A Simple Estimate of the General Population Frequency of the MHC Susceptibility Gene for Autoimmune Polygenic Disease

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Polygenic disease · Autoimmune disease · Diabetes, type 1 · Multiple sclerosis · MHC

Abstract
We wished to determine the frequencies of the MHC and non-MHC susceptibility genes for polygenic autoimmune diseases like type 1 diabetes (IDDM). We used Mendelian inheritance and the Hardy-Weinberg equilibrium to calculate the frequencies of mating pairs and susceptible offspring under classical recessive and dominant inheritance of the MHC susceptibility gene. We then analyzed the distribution of haplotype sharing by affected sib pairs of the 4 MHC haplotypes in each of the kinds of mating pairs in terms of the frequency of the disease susceptibility gene. For IDDM, the analysis was consistent with a recessive, but not a dominant, MHC susceptibility gene of frequency 0.525 at a distribution of 55, 38 and 7% of affected sib pairs who share 2, 1 and 0 MHC haplotypes, respectively. A simple relationship was obtained: if inheritance is recessive, the MHC susceptibility gene frequency is the square root of the fraction of affected sib pairs who share no MHC haplotypes multiplied by 4. For recessive inheritance, affected sib pairs who share no haplotypes are solely in families where both parents are homozygous MHC-susceptible. Although homozygous MHC susceptibles represent over 25% of the population, only 2–3% of them are IDDM-susceptible at non-MHC susceptibility loci, also required for disease expression. Predictions from our analysis fit all published observations of the familial occurrence of disease. The analysis is general, simple and provides a single estimate (not a range) of the MHC susceptibility gene frequency. This approach should be applicable to other MHC-determined polygenic diseases.

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Introduction

We developed a method based on Mendelian genetics to calculate the frequency of the MHC disease susceptibility gene and the frequency of susceptible individuals at non-MHC loci for type 1 diabetes (IDDM) and other autoimmune diseases. There is great current interest in identifying non-MHC susceptibility genes for IDDM [1, 2]. This effort would be helped by an accurate single estimate of MHC susceptibility gene frequency.

The model we developed provides evidence for recessive inheritance of the MHC susceptibility gene for IDDM. It is consistent with observed familial occurrence of the disease such as the frequencies of affected sibs, MHC-identical sibs, and parents and children of patients and also predicts the relative frequencies of 2, 3 or more affected sibs. Remarkably, the MHC susceptibility gene (or genes) for IDDM is more common than the wild-type gene in Caucasians.

Background

IDDM is a polygenic MHC-determined autoimmune disease in which as many as 18 non-MHC loci may be involved [1, 2]. We focus on this disease because so much more work has been done with genetic analysis of IDDM than with other MHC-associated autoimmune diseases. Most immediate relatives of patients with IDDM do not have the disease. The conclusion of this paper that over half of Caucasian MHC haplotypes carry IDDM susceptibility genes might seem surprising, especially since we also show that non-MHC IDDM susceptibility genes are common. The seeming contradiction exists only because we tend to have a conceptual bias that predisposes us to think chiefly in terms of rare monogenic disease.

The IDDM disease concordance rate of only 30–50% in monozygotic (genetically identical) twins [3, 4] defines an important part of the mystery: incomplete penetrance of susceptibility genotypes. Yet another puzzling observation is MHC haplotype sharing in affected sib pairs. In a rare monogenic MHC recessive disease, we expect 100% MHC identity (both MHC haplotypes shared) and in a rare dominant monogenic disease we expect 50% sharing. The observed sharing in European Caucasians, summarized from the world literature [5], is 55% for 2, 38% for 1 and 7% for no MHC haplotypes shared by the affected sib pairs.

Our method, like earlier methods, seeks to define the frequency of the MHC disease susceptibility gene (or collective susceptibility alleles) for IDDM in terms of MHC haplotype sharing by affected sib pairs. Only affected sib pairs are considered. Therefore, penetrance, non-MHC genes, ascertainment bias and environmental factors are all eliminated from the estimation of MHC gene frequency. We describe our reasoning at each step of the analysis in prose where possible. The mathematics of the model is presented in the Appendix.

What Is Incomplete Penetrance?

In many MHC-associated diseases, genetically fully susceptible individuals may not have disease. This is referred to as incomplete penetrance of susceptibility genes. Here, we will deal summarily with the question of incomplete penetrance because, by virtue of disease presence, disease susceptibility genes are 100% penetrant in affected sibs. Therefore, penetrance does not affect haplotype sharing in affected sib pairs nor the derivation of the MHC disease susceptibility gene frequency but serves simply as a multiplier, converting
numbers of fully susceptible subjects to patients. We have dealt with incomplete penetrance at length elsewhere [6].

The concordance rate in monozygotic twins of diabetic patients of 30–50% [3, 4] defines what we call ‘baseline penetrance’, i.e. the rate in completely genetically susceptible individuals. Lower rates of penetrance, which we define as ‘apparent penetrance’, are observed in MHC-identical sibs of patients who have around 16% [7, 8], in sibs in general with 5–6% [7–9], in parents and children with 3–5% [10] (table 1), and in unrelated persons with HLA markers for IDDM in the general population with 3–5%. These apparent penetrance rates reflect baseline penetrance and the different frequencies of MHC and non-MHC disease susceptibility genes in the different groups. Family members of a patient have a higher frequency of all genes involved in disease susceptibility than the general population. Families with more than 1 affected member have an even higher frequency of all susceptibility genes. HLA marker-positive unrelated people are specifically enriched only in MHC susceptibility genes, whereas MHC-identical sibs of patients are enriched in non-MHC susceptibility genes in addition to being MHC-susceptible. It is the differences in the frequencies of susceptibility genes and not environmental factors that account for the differences between baseline penetrance in monozygotic twins and apparent penetrance in the other groups of subjects. This is underscored by the fact that dizygotic twins of patients have the same apparent penetrance as sibs in general [11].

### What Mating Pairs Give Rise to MHC-Susceptible Offspring?

In order to be able to analyze the affected sib pairs for MHC haplotype sharing, we need to know the kinds of parents and their frequencies, in terms of MHC susceptibility haplotypes, that can have MHC-susceptible children. This will differ under recessive and dominant inheritance. Since there are 2 kinds of alleles, susceptibility or D and wild-type or d, there are 6 possible mating pairs involving homozygotes and heterozygotes for these. For a recessive disorder, only the 3 mating types that give rise to DD homozygotes have susceptible offspring. These are $Dd \times Dd$, $DD \times Dd$, and $DD \times DD$. For dominant disease, all matings except $dd \times dd$ produce susceptible ($DD$ or $Dd$) offspring. The frequencies of sus-

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**Table 1.** Familial features of type 1 diabetes predicted by this analysis and observed

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Observed</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected sibs, %</td>
<td>1.7, 3.2, 3.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4–11 (5.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6–8</td>
</tr>
<tr>
<td>Affected MHC-identical sibs, %</td>
<td>14.6</td>
<td>16–17</td>
<td>6–8</td>
</tr>
<tr>
<td>Affected children or parents, %</td>
<td>3.9</td>
<td>1.8–5.4 (3.4)</td>
<td>6–9</td>
</tr>
</tbody>
</table>

Figures in parentheses represent average percentage.

<sup>a</sup> Estimates are for 3, 5 and 7 children in a family.

<sup>b</sup> Family size unspecified.
Table 2. MHC haplotype sharing in MHC-susceptible sibs in relation to a recessive MHC susceptibility gene D with frequency $p$ and wild-type gene $d$ with frequency $1-p$

<table>
<thead>
<tr>
<th>Mating type</th>
<th>Mating type frequency</th>
<th>Proportion of susceptible children</th>
<th>MHC haplotypes</th>
<th>ac</th>
<th>bc or ad</th>
<th>bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Dd \times Dd$</td>
<td>$[2p(1-p)]^2 = 4p^2 - 8p^3 + 4p^4$</td>
<td>1/4</td>
<td>$p^2 - 2p^3 + p^4$</td>
<td>$p^3 - p^4$</td>
<td>0.25$p^4$</td>
<td>$0.5p^3$</td>
</tr>
<tr>
<td>$Dd \times DD$</td>
<td>$2[2p(1-p)p] = 4p^3 - 4p^4$</td>
<td>2/4</td>
<td>$p^3 - p^4$</td>
<td>$p^3 - p^4$</td>
<td>0.25$p^4$</td>
<td>$0.5p^3$</td>
</tr>
<tr>
<td>$DD \times DD$</td>
<td>$p^3$</td>
<td>4/4</td>
<td>$p^2 - 0.25p^4$</td>
<td>$p^3 - 0.5p^4$</td>
<td>0.25$p^4$</td>
<td>$p - 0.5p^2$</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>$1 - p + 0.25p^2$</td>
<td>$p - 0.5p^2$</td>
<td>0.25$p^2$</td>
<td></td>
</tr>
<tr>
<td>Fraction of total</td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Only mating pairs yielding susceptible offspring for recessive inheritance are shown.

Table 3. MHC haplotype sharing in MHC-susceptible sibs in relation to a dominant MHC susceptibility gene D with frequency $p$ and wild-type gene $d$ with frequency $1-p$

<table>
<thead>
<tr>
<th>Mating type</th>
<th>Mating type frequency</th>
<th>Proportion of susceptible children</th>
<th>MHC haplotype sharing by index case with ac</th>
<th>ac</th>
<th>bc or ad</th>
<th>bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>$DD \times DD$</td>
<td>$p^4$</td>
<td>4/4</td>
<td>$0.25p^4$</td>
<td>$0.5p^4$</td>
<td>$0.25p^4$</td>
<td>$0.25p^4$</td>
</tr>
<tr>
<td>$DD \times dd$</td>
<td>$2p(1-p)^2 = 2p^2 - 4p^3 + 2p^4$</td>
<td>4/4</td>
<td>$0.5p^3 - 0.5p^4$</td>
<td>$0.5p^3 - 0.5p^4$</td>
<td>$0.5p^2 - 0.5p^4$</td>
<td>$0.5p^2 - 0.5p^4$</td>
</tr>
<tr>
<td>$Dd \times dd$</td>
<td>$2[(2p(1-p)(1-p)] = 4p - 12p^2 + 12p^3 - 4p^4$</td>
<td>2/4</td>
<td>$p^2 - 3p^3 + 3p^4 - p^4$</td>
<td>$p^3 - 3p^3 + 3p^4 - p^4$</td>
<td>$p^3 - 3p^3 + 3p^4 - p^4$</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>$p - 1.5p^2 + p^3 - 0.25p^4$</td>
<td>$p - 1.5p^2 + p^3 - 0.25p^4$</td>
<td>$1.5p^2 - 2p + 0.75p^4$</td>
<td>$1.5p^2 - 2p + 0.75p^4$</td>
</tr>
<tr>
<td>Fraction of total</td>
<td></td>
<td></td>
<td>$p^2 + 2p(1-p)$</td>
<td>$p^2 + 2p(1-p)$</td>
<td>$p^2 + 2p(1-p)$</td>
<td>$p^2 + 2p(1-p)$</td>
</tr>
<tr>
<td>Shared haplotypes</td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Only mating pairs yielding susceptible offspring for dominant inheritance are shown.

Susceptible offspring derived for each mode of inheritance from the Hardy-Weinberg equilibrium and the proportions of sharing of 2, 1 or 0 MHC haplotypes are given in the Appendix, tables 2 and 3.

Why Do Some Affected Sib Pairs Share No MHC Haplotypes?

The explanation for the deviation of the MHC haplotype sharing distribution from that of either rare monogenic recessive or dominant Mendelian inheritance is that the
MHC disease susceptibility gene is remarkably common. One way of looking at this is to consider HLA-DR3/DR4 heterozygotes, particularly common among type 1 diabetics [12]. The great majority of these HLA-DR3/DR4 persons (over 95%) in the general population do not have IDDM. This is primarily because they do not have the other, non-MHC susceptibility genes necessary to have diabetes. Furthermore, only 30–50% of fully susceptible persons will have the disease because of incomplete baseline penetrance. Therefore, all disease susceptibility genes in a polygenic disease must be common if the disease, such as IDDM, has a prevalence of 3 per 1,000, and penetrance is incomplete.

It follows that the general population has many people who are homozygous for MHC haplotypes that carry susceptibility to IDDM. In rare recessive monogenic disorders, it is the mating pair involving 2 heterozygous carriers that usually produces affected offspring. In common polygenic disease many parents are homozygous MHC-susceptible, but most of these do not have disease. In this situation, it is common that both parents are MHC-susceptible homozygotes (DD × DD, or, more accurately, D(a)D(b) × D(c)D(d), since the 4 D-bearing haplotypes usually carry different marker alleles). It is these homozygous susceptible parents (and only these) who give rise to the nonsharing affected sib pairs in a recessive disorder (fig. 1, Appendix, table 2). Note that in a DD × DD mating, all the offspring are DD homozygous susceptible and MHC haplotype sharing is random: 1/4 MHC-iden-
Fig. 2. Predicted frequencies of 2, 1 and 0 haplotypes shared for recessive (a) and dominant (b) inheritance of an MHC disease susceptibility gene at various frequencies of D. Observed haplotype distribution frequencies for multiple sclerosis (MS) and type 1 diabetes (IDDM) are marked. Note that for MS, the distribution fits either form of inheritance. There is no dominant solution for IDDM.

tical to the patient, ac, 1/2 haploidentical, ad or bc, and 1/4 nonsharing or bd. Both in these families and in the overall population, the nonsharing bd affected sibs represent 1/4 $p^2$, or 1/4 the square of the MHC susceptibility gene frequency. Thus, we have a simple way to estimate the MHC disease gene frequency $p$ in the general population.

What Is the Relationship between MHC Haplotype Sharing and Disease Gene Frequency?

Since, for recessive inheritance, the frequency of MHC haplotype nonsharing affected sib pairs equals 1/4 of $p^2$, if this frequency is 0.07, it follows that $p^2$ is 4 times 0.07 or 0.28. Therefore, 0.28 is the fraction of the general population who are MHC disease susceptibility gene homozygotes (susceptibles). The square root of this frequency, 0.525, is $p$, the frequency of the MHC disease susceptibility gene, D.

Haplotype sharing distributions at different hypothetical gene frequencies for recessive and dominant inheritance are shown in figure 2. The figure is constructed by substituting specific gene frequencies in the formulas given in ‘fraction of total’ in Appendix and tables 2 (recessive) and 3 (dominant). The fraction of affected sib pairs sharing 1 haplotype in dominant inheritance is never less than 46% and that of pairs sharing 2 never exceeds 50%. Since there is no dominant gene solution to haplotype sharing in IDDM sib pairs where I-haplotype sharing is 38% and 2-haplotype sharing exceeds 50%, the dominant mode of inheritance is excluded and, therefore, expression of the IDDM MHC susceptibility gene must be recessive. The frequency of the MHC susceptibility gene has

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been calculated from affected sib pair MHC haplotype sharing reported in European Caucasians as a group [5].

As a check, we can see if this gene frequency is consistent with the observed fraction of affected sib pairs who share 1 or 2 haplotypes. Using the formulas in the Appendix and table 2, for recessive inheritance, one obtains 39% (compared with the observed 38%) for the sharing of 1 haplotype and 54% (compared with 55%) for the sharing of 2 haplotypes. Thus, observed and calculated sharing fractions agree, suggesting recessive inheritance of MHC disease susceptibility genes for IDDM as well as supporting our analysis. One would expect MHC haplotype sharing in affected sib pairs to vary in different European Caucasian (and other) populations because the prevalence of IDDM varies and the number of disparate affected sibs is dependent on the frequency of the MHC susceptibility gene.

Application of this method of analysis to multiple sclerosis (MS), another autoimmune disease, is instructive. Using an estimate of MHC haplotype sharing in sib pairs affected by multiple sclerosis of 40% (2 haplotypes), 47% (1 haplotype) and 13% (0 haplotypes) [13, 14], either a dominant MHC susceptibility gene with frequency 0.2 or a recessive MHC susceptibility gene with frequency 0.74 would be consistent with the data. Ironically, these values lie in the only region where the recessive and dominant distributions coincide (see fig. 2). Thus, the observed frequencies for MHC haplotype sharing do not allow us to determine from this analysis whether the MHC susceptibility gene for MS is dominant or recessive.

What Is the Frequency of Non-MHC Susceptibles?

One can easily calculate the frequency of persons in the general population susceptible at all non-MHC loci from the frequency of the MHC susceptibility gene for a disease, since the prevalence of susceptibles in general is equal to the product of the frequencies of susceptibles at all susceptibility loci. For IDDM, with a frequency of MHC susceptibles of 0.275, the frequency of non-MHC gene susceptibles is 0.022 (prevalence of susceptibles of 0.006 divided by 0.275). If there were 2 recessive non-MHC genes of the same frequency, they would each have a frequency of 0.38 (susceptibles at each locus = 0.38 × 0.38 or 0.144, and 0.144 × 0.144 = 0.022). If there were more, their frequencies would be still higher. Without more information, we cannot determine the number, frequencies or modes of inheritance of the non-MHC genes.

What Are the Predictions of Our Analysis?

Table 1 presents the predictions of IDDM-affected family members from our analysis compared with published observations. It is clear that the analysis provides estimates that are consistent with reported observed estimates. For example, our predicted frequency of 3.9% of affected children or parents of patients agrees remarkably well with the observed frequencies of 1.8–5.4% with an average of 3.4%. Similarly, the predictions of our model of the ratio of 2 to 3 to 4 children in a family agree well with published estimates (60:70:1 compared with 69:66:1). The prediction with respect to affected sibs depends greatly upon family size, but it, too, falls within the observed range.
What Previous Observations Are Explained by the Current Analysis?

The common occurrence of MHC susceptibility gene-homozygous parents helps explain the excess of ‘diabetic’ haplotypes among control family haplotypes [15] in families with more than 1 patient [16], and the higher frequency of nonsharing of MHC haplotypes in families with 2, 3 or more affected sibs [5, 17]. This is because families with multiple patients would be expected to have even higher frequencies of all susceptibility genes than those with only one. The apparently ‘higher risk’ to IDDM-affected sibs who share no HLA haplotypes with the index case [4, 11] results solely from the fact that, in such families, every HLA haplotype carries a susceptibility gene. It is not necessary to invoke additional factors in disease predisposition [18].

What Advantages Does Our Method Have Over Previous Methods?

Our approach to defining the frequency of the MHC susceptibility gene is simple, direct, specific and based on standard Mendelian inheritance. We use the mating pair frequencies yielding susceptibles and the proportions of kinds of affected offspring directly to define MHC haplotype sharing. Thus, we define MHC haplotype sharing in terms of the 4 MHC haplotypes normally present in families, not just the disease susceptibility and wild-type alleles of earlier analyses [18–27]. Our method provides a specific estimate, rather than a range, for the MHC susceptibility gene frequency and for the composite frequency of non-MHC gene susceptibles. This allows us, for the first time, to compare the predictions of our analysis with observed familial occurrence of disease. This analysis allows definitive rejection of dominant inheritance of the MHC susceptibility gene for IDDM, and thus provides further evidence for recessive inheritance. Recessive inheritance of the MHC susceptibility gene for IDDM was previously strongly suggested by the distribution among type 1 diabetics of homozygotes and heterozygotes for BF*F1 [28] and other features of MHC haplotype distribution in patients [29, 30].

Our analysis differs from published analyses in its simplicity. Our estimates follow directly from gene frequencies, mating pair frequencies, and MHC haplotype sharing in susceptibles from each kind of mating pair. Earlier authors have used more complicated mathematical methods to analyze sib pair data. These methods have yielded estimates with wide ranges for the frequency of the MHC disease susceptibility gene. Thomson [18] and Thomson and Bodmer [20], for example, using this approach, obtained an MHC gene frequency of 0.37 ± 0.08 (95% confidence limits). At observed MHC haplotype sharing ratios [5], our estimate lies outside this 95% confidence range.

Previous methods do not explain the source of MHC haplotype nonsharing in affected sib pairs. Rather, nonsharing is considered to indicate a ‘different genetic mechanism’ [17] than is operating in the haplotype-sharing sibs. In our view, since the MHC susceptibility gene is not rare, nonsharing sibs are to be expected.

Our analysis closely predicts: (1) distribution of sharing of 2, 1 and 0 MHC haplotypes by affected sib pairs, (2) the frequency of disease in all sibs of a patient, (3) the frequency of disease in MHC-identical sibs of a patient, and (4) the frequency of families with 2, 3, 4, or more diabetic sibs.

The approach outlined in this paper can be used to help us understand other MHC-associated diseases of a complex nature such as...
ankylosing spondylitis, systemic lupus erythematosus, and other disorders that involve partial penetrance and susceptibility determined by genes within the MHC and other loci.

Acknowledgments

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Appendix

What Mating Pairs Give Rise to MHC-Susceptible Offspring?

The relationship between $p$, the frequency of the MHC disease gene $D$, and $(1 - p)$, the frequency of its wild-type allele $d$ and MHC haplotype sharing in the susceptible offspring of relevant mating pairs, is given in table 2 (recessive) and table 3 (dominant). The first column gives the relevant mating pairs of 36 possible for recessive and 5 of 6 for dominant. The second column gives the frequency in the general population of each mating pair in terms of $p$. Let us consider how these frequencies were derived for the recessive case from the Hardy-Weinberg equilibrium.

The population frequency of homozygotes for $D$ is equal to $p^2$, of heterozygotes is equal to $2p(1 - p)$ and of homozygotes for the wild-type allele $d$ is equal to $(1 - p)^2$. One determines the frequency of any mating pair by multiplying the frequencies of its components. For example, the frequency of the $DD \times DD$ pair (homozygous and heterozygous MHC disease-susceptible) equals $p^2 \times 2p(1 - p)$. This simplifies to $4p^3 - 4p^2$. Half of this couple's offspring, or $2p^2 - 2p^2$, are susceptible. The third column of table 2 states the proportion of offspring of each kind of mating pair who are susceptible. Typically, a family will have 4 different MHC haplotypes. By common convention, the father's haplotypes are labeled $ab$ and the mother's $cd$. The index case (patient) is $ac$. In the last 3 columns, the proportions are given of susceptible children who are HLA-identical to an index case with the haplotypes $ac$, who are haplotype identical (share 1 haplotype) with $ad$ or $bc$, and who share no MHC haplotypes ($bd$). These proportions are all given in terms of the general population frequency $p$ of the disease gene $D$. For the $DD \times DD$ mating pair, $p^3 - p^2$ will share both haplotypes (and be HLA-identical to the patient, or $ac$) and $p^2 - p$ will share only 1 haplotype and be HLA-identical, $ad$ or $bc$.

Why Do Some Affected Sib Pairs Share No MHC Haplotypes?

Since, for recessive inheritance, the frequency of MHC haplotype nonsharing affected sib pairs (bd) = $0.25p^2$ (table 2, fraction of total), if this is 0.07, it follows that $p^2$ is 4 times this or 0.28. Therefore, 0.28 is the fraction of the general population who are MHC disease susceptibility gene homozygotes. The square root of this frequency, 0.525, is $p$, the frequency of the MHC disease susceptibility gene, $D$, QED.

For the dominant case, nonsharing can arise from 4 of the 5 mating pairs that produce susceptibles (table 3). The only one that does not is the pair that usually gives rise to susceptibility for rare monogenic disease, $DD \times dd$. Application of the formulas of table 3 provides a solution for the frequency $p$ of a dominant MHC disease susceptibility gene $D$.

What Is the Frequency of Non-MHC Susceptibles?

The frequency of MHC susceptibles is $p^2$ for a recessive and $p^2 + 2p(1 - p)$ for a dominant MHC susceptibility gene $D$. Because non-MHC susceptibility genes would be inherited independently of the MHC susceptibility gene, the frequency of individuals susceptible to IDDM in the total population would be 0.006 (the population prevalence of 0.003 divided by the penetrance). The population prevalence in multiplicative gene interaction would be the product of the fractions of susceptible individuals at the MHC and all non-MHC gene loci. For IDDM, with a frequency of MHC susceptibles of 0.275, the frequency of non-MHC gene susceptibles at a population prevalence of 0.003 and penetrance of 0.5 is 0.006 divided by 0.275 or 0.022.
References


