AAT repeat	PPMS risk
	microsatellite	
<i>CFH</i>	Tyr402His	PPMS risk
<i>NQO1</i>	C ⁶⁰⁹ T	PPMS risk
<i>PGN</i>	G ⁴⁹	PPMS risk
Genes of unknown function		
<i>ADAMTS14</i>	CC genotype of SNP6 C/T	PPMS risk
<i>C10orf27</i>	T allele of rs2254174	PPMS risk

RFLP, restriction fragment length polymorphism.

in childhood, although adult-onset cases may occur (van Geel et al., 2001). Because the ALDP gene is on the X chromosome, the disease predominantly affects males, although rare female cases are described (Menage et al., 1993). The adult-onset presentation is often adrenomyeloneuropathy that clinically manifests as a progressive spastic paraparesis. MRI of the brain shows white-matter disease in approximately 50% of cases (Aubourg et al., 1992; Eichler et al., 2007). Adult cerebral ALD, a more aggressive form with prominent cognitive decline and psychiatric symptoms, will evolve in approximately 10% of cases. Adrenocortical dysfunction, sometimes with the clinical manifestations of Addison's disease, frequently occurs. CSF abnormalities with pleocytosis and intrathecal synthesis of immunoglobulins can occur in ALD and further complicates distinction of ALD from MS (Krenn et al., 2001). Diagnosis of ALD relies on plasma very-long-chain fatty acid

(VLCFA) determination and characterization of the ALD mutation can be helpful in some heterozygous women who have normal VLCFA levels. Allogeneic bone marrow transplantation can arrest the disease in some cases (Orchard and Tolar, 2010).

Metachromatic leukodystrophy (MLD)

MLD is an autosomal recessive lysosomal storage dysmyelination disease caused by mutations in arylsulfatase A. The majority of cases occur in childhood; however, adult-onset forms of the disease can share similarities with MS (Hirose and Bass, 1972; Klemm and Conzelmann, 1989; Kappler et al., 1991; Rauschka et al., 2006; Gieselmann, 2008). The adult-onset form typically manifests as personality change with progressive dementia. Gait disturbance and urinary incontinence can also occur early in the disease course followed by optic atrophy, horizontal nystagmus, epilepsy, and progressive spastic paraparesis. MRI shows typically symmetric confluent areas of abnormal signal change on T2-weighted imaging affecting the white matter. Additional diagnostic studies that can help differentiate MS from MLD include leukocyte arylsulfatase A activity, urine sulfatide concentration, tibial nerve conduction studies that are prolonged in MLD, and potentially sural nerve biopsy.

Galactocerebrosidase deficiency (krabbe disease)

Galactocerebrosidase deficiency, also known as Krabbe disease, is another autosomal recessive lysosomal storage dysmyelination disease caused by mutation in the galactocerebrosidase-galactosidase gene. Like MLD, the manifestations are typically in childhood, although extremely rare adult-onset forms are described (Kolodny et al., 1991; De Gasperi et al., 1996; Satoh et al., 1997; Lissens et al., 2007; Romano et al., 2009). Clinical manifestations include progressive weakness, tremor, ataxia, dysarthria, nystagmus, other bulbar signs, urinary incontinence, and cognitive decline. MRI shows typically symmetric white-matter disease. Peripheral nerve involvement helps distinguish galactocerebrosidase deficiency from MS. Determination of the white blood cell galactocerebrosidase enzyme activity leads to diagnosis of adult-onset Krabbe. Treatment with bone marrow transplantation is reported to arrest progression and improve neurologic disability (Lim et al., 2008).

Pelizaeus–merzbacher disease

A 49-year-old woman with a 10-year history of progressive spastic – ataxic gait, spasticity, weakness, hyperreflexia with Babinski signs, muscle spasms, nocturia, and dysarthria – was diagnosed with PPMS based on changes

on brain and cervical spine MRI consistent with CNS demyelination as well as intrathecal synthesis of gamma-globulins (Warshawsky et al., 2005). She was found to carry a novel point mutation in the proteo-lipid protein (*PLP1*) gene Leu30Arg (c. 89 T > G) after her son died at age 10 from Pelizaeus–Merzbacher disease. The authors suggest that the mother's symptoms might be due to heterozygous symptoms from this mutation. In Pelizaeus–Merzbacher disease, heterozygous mothers of severely affected children do not typically manifest symptoms. In cases with severe *PLP1* mutations enabling selective survival of normal oligodendrocytes over oligodendrocytes that express the mutant *PLP1* allele, X inactivation is thought to be skewed. The authors did not consider the possibility that this patient had PPMS and was also an unaffected carrier of Pelizaeus–Merzbacher disease.

LaminB1

A late-onset autosomal dominant leukodystrophy that shares clinical similarities with PPMS is caused by duplication of the *laminB1* gene on chromosome 5q31 (Coffeen et al., 2000; Padiath et al., 2006). The onset is in the fourth or fifth decade of life and the disease is characterized by insidious loss of motor skills (pyramidal and cerebellar) resulting in complete loss of voluntary movement over 20 years. The brain MRI shows symmetric white-matter hyperintensities in the PVWM as well as bulbar white matter. The clinical distinguishing feature is early dysautonomia, an uncommon feature of PPMS. These studies raise the possibility that *laminB1* might be involved in immunopathogenesis in MS.

Mitochondrial cytopathies

Although not typically misdiagnosed as PPMS, mitochondrial cytopathies including MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like syndrome), MERRF (myoclonus, epilepsy, and ragged red fibers), Kears–Sayres syndrome, Leber's hereditary optic neuropathy (LHON), and Leigh syndrome (subacute necrotizing encephalomyelopathy), share some clinical and radiographic features with MS and clinical overlap with MS has been reported (Lees et al., 1964; Franks and Sanders, 1990; Harding et al., 1992; Kellar-Wood et al., 1994; Taylor et al., 1998; Kuker et al., 2007; Palace, 2009). LHON is most often described as having potential overlap with MS. Although LHON typically presents with progressive and painless central visual loss in young men, in women LHON has been associated with an MS-like illness. It is not clear whether the neurologic manifestations of these cases are accounted for by co-occurrence of MS in patients with LHON or whether there is a causative relationship

between the mitochondrial cytopathy and demyelination. Nevertheless, the occurrence of painless, progressive visual loss with optic atrophy in a patient with otherwise typical features of MS should prompt further evaluation for mitochondrial disease.

Neurofibromatosis (*NF1/OMgp*)

Several patients with neurofibromatosis type 1 and PPMS have been described ([Pipatpajong and Phanthumchinda, 2011](#)). The oligodendrocyte myelin glycoprotein (OMgp) is imbedded in an intron of the *NF1* gene. Examination of the *OMgp* gene did not find any consistently associated mutations in PPMS patients ([Johnson et al., 2000](#)).

Hereditary spastic paraplegia

The hereditary spastic paraplegias are a diverse group of inherited diseases that share a common phenotype: progressive, usually symmetric, spastic paraparesis, clinical features that are similar to those of PPMS. These disorders can be divided into “pure” hereditary spastic paraplegia and complicated hereditary spastic paraplegia when other neurologic manifestations are present. Brain MRI and CSF analysis in these patients are not consistent with MS.

CONCLUSION

Despite the appealing notion that the clinical distinction between PPMS and relapsing-onset MS is due to genetic variation, definite genetic differences between these two forms of MS have not been found. Recent high-throughput genome-wide screens for the first time have identified genes associated with MS susceptibility outside the MHC ([Hafler et al., 2007](#); [De Jager et al., 2009](#); [Sawcer et al., 2011](#)). The genetic variants identified thus far have weak, or at best modest, contributions to MS susceptibility and have required very large datasets of cases and controls as well as sophisticated methods to adjust for the confounding effects of population stratification. If the genetics that may distinguish PPMS from RRMS are similar to that which distinguishes RRMS from healthy controls then very large datasets will be needed to discern genetic differences that distinguish the MS disease course. Genome-wide screens have not been applied to PPMS and, given the relative scarcity of PPMS, will require analysis of samples gathered from many centers. The IMSGC, a collaborative effort involving shared DNA samples from over 20 countries, ultimately may provide the means by which such a dataset of primary progressive patients may be brought together. In conjunction with further investigation into the candidate genes described above, as well as the genes

for some of the intriguing PPMS phenocopies, it is hoped that specific genetic variants associated with PPMS finally will be identified by this collaborative effort.

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