Integration of genetic risk factors into a clinical algorithm for multiple sclerosis susceptibility: a weighted genetic risk score

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Summary
Background Prediction of susceptibility to multiple sclerosis (MS) might have important clinical applications, either as part of a diagnostic algorithm or as a means to identify high-risk individuals for prospective studies. We investigated the usefulness of an aggregate measure of risk of MS that is based on genetic susceptibility loci. We also assessed the added effect of environmental risk factors that are associated with susceptibility for MS.

Methods We created a weighted genetic risk score (wGRS) that includes 16 MS susceptibility loci. We tested our model with data from 2215 individuals with MS and 2189 controls (derivation samples), a validation set of 1340 individuals with MS and 1109 controls taken from several MS therapeutic trials (TT cohort), and a second validation set of 143 individuals with MS and 281 controls from the US Nurses’ Health Studies I and II (NHS/NHS II), for whom we also have data on smoking and immune response to Epstein-Barr virus (EBV).

Findings Individuals with a wGRS that was more than 1·25 SD from the mean had a significantly higher odds of MS in all datasets. In the derivation sample, the mean (SD) wGRS was 3·5 (0·7) for individuals with MS and 3·0 (0·6) for controls (p<0·0001); in the TT validation sample, the mean wGRS was 3·4 (0·7) for individuals with MS versus 3·1 (0·7) for controls (p<0·0001); and in the NHS/NHS II dataset, the mean wGRS was 3·4 (0·8) for individuals with MS versus 3·0 (0·7) for controls (p<0·0001). In the derivation cohort, the area under the receiver operating characteristic curve (C statistic; a measure of the ability of a model to discriminate between individuals with MS and controls) for the genetic-only model was 0·70 and for the genetics plus sex model was 0·74 (p<0·0001). In the TT and NHS cohorts, the C statistics for the genetic-only model were both 0·64; adding sex to the TT model increased the C statistic to 0·72 (p<0·0001), whereas adding smoking and immune response to EBV to the NHS model increased the C statistic to 0·68 (p=0·02). However, the wGRS does not seem to be correlated with the conversion of clinically isolated syndrome to MS.

Interpretation The inclusion of 16 susceptibility alleles into a wGRS can modestly predict MS risk, shows consistent discriminatory ability in independent samples, and is enhanced by the inclusion of non-genetic risk factors into the algorithm. Future iterations of the wGRS might therefore make a contribution to algorithms that can predict a diagnosis of MS in a clinical or research setting.

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Introduction Multiple sclerosis (MS) is an inflammatory disease of the CNS. Several genetic and environmental susceptibility factors for MS have been identified, including HLA and non-MHC loci.1 Genome-wide association studies for Crohn’s disease and type 1 diabetes mellitus2 have identified more than 40 susceptibility alleles for each of these inflammatory diseases; therefore, ongoing genomewide association studies for MS will probably identify many more susceptibility loci. Unlike HLA DRB1*1501, most of the genetic risk factors identified so far have only a slight effect on susceptibility to MS (with odds ratios that range from 1·1 to 1·2); however, the risk alleles in these loci are common in people of European ancestry, with allele frequencies of 0·1–0·9. To date, there is little information on how this growing set of genetic susceptibility factors is affected by environmental risk factors such as infection with the Epstein–Barr virus (EBV), smoking, and serum vitamin D concentrations.3

Although the early results from whole-genome association studies have not yet been used clinically, the translation of genetic and epidemiological risk factors to the clinic is needed. An important goal to understand the genetic basis of MS is to investigate the use of these allelic variants to predict disease risk, so that environmental changes or therapeutic interventions can be initiated before the inflammatory demyelinating process starts. By combining family history with a quantitative measure of genetic risk, a screening method might eventually be implemented that could identify clinically silent evidence of disease among first-degree relatives of patients with MS, who are...
20–50 times more likely to develop MS than are the general population. Although these individuals have a high risk of developing MS, the absolute risk is only 2–5%. Therefore, in high-risk populations and in individuals who have had an initial episode of neurological deficit with an unclear cause, novel clinical screening methods could be used to guide the selection of those individuals who will benefit most from early imaging. The early detection of an inflammatory demyelinating illness is useful because early treatment of individuals who have had one episode of inflammatory demyelination is beneficial for reducing the accumulation of neurological disability.

We report the efficacy of a weighted genetic risk score (wGRS) that combines weighted odds ratios from each of 16 loci that have been associated with MS1 for prediction of a diagnosis of MS in three independent cohorts. We also assessed the added effect of the integration of clinical parameters and paraclinical measures of environmental exposure into the algorithm.

**Methods**

**Participants**

Each of the four sample collections was collected for a different purpose by different investigators and is independent of the other collections. All participants were recruited for studies that were approved by the institutional review boards or ethics committee of the respective institutions, and all gave written informed consent for their DNA to be collected for genetic analysis. All participants with MS met the revised McDonald diagnostic criteria.7 The alleles and odds ratios included in our model were selected from the replication arm of a meta-analysis1 that comprised cohorts from the UK and USA (table 1). In this study, we refer to this combined set of samples as the derivation samples: 2215 individuals with MS or clinically isolated syndrome (CIS) and 2189 healthy controls were included. The origin of the derivation samples has been described previously and their characteristics are outlined in table 1. The MS susceptibility loci of the derivation samples are the only ones that have been previously published; none of these individuals are included in any of the other three sample collections.

The first validation set includes individuals recruited by Bayer Schering Pharma for therapeutic trials (table 2). This sample collection is labelled as the therapeutic trial (TT) collection. One of these trials—Betaseron/Betaveron in newly emerging multiple sclerosis for initial treatment (BENEFIT)9—studied individuals with CIS. The other three trials—Betaveron Efficacy Yielding Outcomes of a New Dose (BEYOND),7 long-term follow-up of patients enrolled in the pivotal study of Betaveron in relapsing-remitting multiple sclerosis (LTF),8 and the phase 2 study in patients with relapsing-remitting multiple sclerosis to evaluate the safety, tolerability, and effects as seen on monthly MRI of the CCR1 antagonist ZK 811752 (CCR1)10—studied individuals with MS. The TT cohort included 1340 patients. At the time of enrolment, 1132 of these individuals had a diagnosis of relapsing-remitting MS in accordance with the McDonald criteria and 208 had a diagnosis of CIS with MRI signs that were suggestive of demyelination. 95 of the patients with CIS developed MS during up to 5 years of observation. In these analyses, patients with MS were matched to 1109 controls from a
genome scan for early myocardial infarction (the MIGEN study). Because there is no known association between MS and early myocardial infarction, the controls in the MS analysis include healthy controls and individuals with early myocardial infarction from the MIGEN study who were not included in our recent meta-analysis of MS genome-wide association studies. Therefore, these controls are not specifically matched to the TT cohort but are individuals of European ancestry who have a general prevalence of 0–001 for a diagnosis of MS.

The second validation set, from the Nurses’ Health Study (NHS) and Nurses’ Health Study II (NHS II) cohorts, contributed 143 individuals with MS and 281 matched controls; these have been described in earlier publications, and their characteristics are described in table 2.

To assess the role of our wGRS in the conversion of individuals from CIS to a diagnosis of MS, we analysed a subset of individuals from the TT collection who were in the placebo arm of the BENEFIT study. All participants were followed up for 24 months, and a diagnosis of clinically definite MS was made on the basis of established criteria. We also analysed the data from a cohort of patients with CIS from the Observational Study of Early Interferon beta-1a Treatment in High Risk Subjects after CIS (SET) who were recruited in Prague, Czech Republic. Inclusion criteria for this study were a diagnosis of CIS, at least two hyperintense lesions seen on MRI, and oligoclonal bands in the CSF. These patients were enrolled in the SET study within 4 months of the first symptoms. All patients were treated with interferon beta-1a and were followed up for 24 months, and all clinical events were recorded.

Procedures and statistical analyses

We included 16 single nucleotide polymorphisms (SNPs) in our wGRS algorithm. These SNPs were chosen at the end of the replication stage of the meta-analysis: nine of the SNPs are located in validated MS susceptibility loci that were reported to exceed genome-wide significance (p<5x10⁻⁸) in the meta-analysis or in previous publications; and seven of the SNPs were strongly suggestive of association with MS in the meta-analysis (p<10⁻⁴ in the final joint analysis). Four of these SNPs were previously validated as susceptibility markers for other inflammatory diseases. Since then, these seven SNPs have been validated in other sample collections (P De Jager, unpublished data).

For the derivation samples, genotype data were acquired as part of our previous study, by use of the Sequenom MassArray platform and its iPLEX format. The same platform was used to acquire data on the participants in the NHS/NHS II and SET cohorts. Genotypes for the TT and MIGEN individuals were collected using Affymetrix Genechip 6.0 arrays.

We developed a wGRS that used the allelic odds ratios from our previous study to ascertain the strength of the genetic association with each allele. We calculated a wGRS that included two MHC alleles and 14 non-MHC risk alleles. The weighted score is preferred over a simple-count genetic score risk that is equal to the sum of the number of risk alleles carried because the HLA DRB1*1501 allele has a substantially higher odds ratio for MS susceptibility than do the recently discovered SNPs (table 3). The wGRS was calculated by multiplying the number of risk alleles for each SNP by the weight for that
SNP, and then taking the sum across the 16 SNPs, according to the following formula:

$$\text{GRS} = \sum_{i=1}^{16} w_i X_i$$

where $i$ is the SNP, $w_i$ is the weight for SNP $i$, and $X_i$ is the number of risk alleles (0, 1, or 2).

Table 3 shows the weights for each SNP, where the weight is the natural log of the odds ratio for each allele. By use of the odds ratio from the replication stage of our analysis, we have minimised the effect of inflation of the odds ratios that would be expected in a risk-allele discovery study. In addition, the standard errors of those estimates were all small, in view of the large sample sizes from these analyses. We repeated our wGRS calculations to take into account the variance of the odds ratio estimates, but this did not affect our results.

To assess the effect of the $\text{HLA DRB1*1501}$ allele, we also calculated a wGRS without HLA (ie, no $\text{HLA DRB1*1501}$) that included only the common variants that have modest effects on MS susceptibility. After the individuals with more than 10% of their genotype data missing were removed, any individual with information missing for a particular SNP was assigned a value of twice the risk allele frequency for that SNP, which is the expected value for that SNP in the population. Because there is currently no evidence of epistasis among these susceptibility loci, we have not added terms for interaction between the loci in our algorithm. In each set of samples, the distribution of the wGRS was plotted separately for individuals with MS and controls and compared with two independent sample $t$ tests. All analyses were done using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Because a continuous score is difficult to interpret on an individual level when a physician needs to explain the results of the wGRS to a patient, we partitioned participants into different categories of risk. These categories were created from the means and SD from the control samples that were specific to each population. The seven categories were defined as 0.25, 0.75, and 1.25 SD from the mean; the extreme categories were less than 1.25 or greater than 1.25 SD from the mean. The division of our score into seven categories provided a robust distribution that enabled us to break down the groups with the highest and lowest risk but still ensure that there were statistically sufficient numbers of individuals with MS and controls in the extreme categories. To avoid exaggerating the odds ratio associated with a specified subject category, we used the largest subset of participants that contained the mean of the healthy control population (category 4) as the reference category. These individuals can be regarded as those with the mean risk of the assessed population. Within each dataset, we fitted a single logistic regression model (controlling for sex in the derivation and TT samples and for smoking status and titres of anti-EBV nuclear antigen 1 [EBNA1] in the NHS/NHSII
sample) with dummy variables for wGRS groups, to study
the association of wGRS with MS; we compared each
category of wGRS with the reference median category 4
(table 4). An ordinal wGRS variable based on our categories
was used to calculate p values for trends. We also calculated
the odds ratio of MS comparing the individuals in the
highest wGRS category with those in the lowest wGRS
category.

To ascertain how well our wGRS predictors discriminate
between individuals with demyelinating disease and
controls, we generated receiver operating characteristic
(ROC) curves by plotting the sensitivity of the continuous
wGRS score against 1–specificity and calculating the
area under the ROC curves (C statistic) for each
population. The C statistic is a measure of the ability of
the model to discriminate between individuals with MS
and controls for every possible pair of case and control. To
assess the degree to which the HLA DRB1*1501 allele
contributes to the wGRS, we plotted ROC curves for a
wGRS that excluded HLA DRB1*1501 and for the wGRS
that included HLA DRB1*1501. The C statistic of each
curve was compared by use of a non-parametric approach,
as described by De Long and colleagues.14 When available,
additional susceptibility factors were considered: in the
TT cohort, sex was added to the model; and in the NHS
cohorts, smoking and EBV titres were added to the
model.

The patients with CIS in the TT cohort were from the
placebo arm of the BENEFIT study and were assessed for
24 months for evidence of activity of clinical disease. The
last visit in the study was scheduled for between day 692
and day 741. Therefore, the time to a diagnosis of MS is
defined as a right-censored variable: the time to MS is
censored if the patient was lost to follow-up at any time
up to day 692, or at day 692 if clinically definite MS had
not been diagnosed before then. The association between
the wGRS and the time to diagnosis of MS was assessed
with the proportional hazards model. Non-linearity of the
regressor wGRS was tested by including a quadratic term
for wGRS, and the proportional hazards assumption was
tested by including a time-dependent covariate that was
the interaction between wGRS and log(time). The model
was also extended to include the variables age and sex.

Role of the funding source
The study sponsor had no role in the study design,
collection, analysis or interpretation of the data, or
writing of the report. The corresponding author had full
access to all the data in the study and final responsibility
for the decision to submit for publication.

Results
The wGRS was based on the odds ratios reported for the
MS susceptibility loci, which were calculated from the
data from the replication arm of our recent meta-analysis.1

Figure 2: Odds ratios for risk categories defined using the wGRS
(A) Derivation samples. Data are presented only for patients with MS. Seven categories of genetic risk are defined
in the derivation samples, with category 1 being the lowest risk category. The distribution of patients with MS
among the seven risk categories is plotted in blue as a histogram and is skewed because these individuals have a
greater risk of MS than do healthy controls. The log of the odds ratio (red triangle) for MS susceptibility of each risk
category is superimposed in red with the 95% CI for that estimate (red line). (B and C) Therapeutic trial and NHS/
NHS II validation samples, respectively. The distribution of wGRS in the seven categories of risk that are defined
in each of the two sample collections used in validation exercises is shown. wGRS=weighted genetic risk score.
MS=multiple sclerosis. NHS/NHS II=Nurses’ Health Study and Nurses’ Health Study II sample collection.
We expected our current wGRS model to be over-fitted when it was applied to these cohorts as we used these data when we developed the model. However, empirically, the effect might be slight. Figure 1 shows the distribution of wGRS in the derivation and validation samples. Both sets of curves show a clear separation between the distribution of the individuals with MS and that of the healthy controls. In the derivation sample, the mean (SD) of the wGRS was 3·5 (0·7) for individuals with MS and 3·0 (0·6) for the controls (p<0·0001); the mean for the TT validation sample was 3·4 (0·7) for individuals with MS versus 3·1 (0·7) for controls (p<0·0001); and the mean for the smaller NHS/NHS II dataset was 3·4 (0·8) for individuals with MS versus 3·0 (0·7) for controls (p<0·0001).

Another way to show the difference in the distribution of wGRS between individuals with MS and controls is to partition the participants. We did this by defining risk categories, starting at the mean wGRS in the controls of a sample collection and grouping individuals who are within 0·25 SD of the mean as category 4. Individuals in category 4 approximate to the group of participants with the mean population risk of MS (figure 2). Six subsequent categories (1–3 and 5–7) are defined by the increasing intervals of wGRS. In the set of combined derivation samples, category 7 individuals (ie, those with the largest wGRS) had 3·6 times (95% CI 2·9–4·3) increased odds of developing MS compared with those in category 4, the mean population risk (table 4). When controlling for sex, in view of the greater proportion of women with MS, the odds for category 7 versus category 4 was unchanged (3·7, 2·8–4·3). When category 7 was compared with category 1, which contains the individuals with the lowest risk of MS, there was a 10·1 (6·9–14·7) times increase in the odds of developing MS. In the validation TT sample, individuals in category 7 (ie, those with the largest wGRS) had a mean increase in odds of developing MS of 2·4 (1·8–3·2) compared with individuals in category 4 (figure 2). When controlling for sex, the odds were 2·3 (1·7–3·0) for category 7 compared with category 4. The risk increased to 4·5 (3·0–7·0) when category 7 was compared with category 1.

The cohort of 182 patients with CIS from the SET study had the same distribution of wGRS as did individuals in the NHS/NHS II samples that all have a diagnosis of MS (p=0·98), suggesting there is little difference between genetic susceptibility to CIS or MS. We also assessed the possibility that the genetic factors associated with susceptibility (ie, with the onset of inflammatory demyelination) have a role in disease course, by assessing...
whether the wGRS of individuals with CIS is associated with the time from the onset of symptoms to the time of a second demyelinating event, and hence a diagnosis of MS, in the Czech SET and TT cohorts. In the subset of patients with CIS in the placebo group of the TT collection, the estimated hazard ratio from the univariate proportional hazards model for wGRS was 1.00 (95% CI 0.71–1.41; p=0.99). The estimated hazard ratio did not change substantially after age and sex were included. There was no evidence for a non-linear association of wGRS with the log hazard ratio (p=0.74) or for a deviation from the proportional hazards assumption (p=0.087). The individuals in the Czech SET study had a similar finding: the univariate proportional hazards model for wGRS was 0.82 (0.54–1.26; p=0.36).

Discussion

Genome-wide association scan methods have been successful in discovering susceptibility loci for MS and other inflammatory diseases, and the repertoire of susceptibility alleles will expand further when ongoing whole-genome scans are completed. For the most part, the susceptibility alleles that have been identified so far fit the profile targeted by genome-wide association studies: we have discovered alleles with a frequency more than 0.05 and small odds ratios (1.1–1.3). Whether the wGRS was 0.82 (0.54–1.26; p=0.36).

Figure 3: ROC curves for models predicting a diagnosis of multiple sclerosis or clinically isolated syndrome

(A) Derivation samples. The results for three separate models to predict a diagnosis of MS are plotted: wGRS without HLA DRB1 that includes 15 susceptibility loci and the HLA DRB1*1501 allele (blue); wGRS with HLA DRB1 that includes 15 susceptibility loci and the HLA DRB1*1501 allele and sex (green); wGRS with HLA DRB1 that includes 15 susceptibility loci and the HLA DRB1*1501 allele (red); wGRS with HLA-DRB1 and smoking and EBV titre (C statistic=0.683).

(B) TT samples. We repeated the analysis shown in A with the TT validation samples. The same presentation scheme is used. (C) NHS/NHS II samples. The analysis method is the same in the NHS/NHS II validation samples as it was in A and B. These participants are all women. The third model that is plotted (green line) includes all 15 susceptibility loci, the HLA DRB1*1501 allele, and sex (green).
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Nonetheless, although the predictive ability of the algorithm is robust, it is not ready for clinical deployment. The C statistics from our wGRS analyses show that much of the variance in MS susceptibility is not explained by the current models. Indeed, even with a larger complement of the potential 50 or more MS susceptibility loci, the algorithm might not be sufficiently effective. Our investigation of the NHS/NHS II sample collection, which generates a small dataset, suggests that the best strategy will probably require the inclusion of non-genetic susceptibility factors to enhance the algorithm and make it useful in a clinical setting: the environmental risk factors assessed in this study seem to provide information that is non-redundant relative to the genetic data (figure 3). Thus, future prospective studies of the wGRS should include detailed environmental and immunological characterisations. Overall, our best C statistic for the model that includes sex is currently 0·721, which is close to the Framingham Risk Score for coronary heart disease (C statistic about 0·8), which is regarded as clinically useful. Thus, future iterations of the algorithm might reach a level of prediction of MS susceptibility that is also useful in a clinical setting.

Our initial assessment of the wGRS for predicting relapse after an initial episode of inflammatory demyelination suggests that the current version of the algorithm is not useful for this crucial question. The mechanisms involved in the recurrence of inflammatory demyelination might therefore be different from the mechanisms involved at the onset of demyelinating disease. However, although we have assessed two different populations of individuals with CIS (one that was treated with interferon beta-1a and one that was untreated) that show similar results, both sample collections are small and have a short follow-up and a low rate of clinical events. Our results should therefore be interpreted with caution, and further investigations are needed that include other parameters that relate to disease course and disease activity.

How could the wGRS be used in a clinical setting? The inciting event for MS is not observed, remains unknown, and is likely to occur months or years before the onset of clinical symptoms, which are often preceded by asymptomatic CNS lesions. The partitioning of individuals into seven categories might be a way to help the communication of the results of the wGRS to physicians and ultimately to patients. The identification of individuals with a high genetic risk for MS (category 7) might therefore open new avenues of investigation and treatment that could prevent the onset of the disease, rather than modifying its course once it is already symptomatic. In particular, a version of the wGRS might eventually be helpful in stratifying the risk for individuals who are already known to be at high risk, such as those with a first-degree relative with MS, who have a 2–5% risk of MS (20–50 times greater than that of the general population of European ancestry). Because vitamin D deficiency has been associated with MS susceptibility, benign interventions, such as vitamin D screening and supplementation, could be done in individuals in high-risk categories. Furthermore, owing to the benefit of early treatment for minimising later disability in individuals who have had one episode of demyelination, and the observation that many individuals with asymptomatic T2 hyperintense lesions go on to have radiographic or clinical relapses, there might be an argument for MRI screening of the first-degree relatives of patients with MS who are in the top stratum of the wGRS distribution, to identify individuals during the clinically silent stage of the disease.

Overall, our data suggest that information obtained from MS susceptibility loci might provide useful information if used in the context of clinical algorithms that contain other information, such as environmental risk factors. We acknowledge that our estimate of genetic risk is still crude because it contains only a few of the susceptibility loci that are thought to exist. Further assessments of this method are therefore warranted, particularly when loci that are correlated with disease course in MS are discovered and a separate algorithm that can target progression can be designed.

Contributors
PLD, LBC, and EWK designed the study and wrote the manuscript. LBC, JC, SL, and PLD analysed the data. JR, CA, and PLD generated the data. KCS, JFH, RS, CP, MT, PL, EH, DH, AA, and the steering committees of studies to assess IFNβ-1b and a CCR1 antagonist (BENEFIT, BEYOND, LETF, and CCR1 trials) recruited and characterised the participants. DAH, JR, CP, EKW, DH, EH, and the steering committees of studies to assess IFNβ-1b and a CCR1 antagonist reviewed the manuscript. All authors have read and reviewed the submitted version of the manuscript.

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