What Role for Genetics in the Prediction of Multiple Sclerosis?

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For most of us, the foundations of our understanding of genetics were laid by considering Mendelian diseases in which familial recurrence risks are high, and mutant alleles are both necessary and sufficient. One consequence of this deterministic teaching is that our conceptualization of genetics tends to be dominated by the notion that the genetic aspects of disease are caused by rare alleles exerting large effects. Unfortunately, the preconceptions that flow from this training are frequently erroneous and misleading in the context of common traits, where familial recurrence risks are modest, and for the most part the relevant alleles are neither rare, necessary, nor sufficient. For these common traits, the genetic architecture is far more complex, with susceptibility rather than causality resulting from the combined effects of many alleles, each exerting only a modest effect on risk. None of these alleles is sufficient to cause disease on its own, and none is essential for the development of disease. Furthermore, most are carried by large sections of the population, the vast majority of which does not develop the disease. One consequence of our innate belief in the Mendelian paradigm is that we have an inherent expectation that knowledge about the genetic basis for a disease should allow genetic testing and thereby accurate risk prediction. There is an inevitable feeling that the same should be true in complex disease, but is it?

What Is the Underlying Genetic Architecture in a Complex Trait?
The enormous size of the human population coupled with the extreme length of the genome sequence means that although any 2 individuals typically only differ by 0.1% at the genomic level, there are still billions of variants prevalent in the population as a whole. International efforts to identify and catalog human genetic variation, such as HapMap (http://www.hapmap.org) and the 1000 Genomes project (http://www.1000genomes.org), have provided empirical support for the expected inverse relationship between the frequency of a variant allele and the number of variant alleles with the same frequency. Common variants, where both alleles have a frequency of >1%, are far less numerous than rare variants. On the other hand, common variants account for most (90%) of the difference between any 2 individuals. With approximately 10 to 15 million common variants and billions of rare variants in the human population, identifying which are relevant in any given disease has proven to be extremely challenging.

In principle, each and every genetic variant is likely to have some effect on function and thereby on the risk of disease; under this ultimate polygenic/biometric model, all variants are expected to exert some effect on risk. However, the effects attributable to individual variants are likely to differ greatly, with some exerting much larger effects than others, and most exerting little or no meaningful effect. Under this model, we expect that both rare and common variants will influence the risk of a disease, with the relative contributions varying between diseases. At a population level, the prevalence and familial recurrence risks of a disease are a reflection of the combined effects of the prevailing risk allelic architecture (see Box 1). In this context, Mendelian disease can be seen to represent an unusual extreme, in which a few rare variants exert profound effects and familial recurrence risks are maximal.
Risch suggested that $\lambda_s$, the relative recurrence risk in the siblings of an affected individual, was a useful way to summarize the amount of familial clustering in a disease, and showed that this value could easily be partitioned between relevant loci and was predictive of the power to identify linkage. By definition, $\lambda_s$ is the ratio between the lifetime risk of the disease in the siblings of an affected individual and the lifetime risk of the disease in the general population. Both of these risks are difficult to measure reliably, and Guo has pointed out that in general the denominator will be underestimated, whereas the numerator will be overestimated. As a result, estimates of $\lambda_s$ are almost always positively biased. Review articles frequently specify $\lambda_s$ but rarely provide much guidance to the data behind these quoted values. These data are often remarkably difficult to track down and invariably associated with wide confidence intervals that are rarely, if ever, acknowledged in reviews. As epidemiological studies have become larger and more discriminating, the value of $\lambda_s$ has fallen in almost all complex traits, including multiple sclerosis (Fig 1). In a recent attempt to integrate available epidemiological evidence relating to multiple sclerosis, Butterworth found that the lifetime incidence in multiple sclerosis is likely to be higher than previously estimated, a finding that would further reduce the $\lambda_s$. The real value for $\lambda_s$ seems likely to be $\leq 1.2$.

**Predicting Disease**

Before any form of assessment, all individuals in a population have the same risk of disease (the population prevalence). In multiple sclerosis, this prior risk is low (0.001). Although susceptibility loci have only a modest individual effect on this prior probability, the ability to discriminate those who will, from those who will not, develop the disease inevitably increases with each additional relevant locus considered. It turns out, however, that even if all relevant loci were known and tested, disease can only be reliably predicted in relatively few individuals, unless $\lambda_s$ is very large. For multiple sclerosis, $\lambda_s$ is at best 10, indicating that very few individuals (<0.1%) would have a risk of >10% (Fig 3). The distribution of risk shown in the figure reflects the complexity of risk in the population.
bined effects of all risk alleles (known and as yet unknown), and thus represents the maximum level of information that could possibly be defined genetically. It is clear that the vast majority of the population have a very similar level of risk; indeed, on average the relative risk of the disease between any 2 individuals is just 11.3, a rather limited value in the context of a disease with a prevalence of 0.001. In other words, most of the population carries risk alleles, but only a very few individuals carry a substantially larger than average number of these alleles. In principle, an individual could be homozygous for all known risk alleles and thereby have a very high risk of disease. However, such individuals are extremely uncommon. Most individuals carry similar levels of genetically determined risk, and relatively few individuals can have their ultimate disease status accurately predicted from genetic testing (see Box 2).23

In considering the issue of prediction, it is also worth remembering that most of the individuals at very high risk will have a family history of the disease (even if they do not eventually develop multiple sclerosis), and thus to some extent this genetic analysis adds relatively little additional information that cannot already be inferred from family history.24 In some sense then, this logic has come full circle; those individuals with the highest genetic risk will largely declare themselves ahead of typing by virtue of the fact that they will have affected relatives.

To date, 9 non-MHC susceptibility alleles have been established in multiple sclerosis (Table),25–28 with many more expected to follow in the next few years. Together with the risk attributable to the MHC, all known loci account for a λs of approximately 1.6. The distribution of risk attributable to the currently known susceptibility alleles (MHC and non-MHC) is considerably more limited than that due to all loci (Fig 4). It is clear from this figure that based on current knowledge, genetic screening would only be able to identify a very few individuals with at worst a modest 1% risk of developing the disease.

**Can Genetic Testing Help with Differential Diagnosis or Prognosis?**

Once an individual develops symptoms consistent with multiple sclerosis, the prior probability of the disease goes up significantly, and we could therefore imagine that genetic testing might be more useful in helping to refine diagnosis rather than predict disease. However, in this setting the utility of the testing depends on typing single-nucleotide polymorphism (SNPs), which differentiate multiple sclerosis from the alternate diagnoses rather than from the general background population. It is not clear that susceptibility SNPs will achieve this unless the pathogenesis of the alternate diagnoses are clearly distinct (have a different underlying genetic architecture). In the case of clinically isolated syndromes (CIS), for example, it seems likely that those cases that do not progress to multiple sclerosis are simply milder versions of the same disease process. In this setting, it is unlikely that the genetic architecture underlying cases that do not relapse will be significantly different from that underlying multiple sclerosis itself. Thus although the prior probability of multiple sclerosis must be higher in neurology outpatient clinics, the utility of testing susceptibility SNPs is likely to be reduced. The more distinct the alternate diagnosis, the
Once the diagnosis of multiple sclerosis is established, we might ask if genetic testing could help in predicting disease features such as course or severity. Unfortunately, available evidence suggests that the genetic influences on clinical features are significantly less marked than those influencing susceptibility. It is thus unsurprising that there has been little if any progress in identifying genetic variants that influence the course or the severity of the disease. It remains possible that such variants could be identified, but unless they are unexpectedly more influential than the effects determining susceptibility, it seems unlikely that testing will be any more productive than in the case of susceptibility.

One consequence of the biometric model is that affected individuals are inevitably highly heterogeneous in terms of the particular set of susceptibility alleles they carry. In this setting, high levels of clinical heterogeneity might simply reflect the underlying heterogeneity in the distribution of risk alleles amongst cases. For example, severity might simply correlate with the absolute level of genetic risk. Once sufficient risk alleles are identified, it should be possible to test this theory. If this were confirmed, then genetic testing might contribute some information distinguishing CIS from multiple sclerosis.

Additional Nongenetic Risk Factors

Even without genotyping, we know of a number of factors that influence the risk of developing multiple sclerosis. Gender is the most obvious example. Compared with the population as a whole (see Fig 3), the risk for females is shifted to the right, whereas that for males is shifted to the left (Fig 5). These shifts are modest and have little effect on the number of individuals at the extreme of risk. It is clear that combining extra
information from demographic and perhaps ultimately environmental risk factors (eg, past history of infectious mononucleosis or smoking) is sure to improve risk prediction, but it seems unlikely that this will compensate for the effects of the low prior probability of developing multiple sclerosis unless considerable risk could be accounted for or there was some form of strong interaction between genetic and environmental risk factors.

**Conclusion**

The logic and conclusions outlined above are probably applicable to most complex traits. For most, \( \lambda_s \) has almost certainly been overestimated in the past and is in reality likely to be \( \ll 10 \). In this setting, the multiplicative biometric model indicates that very few individuals will carry a level of genetically determined risk that would allow confident prediction. This situation is common in medicine, where we are familiar with the fact that for many conditions, the majority of cases arise in the very large number of people at modestly increased risk rather than the few people who are at very high risk (cf blood pressure in stroke or coronary heart disease).\(^{30}\) Of course, the utility of genetic testing could be very much better if in fact susceptibility to multiple sclerosis is determined by a multitude of very rare alleles, each exerting very large effect. However, the available data make this extremely unlikely. Segregation analysis is against significant heterogeneity,\(^{5,17}\) large extended families are practically unheard of,\(^{31}\) and there is no significant evidence for linkage out-
Consider 3 populations that differ only in terms of the frequency of a single risk allele and are equivalent in all other respects (Fig 6). In accordance with the number of individuals carrying the risk allele, the prevalence of disease will be highest in population C and lowest in population A. On the other hand, for reasons that are perhaps less intuitively obvious, familial recurrence risk will be greatest in population B and uninfluenced by this particular risk allele in the other 2 populations. In population A, no one carries the risk allele, whereas in population C, everyone is homozygous for the allele. In these populations then, the rate of risk allele carriage is unrelated to disease status, and therefore the frequency of this risk allele is no greater in the relatives of affected individuals than it is for unaffected individuals. In population B, on the other hand, affected individuals are more likely to carry the risk allele than unaffected individuals, and therefore the recurrence risk will be increased in the relatives of affected individuals, who will necessarily also have a higher rate of carrying this allele. In short, whereas prevalence reflects the combined burden of risk alleles in the population as a whole, familial recurrence risk is a reflection of the variation in the risk burden between individuals. The greater the extent to which individuals vary in terms of their genetically determined risk, the greater will be the extent of familial clustering. For example, in a Mendelian dominant trait, the risk varies considerably between individuals, being effectively zero in individuals who do not carry the risk allele and complete in those who do. In this situation, disease is effectively only seen in the relatives of affected individuals. The extent of familial clustering is thus a reflection of the extent to which genetic risk varies between individuals.

Clayton22 and Pharoah et al35 have shown that under a biometric model, log(risk) in the population will be approximately normally distributed with a mean (µ) and a variance (σ²) that are determined by the population prevalence (K) and the sibling recurrence risk (λs), according to the formulae shown below:

\[ \sigma^2 = 2\log(\lambda_s) \]  
(1)

\[ \mu = \log(K) - \sigma^2/2 \]  
(2)

The figures in this paper are plotted using these approximations to estimate the distribution of risk in the population. It is worth noting that the distribution of risk in cases has the same variance but a mean of \( \log(K) + \sigma^2/2 \). The risk profiles of the cases and controls thus overlap to an extent that is dependent on \( \lambda_s \). Even if \( \lambda_s \) for multiple sclerosis were 40, there would still be a substantial proportion of cases (14%) that had levels of risk below the 95th percentile seen in the general population (Fig 7). The percentage of lower risk cases would only fall below 10% for diseases where \( \lambda_s \) was >72. At a \( \lambda_s \) of 10, almost a third of cases have a level of risk below the 95th percentile of risk seen in the general population.

The extent to which these discoveries influence an individual’s risk of developing disease is only one, rather unimportant as it turns out, dimension in which their relevance might be measured. In terms of the population attributable fraction (the proportion of cases that would disappear if a risk factor were removed from a population),38 these loci can be seen to represent enormous effects (see Table). In considering the value of these new discoveries, we should also remember that to date virtually all that have been identified are associated anonymous variants, and it will take considerable further work to understand these associations. Efforts at fine mapping to establish the causal variants and functional studies to fully understand how these variants are involved in pathogenesis are only just beginning. Ultimately, it is these aspects that are likely to be the most rewarding and enlightening. It is too soon to judge what value these discoveries will ultimately yield, but these benefits seem likely to be profound.

Our discourse is not intended to undermine the entire notion of genetic profiling, only to put this issue into a more pragmatic and realistic context. For a disease like multiple sclerosis, where prevalence and \( \lambda_s \) are modest, it seems unlikely that risk profiling will find any meaningful role in clinical practice; on the other hand, such profiling could prove to be of much greater value in a research setting. The power of functional studies could be enhanced by concentrating on controls with lower levels of risk and cases with higher levels of risk. Similarly unaffected individuals with high risk and affected individuals with low risk could be especially informative when trying to understand the role of the environment. As genetic factors influencing natural history and response to treatment emerge, prognostic and pharmacogenomic profiling might have far more clini-
Box 2

It seems reasonable to expect that the ability to predict who will develop multiple sclerosis would have meaningful clinical benefits, such as allowing expensive, invasive, or potentially dangerous preventative strategies to be reserved for those at greatest risk. At first sight it also seems possible, if not probable, that genetic testing might enable such prediction. If all variants influencing susceptibility to multiple sclerosis had been defined, then in principle a “diagnostic chip” could be created which would accurately genotype all these variants, determine an individual’s genetic risk (genetic profile), and thereby discriminate between those who will and those who will not develop the disease. Unfortunately, although this is a seductive logic in practice, this approach would be unlikely to be useful in multiple sclerosis (see Fig 3). For example, if we used this chip to screen a population of 100,000 newborns, then on average we would identify just 64 individuals with a risk of ≥10%. Ultimately, only 14 of these would actually develop the disease. Because 100 of the screened individuals would ultimately be expected to develop multiple sclerosis, it is also clear that this genetic screening effort would have missed most of the eventual cases (86/100). Including gender in our assessment adds very little; in a population of 100,000 (50,000 males and 50,000 females), we would expect to identify 61 females with a risk of ≥10% and 10 males with a risk of ≥10%. This total of 71 at-risk individuals is greater than the 64 we were able to identify based on genetics alone, reflecting the extra information we gained by including gender in the assessment.

The relative proportion of false positives and false negatives clearly depends on the threshold we choose to define people as being at risk. The receiver operating characteristic (ROC) curve provides a useful way to summarize such data (Fig 8). Considering the ROC for the hypothetical chip described above shows that 50% of the cases occur among the 1.6% of the population that are at greatest risk. At first sight, these figures seem appealing and suggest that perhaps genetic profiling might provide a useful way to identify a significant proportion of those at risk. However, the low absolute risk of multiple sclerosis (the prevalence, 0.001) implies a low positive predictive value, meaning that even within this high-risk group, those who will ultimately develop the disease constitute only 3% of the total. If a preventative strategy were applied in this setting, the majority of those treated would be exposed unnecessarily (97%), and the cost per case prevented would be >30× the unit cost of the intervention. In considering these numbers, it is worth remembering that this level of risk (3%) is approximately the same as the familial recurrence risk in close relatives of affected individuals, suggesting that a program in which preventative treatments were simply given to those with a family history of the disease might be as effective, and would of course completely avoid the need for genotyping. In other words, in multiple sclerosis genetic profiling would add very little beyond that which could already be deduced from family history, as with other traits with strong familial clustering.

For interventions that are safe, noninvasive, and cheap (ie, cost less per person than the cost of genotyping), screening would be pointless, because it would be far more cost effective to simply apply such interventions to the whole population in an unselected fashion. If the cost of an intervention were high, then the absolute cost of a preventative program would be prohibitive even if screening by genotyping were free. Clearly, there is a middle ground where a program might be affordable (particularly when weighed against the full cost of the disease prevented); in this situation, screening might provide a means to maximize the benefit from any investment by identifying those at greater risk. However, the health and financial costs to the large numbers of false-positive (treated) and false-negative (untreated) individuals would have to be very low if this were to be a useful approach.

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References


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