Estimating the proportion of variation in susceptibility to multiple sclerosis captured by common SNPs

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Multiple sclerosis (MS) is a complex disease with underlying genetic and environmental factors. Although the contribution of alleles within the major histocompatibility complex (MHC) are known to exert strong effects on MS risk, much remains to be learned about the contributions of loci with more modest effects identified by genome-wide association studies (GWASs), as well as loci that remain undiscovered. We use a recently developed method to estimate the proportion of variance in disease liability explained by 475,806 single nucleotide polymorphisms (SNPs) genotyped in 1,854 MS cases and 5,164 controls. We reveal that 30% of MS genetic liability is explained by SNPs in this dataset, the majority of which is accounted for by common variants. These results suggest that the unaccounted for proportion could be explained by variants that are in imperfect linkage disequilibrium with common GWAS SNPs, highlighting the potential importance of rare variants in the susceptibility to MS.

Results

For this study, we used genome-wide genotype data for 475,806 autosomal SNPs collected from 1,854 MS cases and 5,164 controls sampled from the United Kingdom (UK)⁶. After assessing the relatedness between individuals, and thus accounting for effects of population structure, we first estimated the proportion of variance explained by all autosomal SNPs simultaneously. This analysis revealed that 30.7% (standard error (SE) = 0.5%) of the variance in liability to MS is accounted for by SNPs in this dataset.

We next partitioned SNPs by autosome and recalculated the proportion of variance explained by variants found on each chromosome (Table 1); estimated values ranged from ~0–8% per chromosome. Not surprisingly,
given the known contribution of the MHC, which is located on chromosome 6, SNPs on this chromosome account for 8.11% of the variance (SE = 0.72%). By calculating the proportion of the genome represented by each chromosome (not including the length of sex chromosomes), we tested for a correlation between the variance explained by each chromosome relative to its size, excluding chromosome 6 (Figure 1). Although it was evident that several of the smaller chromosomes contributed less to the overall variance than several of the larger chromosomes, the overall trend was not significant (r = 0.336, P = 0.136). To assess the contribution made by common versus rare variants, we also binned SNPs based on minor allele frequency (MAF; Figure 2). From this, we observed that common variants (MAF > 0.1; ∼4–6%), which are most abundantly sampled on GWAS arrays, make a greater contribution than rare variants (MAF < 0.1; ∼2.8%). However, because of the unequal number of SNPs in each bin, we also binned SNPs by quintile (Figure 3). Based on this analysis, we found that all quintiles displayed an equivalent variance, highlighting that no particular frequency of MAF makes a larger or smaller contribution to MS, and that all should be captured and tested.

Lastly, we carried out an association analysis using only the UK GWAS data. We identified 15 associated autosomal SNPs in this cohort outside of the MHC with P values < 1 × 10⁻⁵. These SNPs, their positions (hg18; NCBI Build 36.1), and the nearest RefSeq gene to each are listed in Table 2. Using association analysis data, we also examined the contribution made by all associated SNPs to the observed variance after binning by P value, including those SNPs within the MHC (Table 3).

**Discussion**

Using available data from a large UK case-control cohort16, we have conducted a comprehensive assessment of the contribution of genome-wide SNPs on the variance in liability to MS. The power of the approach used here is that contributions of genotypes at all available loci across the genome (in this case, 475,806), rather than only a set of identified MS risk loci, can be accounted for using this method. Thus, from our analysis, we conclude that approximately 30% of MS heritability is explained by variants on current GWAS arrays, including SNPs on chromosome 6, which alone account for ∼8% and reflect the major contribution of the MHC. The role of the MHC in MS has long been known; specifically, HLA-DRB1*1501 confers a 2-fold increase in risk13. However, the underlying genetic architecture of MS is presumed to be polygenic, involving a large number of loci with smaller effects22,23. Our findings lend support to this notion, as we observed that the genetic contributions of SNPs on autosomes other than chromosome 6 were at least in part correlated to autosome length. However, this relationship was not significant, and not as convincing as that illustrated previously for other polygenic disorders17,21. This might hint at the possibility that some unidentified MS risk loci have slightly larger effects than others, which has been discussed recently23. Additionally, our study was smaller than that

| chr | Variance Explained | Standard Error |
|-----|--------------------|---------------|
| 1   | 0.011606           | 0.006417      |
| 2   | 0.010433           | 0.006207      |
| 3   | 0.021433           | 0.006129      |
| 4   | 0.002666           | 0.005454      |
| 5   | 0.021062           | 0.005955      |
| 6   | 0.081112           | 0.007155      |
| 7   | 0.013365           | 0.005453      |
| 8   | 0.000678           | 0.004836      |
| 9   | 0.006747           | 0.004896      |
| 10  | 0.005168           | 0.004938      |
| 11  | 0.003246           | 0.004827      |
| 12  | 0.014884           | 0.005266      |
| 13  | 0.005035           | 0.004257      |
| 14  | 0.008067           | 0.004431      |
| 15  | 0.01251            | 0.004326      |
| 16  | 0.01705            | 0.004983      |
| 17  | 0.015371           | 0.004533      |
| 18  | 0.003484           | 0.004116      |
| 19  | 0.007125           | 0.003979      |
| 20  | 0.007533           | 0.004086      |
| 21  | 0.002963           | 0.002963      |
| 22  | 0.003493           | 0.003107      |

**Table 1** | Proportion of variance in MS liability explained per chromosome

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**Figure 1** | Contribution of GWAS SNPs and chromosome length. The proportion of variance in MS liability explained by SNPs partitioned by autosome (based on data from Table 1, excluding chr 6) relative to chromosome size, which was determined by dividing the length of each autosome by the sum of the lengths of all autosomes.
GWAS SNPs are in imperfect linkage disequilibrium (LD) with disease-causing variants. Again, this points to the possible importance of rare variants, as allele frequency differences between causative alleles and genotyped SNPs impact LD, and may also implicate a potential role for structural variants (e.g., large deletions or duplications), which are also only partially represented by neighboring SNPs, especially those that are multi-allelic and in regions of the genome characterized by segmental duplication\textsuperscript{27}. Imputation based methods to increase the number of common variants tested can also be applied to datasets such as the one used here, but it has recently been observed in schizophrenia that the application of imputation methods only yielded an approximate 2\% increase in heritability estimates\textsuperscript{21}.

In conclusion, we estimate that approximately 30\% of genetic variation in liability to MS is captured by considering all genotyped SNPs simultaneously. The remaining missing heritability most likely reflects imperfect LD between causal variants and the genotyped SNPs.

### Methods
Genotypes for UK MS cases and controls were obtained from GWAS data recently generated by the International Multiple Sclerosis Genetics Consortium and the Wellcome Trust Case Control Consortium\textsuperscript{21}. Estimates of the proportion of variance explained were calculated using the Genome-wide Complex Trait Analysis (GCTA) tool (http://gump.qimr.edu.au/gcta/\textsuperscript{17–21,28}). Genetic relatedness between individuals was conducted by principal component analysis using the GCTA tool; for this step, the threshold used to identify and remove related individuals was set to a pairwise genetic relationship value of >0.025 (no individuals met this criteria). The top 20 eigenvectors from this analysis were then used as covariates in a restricted maximum likelihood analysis, again conducted within the GCTA tool; this was used to estimate the proportion of the variance explained by SNPs at the genome-wide level, and after partitioning SNP data by autosomes, MAFs, and quintiles. Assembly statistics for GRCh37 (hg19) were used to calculate autosome lengths (autosome length/total length of all autosomes). Association analysis of GWAS SNPs was conducted using PLINK (http://pngu.mgh.harvard.edu/purcell/plink/)\textsuperscript{29}.

### Table 2 | Top SNPs from association analysis using UK GWAS data

| SNP   | Chr | Position | Gene      | \(P\) value |
|-------|-----|----------|-----------|-------------|
| rs6662618 | 1   | 92707999 | GF11      | 1.95E-06    |
| rs11805752 | 1   | 101122894 | EXT2      | 9.34E-06    |
| rs16849327 | 4   | 104970212 | ZPLD1, ALCAM | 7.17E-06   |
| rs16869665 | 4   | 20095328 | SLT2      | 3.14E-06    |
| rs2214543 | 7   | 10763417 | NDUF4A4   | 8.31E-06    |
| rs11984075 | 7   | 37403379 | ELMO1     | 6.40E-07    |
| rs10749170 | 10  | 116302100 | ABLIM1    | 5.67E-06    |
| rs10502249 | 11  | 122009946 | UBASH3B   | 6.38E-06    |
| rs11069349 | 13  | 98572648 | DOCK9     | 1.83E-06    |
| rs727263 | 13   | 98802109 | UBAC2     | 3.26E-06    |
| rs7325474 | 13   | 98827933 | UBAC2     | 4.36E-06    |
| rs9303232 | 17   | 37341634 | TTC25     | 5.30E-06    |
| rs12952314 | 17  | 37398449 | DNAJC7    | 8.18E-06    |
| rs7209012 | 17   | 37414849 | DNAJC7    | 9.42E-07    |
| rs335516 | 18   | 28048065 | MEP1B     | 5.99E-06    |

### Table 3 | Contribution of associated SNPs from UK GWAS dataset to MS liability after binning by \(P\) value

| Bin \(P\) value | \# of SNPs | Variance Explained | Standard Error |
|----------------|------------|--------------------|----------------|
| 1.00E-03       | 1195       | 0.176747           | 0.007402       |
| 1.00E-04       | 429        | 0.108225           | 0.010376       |
| 1.00E-05       | 298        | 0.069538           | 0.009827       |
| 1.00E-06       | 244        | 0.044657           | 0.008199       |
| 1.00E-10       | 149        | 0.035719           | 0.007789       |

Figure 2 | Contribution of GWAS SNPs partitioned by minor allele frequency. The total proportion of variance explained and standard errors for SNPs in each of five MAF bins. The number of SNPs included in each bin varied slightly (0.0–0.1\%, \(n\) = 76046; 0.1–0.2\%, \(n\) = 112435; 0.2–0.3\%, \(n\) = 97482; 0.3–0.4\%, \(n\) = 89704; 0.4–0.5\%, \(n\) = 86625).

Figure 3 | Contribution of GWAS SNPs partitioned by quintile. The total proportion of variance explained and standard errors for all SNPs tested after binning by quintile. The number of SNPs included in each quintile are as follows: 0.0–0.1\%, \(n\) = 93079; 0.11–0.19\%, \(n\) = 93074; 0.19–0.28\%, \(n\) = 93076; 0.28–0.39\%, \(n\) = 93089; 0.39–0.5\%, \(n\) = 93116).
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**Author contributions**

S.V.R., C.T.W., and G.D. conceived of analysis and analyzed the data. C.T.W. and S.V.R. wrote the manuscript, which was critically revised for important intellectual content by F.B., G.G. The study was supervised by S.V.R.

**Additional information**

Competing financial interests: The authors declare no competing financial interests.

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