Epistasis

Multiple sclerosis and the major histocompatibility complex

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Recent studies in multiple sclerosis (MS) have taken epistasis from speculation and expectation to the reality of its key roles in susceptibility and outcome. Bateson¹ first used the term epistasis to describe the effects on a biologic trait of one gene masking another. Usage has broadened to more generally encompass the explanation of phenotype. Although this has meant gene–gene interactions, environmentally mediated influences up to and including gene modification are part of this concept.² Many prior examples of epistasis in clinical medicine may be unfamiliar but well-documented. Bhende et al.³ first demonstrated that lack of the H antigen, an intermediary point in the production of the corresponding A and B antigens at the ABO locus, prevents the expression of A and B alleles and blood is classed as O. This null phenotype, discovered among the natives of Bombay, India, was called the Bombay phenotype, to distinguish it from that of other individuals with the O blood group. At least two genes, *FUT1* and *FUT2*, encoding alpha (1,2) fucosyltransferases, control this complex epistatic effect.

MS well illustrates informative paradigms for gene–gene interaction in complex disease. For the main association in the major histocompatibility complex (MHC) it is now clear that the notion of *HLA-DRB1*15* acting solely to increase MS risk^{4,5} is a gross oversimplification. Three types of epistasis have been documented in the MHC^{4–6} where *HLA-DRB1*15* haplotypes exert the single strongest effect on MS risk. These dwarf any non-MHC effect but it took large cohorts and systematic methods of analysis to make progress. Several epistatic interactions were uncovered between MHC alleles or haplotypes, fundamental in determining susceptibility to MS. These had remained occult over the three decades since the MHC association was first described because they had to be specifically sought. The key strategy was to examine families lacking *HLA-DRB1*15* to control for the obligate distorted transmission of all alleles from parents secondary to this primary association.^{4,5} When these families were studied, it emerged that

many other alleles were operative in risk. A genotype—rather than allele- or haplotype-dependent hierarchy unfolded (figure). At an individual level this can be grouped into the following three types.

DOMINANT NEGATIVE EPISTASIS *HLA-DRB1*14*, dominantly protective, has a stronger effect in reducing than *HLA-DRB1*15* has in increasing susceptibility. This allele abrogates risk associated with *HLA-DRB1*15*, so that a *HLA-DRB1*14/*15* genotype has a risk of 1 (compared to a *HLA-DRB1*15* allelic risk of 3)⁴ (figure). As yet, no functional explanation can be given for the dominant protective effect of *HLA-DRB1*14*, which extends to other susceptible haplotypes. Understanding this epistatic interaction could be critical for treatment or prevention.

SYNERGISTIC EPISTASIS On its own, *HLA-DRB1*08* modestly increases the risk of MS but when present in conjunction with *HLA-DRB1*15* on the other parental haplotype, it more than doubles the risk associated with a single copy of *HLA-DRB1*15*⁴ (figure). This observation highlights how a variant with a marginal independent effect on risk may turn out to have a strong effect in certain genetic backgrounds. Indeed, using case–control analyses, an association may only be observed when allele frequencies are statistically different. However, if an effect of a gene on disease depends on the presence/absence of other genes, variations across populations in allele frequencies among interacting loci can markedly affect the power to detect effects.⁷ This phenomenon may result in false negative association results.⁷

EPISTASIS AND CLINICAL PHENOTYPE Modifier genes represent biologic phenomena that few clinicians can ignore in the genomic era. *HLA-DRB1*01* and *HLA-DRB1*15* alleles interact to influence MS clinical phenotypes, producing a milder disease course,⁶ but play very little or no role in modifying clinical course independently. These interacting ge-

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Disclosure: The authors report no disclosures.

Figure Genotypic relative risks for multiple sclerosis (MS) for combinations of alleles at the HLA-DRB1 locus

Data derived from *HLA-DRB1* genotyping performed by the Canadian Collaborative Study Group, comprising 2,535 individuals with definite MS and 4,799 of their unaffected first-degree relatives. Analysis was performed as previously described.⁴ X/X = individual with no disease-associated alleles with baseline risk of 1; X = any non-disease-associated allele; 15, 17, 11, 08, 14, 10, 01 = *HLA-DRB1* alleles. All genotypes are statistically significantly different from baseline, except for *HLA-DRB1**14/15 and *HLA-DRB1**11/17. No *HLA-DRB1**14 homozygotes were observed, and it should be noted that *HLA-DRB1**10 and *01 provide greater protection against *HLA-DRB1**15 than *HLA-DRB1**14.

netic variants clearly affect critically important long term phenotypes, holding potential for developing potential therapeutic strategies. *HLA-DRB5**0101 interacts with *HLA-DRB1**15 to reduce the number of autoreactive CD4+ T cells in experimental autoimmune encephalomyelitis, reducing its severity.⁸ *HLA-DRB1**01 may operate in a similar manner. Furthermore, *HLA-DRB1**01 may operate differently in disease susceptibility as compared to clinical outcome.

Recent genome-wide association studies⁹ have received wide attention and more associations may come from small genetic isolates. However, effects confirmed to date with this methodology (explaining perhaps 1% of risk variance) are more than an order

of magnitude smaller than these recently described epistatic effects evident within the MHC. The net effect of the two parental haplotypes in combination can be conveniently called the diplotype.

Although the genetic architecture of the MHC is unlike that of any other region of the genome, and epistasis is likely to have arisen as an evolutionary advantage, the lessons learnt from the MS HLA association are unlikely to be unique. Common episodic neurologic disorders such as migraine and epilepsy seem good candidates for disease-associated gene-masking by epistatic loci.¹⁰ Ion channel variation leading to greater than average inhibitory/excitatory influences may be masked by protective polymorphisms reducing clinical penetrance and expressivity.

Epistasis is no longer a textbook anomaly illustrated by remote animal models. Recent studies show it to be at the heart what is most clinically relevant in MS—susceptibility and disability outcome.

Received August 12, 2008. Accepted in final form October 31, 2008.

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