Three-Allele Synergistic Mixed Model for Insulin-Dependent Diabetes Mellitus

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SUMMARY

Application of the method of antigen genotype frequencies among patients to HLA-DR data pertaining to insulin-dependent diabetes mellitus substantiates the results of Rotter et al. and Thomson that a single-predisposing-allele model is incompatible with the observed data. The method is also modified to take into account the possibility of blanks (untyped antigens) in the assumed homozygotes. The rejection of all intermediate single-allele models is still obtained. A minimum of two HLA-linked predisposing components are necessary to account for the data. The patterns observed are consistent with a three-allele model, in which the two predisposing alleles interact synergistically (negative complementation). Furthermore, a model in which the DR3-associated predisposition allele is recessive in the absence of the other allele and the DR4-associated predisposing allele is additive (dominant) in the absence of the other is more consistent with the data than a model in which both alleles are recessive or additive in the absence of the other. DIABETES 1986; 35:958–63.

A significant excess of HLA-DR3/DR4 individuals over the number expected under a single-allele recessive model has been demonstrated among patients with insulin-dependent diabetes mellitus (IDDM) by Rotter et al.[1] Also, by use of the method of antigen genotype frequencies among patients (AGFAP)[2–7] a significant excess of DR3/DR4 heterozygous individuals over that expected in any single-allele model (i.e., recessive, dominant, or intermediate) has been demonstrated in some data sets.[2]

The results of Rotter et al. have been criticized by Williams[8] on the basis of their implicit assumption that the genotypes in a sample of IDDM patients must necessarily conform with Hardy-Weinberg criteria. The Rotter et al. assumption is valid: For single-predisposing-allele recessive models the genotypic distribution among patients has expectations that are equivalent to Hardy-Weinberg expectations,[2–7] because they are equivalent to a quadratic expansion of a trinomial.[2] The criticism by Williams that the antigen genotype frequencies among IDDM patients do not conform to Hardy-Weinberg expectations actually supports the rejection of the recessive hypothesis.

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METHODS AND RESULTS

We have analyzed data sets included in the analysis of Rotter et al.[1] and some additional data sets,[9–27] with the AGFAP method. These data sets were taken from the literature and are mutually exclusive, for the most part, with possible overlaps noted. Only unrelated affected individuals are included in this analysis. Multiplex data sets were excluded. Our first approach (method A; see Thomson[2]) was analysis of the data based on subdivision by the six DR genotype classes DR3/DR3, DR3/DR4, DR4/DR4, DR3/DRX, DR4/DRX, and DRX/DRX, where DRX denotes any DR antigen allele other than DR3 or DR4. For most of the data sets, unequivocal genotyping is assumed. In the data of Anderson et al.,[19,20] 12 out of 14 DR4-positive individuals could not be unequivocally typed as DR4/DR4 or DR4/DRX. In this case, the most conservative, least significant, possibility is used in the analysis in Table 1 (all 12 are assumed to be DR4/DR4). In all studies there was an excess of DR3/DR4 individuals over the number expected under a single-allele recessive model (Table 1). The deviation from recessive expectations was statistically significant in 9 of the 14 Caucasian studies and 1 of the 2 other studies. (Note that for all single-allele dominant and intermediate models the expected number of DR3/DR4 individuals is less than in the recessive case,[2] so as well as rejecting the single-allele recessive model, the observed data can be used to reject all single-allele additive, dominant, and intermediate models, because the deviations from expectations are even more extreme in these cases.)

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TABLE 1
Observed and expected numbers of DR antigen genotypes among IDDM patients

Data set	Genotypic class						
	DR3/DR3	DR3/DR4	DR4/DR4	DR3/DRX	DR4/DRX	DRX/DRX	
Ref. 9							
Observed	1.0	17.0	9.0	2.0	14.0	0.0	†
Expected	2.6	12.0	14.0	3.9	9.1	1.5	
Ref. 10							
Observed	10.0	37.0	13.0	7.0	10.0	43.0	‡
Expected	8.5	19.5	11.1	27.5	31.3	22.1	
Ref. 11							
Observed	9.0	62.0	6.0	15.0	27.0	3.0	‡
Expected	18.5	39.3	20.9	18.7	19.9	4.7	
Ref. 12							
Observed	18.0	16.0	1.0	12.0	2.0	2.0	NS§
Expected	20.1	12.5	2.0	11.3	3.5	1.6	
Ref. 13							
Observed	0.0	13.0	1.0	26.0	27.0	14.0	†
Expected	4.7	10.1	5.4	19.5	21.0	20.3	
Ref. 14							
Observed	9.0	32.0	21.0	9.0	14.0	8.0	NS§
Expected	9.4	27.9	20.8	12.4	18.5	4.1	
Ref. 15							
Observed	12.0	46.0	11.0	8.0	29.0	6.0	‡
Expected	13.6	33.8	21.0	17.1	21.2	5.4	
Ref. 16							
Observed	1.0	17.0	1.0	14.0	13.0	7.0	†
Expected	5.1	10.0	4.8	12.8	12.4	7.9	
Ref. 17							
Observed	2.0	10.0	2.0	8.0	11.0	7.0	NS§
Expected	3.0	6.9	3.9	9.1	10.3	6.8	
Ref. 18							
Observed	9.0	14.0	4.0	10.0	11.0	9.0	NS§
Expected	7.7	12.2	4.8	14.4	11.3	6.7	
Ref. 19,20							
Observed	3.0	34.0	14.0	15.0	24.0	7.0	*
Expected	7.8	24.4	19.1	15.0	23.5	7.2	
Ref. 21							
Observed	4.0	13.0	4.0	15.0	24.0	13.0	NS§
Expected	4.4	11.1	6.9	16.0	20.0	14.5	
Ref. 22							
Observed	3.0	23.0	4.0	8.0	13.0	2.0	*
Expected	6.5	15.4	9.1	8.7	10.4	2.9	
Ref. 23[a]							
Observed	2.0	14.0	13.0	3.0	16.0	2.0	NS§
Expected	2.2	11.8	15.7	4.8	12.9	2.6	
Ref. 23[b]							
Observed	3.0	23.0	5.0	1.0	7.0	3.0	†
Expected	5.4	14.3	9.5	5.0	6.7	1.2	
Ref. 24							
Observed	12.0	56.0	13.0	25.0	43.0	17.0	‡
Expected	16.5	39.3	23.4	32.7	38.9	16.2	
Total	14/16† ↓	16/16‡ ↑	14/16† ↓	13/16* ↓	12/16* ↑	9/16§ ↑	

Method of antigen genotype frequencies among patients (AGFAP) by Thomson[2] (method A) was used. Expected values for recessive single-allele model are calculated with 6 genotypic classes DR3/DR3, DR3/DR4, DR4/DR4, DR3/DRX, DR4/DRX, and DRX/DRX (see text for details). Significance is based on goodness-of-fit χ^2-test (3 DF because 2 parameters are estimated from data). Expected classes were combined if <5. Summary and significances at bottom of table are result of nonparametric sign test assuming all data sets are independent. Arrows indicate the direction observed values differ from expected. In these data it is likely that overlaps occur between Platz et al.[14] and Christy et al.[21] and between Anderson et al.[19,20] and Rotter et al.[1] Data of Brautbar et al.[23] are for Ashkenazi (a) and non-Ashkenazi (b) Jewish populations. *$P < .05$; †$P < .01$; ‡$P < .001$; §$P > .05$, NS.

Because of blanks and cross-reacting sera, it is not always possible to unequivocally classify an individual as homozygous for an HLA antigen. To obviate the possibility of spurious results due to such misclassification, we have modified the AGFAP approach to also consider the data based on the four DR genotype classes DR3/$\overline{\text{DR4}}$, DR3/DR4, $\overline{\text{DR3}}$/DR4, and DRX/DRX, where $\overline{\text{DR4}}$ denotes any antigen other than DR4, etc. (method B). If the population frequencies of the IDDM-predisposing allele-bearing haplotypes are k_1p_D for DR3-D, k_2p_D for DR4-D, and k_3p_D for DRX-D (with $k_1 + k_2 + k_3 = 1$), then the expectations for the DR classes under the single-allele recessive model are as follows: $2k_1k_2$ for DR3/DR4, $k_1^2 + 2k_1k_3$ for DR3/$\overline{\text{DR4}}$, $k_2^2 + 2k_2k_3$ for $\overline{\text{DR3}}$/DR4, and k_3^2 for DRX/DRX, where the k_i's are the association para-

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meters as defined in Thomson[2] and p_D is the disease-predisposing-allele frequency. There is no analytic solution to estimation procedures for these association parameters; therefore, they must be estimated numerically. Expectations for additive and intermediate models are similarly derived. (A copy of the computer program to calculate expected values for recessive and additive models by use of maximum likelihood estimates of the association parameters is available on request.)

With this approximation, all the data sets, except that of Barbosa et al.,[13] showed a higher observed number of DR3/DR4 individuals than expected (see Table 2). Five of the significant deviations from the previous analysis (method A) were no longer significant; however, 6 of the 15 Caucasian studies and 2 of the 4 other studies showed significant deviation. Under the recessive hypothesis, the observed number of DR3/DR4 patients should be less than or greater than the expected values with equal likelihood when several data sets are analyzed. A nonparametric sign test applied to the data sets in which 16 out of 16 analyzed with method A had observed values greater than expected and 18 out of 19 analyzed with method B had observations greater than expected yields probabilities of observing the data under the recessive hypothesis of $P = .000015$ and $P = .000038$, respectively, for methods A and B. The single-allele recessive model can be rejected on these grounds. As outlined above, because expectations of DR3/DR4 heterozygotes for additive and intermediate models are less than recessive expectations, these models can also be rejected. This test is valid for independent samples and cannot be applied to samples that overlap. When only one of the possible overlapping data sets is included in the analysis, the rejection of all intermediate single-allele models is still obtained with the sign test.

Five of the six antigen genotype classes (method A) of the IDDM data sets are significantly different from recessive expectations (with the nonparametric sign test). These are summarized at the bottom of Table 1. In 16 out of 16 cases the DR3/DR4 class is greater than expected, 14 out of 16 of the data sets have DR3/DR3 and DR4/DR4 classes less than their expectations, 13 out of 16 data sets have DR3/DRX classes less than their expectations, and 12 out of 16 data sets have DR4/DRX classes greater than their expectations.

Recently, Greenberg[28] used DR-antigen genotype frequencies in IDDM patients to reject the recessive model and support a three-allele model for several data sets. The three-allele model used was restrictive in the sense that only those individuals heterozygous for the two predisposition alleles were assumed to be disease susceptible. A less restrictive model would allow several of the six genotypes at the IDDM predisposing locus to get the disease with varying penetrances. The most general three-allele model with two antigens associated with a disease is described below.

If the three disease-locus alleles are designated D_1, D_2 and d with population frequencies p_{D_1}, p_{D_2} and p_d, respectively, and the penetrances of the genotypes are f_5, f_4, f_3, f_2, f_1, and f_0 for D_1D_1, D_1D_2, D_2D_2, D_1d, D_2d, and dd, respectively, then the expected antigen genotype frequencies among IDDM patients can be calculated by use of the following haplotype frequencies: $k_1p_{D_1}$ for A_1-D_1, $k_2p_{D_2}$ for A_1-D_2, $p_{A_1} - k_1p_{D_1} - k_2p_{D_2}$ for A_1-d, $k_3p_{D_1}$ for A_2-D_1, $k_4p_{D_2}$ for A_2-D_2, $p_{A_2} - k_3p_{D_1} - k_4p_{D_2}$ for A_2-d, $k_5p_{D_1}$ for a-D_1, $k_6p_{D_2}$ for a-D_2, and $p_a - k_5p_{D_1} - k_6p_{D_2}$ for a-d, where $k_5 = 1 - k_1 - k_3$, $k_6 = 1 - k_2 - k_4$, and p_{A_1}, p_{A_2}, and p_a are the population frequencies of antigens A_1, A_2, and a, respectively. The frequency of A_1A_1 among IDDM patients, for example, would then be

$$\frac{f_5k_1^2p_{D_1}^2 + 2f_4k_1k_2p_{D_1}p_{D_2} + f_3k_2^2p_{D_2}^2 + 2f_2k_1(p_{A_1} - k_1p_{D_1} - k_2p_{D_2})p_{D_1} + 2f_1k_2(p_{A_1} - k_1p_{D_1} - k_2p_{D_2})p_{D_2} + f_0(p_{A_1} - k_1p_{D_1} - k_2p_{D_2})^2}{f_5p_{D_1}^2 + 2f_4p_{D_1}p_{D_2} + f_3p_{D_2}^2 + 2f_2p_{D_1}p_d + 2f_1p_{D_2}p_d + f_0p_d^2}$$

The other antigen genotype frequencies are calculated similarly.

Three models of particular interest for IDDM are *1*) the case in which the two disease-predisposing alleles are recessive in the absence of the other (i.e., $f_2 = f_1 = f_0 = 0$), *2*) the case in which both disease alleles are additive in the absence of the other ($f_2 = f_5/2$, $f_1 = f_3/2$, and $f_0 = 0$), and *3*) the case in which one allele is recessive and the other additive in the absence of the other ($f_2 = f_5/2$, $f_1 = f_0 = 0$). Numerous examples of expectations under each model, with varying penetrances, allele frequencies, and associations, were subjected to the test of the single-allele recessive model to determine the types of patterns expected when comparing simulated antigen genotype classes with their recessive expectations.

The parameters used in the simulations were chosen to cover a range of biologically reasonable values for IDDM. Each antigen frequency used in the simulated data ranged from 0.05 to 0.15. The two predisposition-allele frequencies ranged from 0.01 to 0.10. The association parameters k_1 and k_4 ranged from 0.4 to 0.9, whereas k_2 and k_3 ranged from 0.05 to 0.15. The penetrances ranged as follows: $f_5 = 1$; $f_4 = 1,2,5$, or 10; $f_3 = 1/5$, or $1/2$, or 1; $f_2 = 0$ or $1/2$; $f_1 = 0$ or $f_3/2$; and $f_0 = 0$. Several hundred parameter sets were analyzed for each of the three models.

Under the restriction that each of the two antigens associated with IDDM is positively associated with only one of the two disease-predisposition alleles (i.e., if k_1 is $> p_{A_1}$, then k_2 is $\leq p_{A_1}$, k_3 is $\leq p_{A_2}$, and k_4 is $> p_{A_2}$), the three models of interest yield distinct patterns of antigen genotype class expectations when analyzed by method A. In all three models with the D_1D_2 genotype having the highest penetrance (negative complementation or synergism), the A_1/A_1 and A_2/A_2 classes are generally less than their expectations under a single-allele recessive model, the A_1/A_2 class is always greater than expected, and the a/a class is equal to expectations. When both alleles are recessive in the absence of the other, both the A_1/a and A_2/a classes are equal to their expected values. When both alleles are additive in the absence of the other, both the A_1/a and A_2/a classes are greater than expected. When one allele is recessive and the other additive, the antigen positively associated with the recessive allele has its heterozygous class less than expected and the other antigen heterozygous class is greater than expected. These patterns are summarized in Table 3.

The pattern observed in the IDDM data sets (see Table 1) is most consistent with the mixed model in which one allele is recessive and the other additive in the absence of the other. Furthermore, the directionality of the pattern indicates that DR4 is most likely associated with an additive compo-

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TABLE 2
Observed and expected antigen genotype frequencies

Data set	Genotypic class				
	DR3/$\overline{DR4}$	DR3/DR4	$\overline{DR3}$/DR4	DRX/DRX	
Ref. 9					
Observed	3.0	17.0	23.0	0.0	NS§
Expected	3.0	16.9	23.0	0.0	
Ref. 10					
Observed	17.0	37.0	23.0	43.0	‡
Expected	35.0	15.5	40.7	28.9	
Ref. 11					
Observed	24.0	62.0	33.0	3.0	†
Expected	31.0	50.1	39.9	1.0	
Ref. 12					
Observed	30.0	16.0	3.0	2.0	NS§
Expected	31.7	13.2	5.0	1.1	
Ref. 13					
Observed	26.0	13.0	28.0	14.0	NS§
Expected	25.5	13.6	27.5	14.3	
Ref. 14					
Observed	18.0	32.0	35.0	8.0	*
Expected	22.6	25.7	39.3	5.5	
Ref. 15					
Observed	20.0	46.0	40.0	6.0	*
Expected	26.0	37.1	45.6	3.3	
Ref. 16					
Observed	15.0	17.0	14.0	7.0	NS§
Expected	18.1	12.7	17.2	5.0	
Ref. 17					
Observed	10.0	10.0	13.0	7.0	NS§
Expected	11.8	7.7	14.8	5.7	
Ref. 18					
Observed	19.0	14.0	15.0	9.0	NS§
Expected	21.0	11.4	17.0	7.6	
Ref. 19,20					
Observed	18.0	34.0	38.0	7.0	NS§
Expected	22.3	28.0	42.0	4.8	
Ref. 21					
Observed	19.0	13.0	28.0	13.0	NS§
Expected	19.6	12.2	28.6	12.6	
Ref. 22					
Observed	11.0	23.0	17.0	2.0	NS§
Expected	13.4	19.3	19.3	1.1	
Ref. 23a					
Observed	5.0	14.0	29.0	2.0	NS§
Expected	5.9	12.8	29.7	1.6	
Ref. 23b					
Observed	4.0	23.0	12.0	3.0	‡
Expected	9.3	14.8	17.0	0.9	
Ref. 24					
Observed	37.0	56.0	56.0	17.0	‡
Expected	45.8	43.9	64.4	11.9	
Ref. 25					
Observed	9.0	20.0	9.0	2.0	*
Expected	12.0	14.9	12.2	0.8	
Ref. 26,27					
Observed	25.0	6.0	12.0	18.0	NS§
Expected	25.1	5.8	12.2	17.9	
Ref. 1					
Observed	19.0	39.0	40.0	10.0	†
Expected	25.7	29.7	46.2	6.3	

Method B for genotypic classes DR3/$\overline{DR4}$, DR3/DR4, $\overline{DR3}$/DR4, and DRX/DRX, where $\overline{DR4}$ is all antigens other than DR4, etc., was used (see text for details). Sixteen data sets used in method A as well as 2 studies on American Blacks[25-27] (data of Reitnauer et al.,[26] also analyzed by Curie-Cohen and MacDonald[27]) and data of Rotter et al.[1] are analyzed here. When expected class was <5, both G test and normal approximation to binomial on DR3/DR4 class were performed.
*$P < .05$; †$P < .01$; ‡$P < .001$; §$P > .05$, NS.

nent, and DR3 is most likely associated with a recessive component. The recessive expectations under method B did not yield distinguishable patterns for the three models.

DISCUSSION

It has been shown that misclassification of individuals, e.g. DR4/DRX rather than DR4/DR4, due possibly to cross-re-

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acting sera, can cause an apparent excess of DR3/DR4 individuals under method A.[2] However, no such explanation is available for the excesses observed with method B. Our analysis substantiates the results of Rotter et al.,[1] Thomson,[2] and the suggestion of Svejgaard and Ryder[29] that a single-allele model is incompatible with the IDDM HLA-DR data. Three-allele synergistic (or negative complementation) models yield patterns consistent with IDDM HLA-DR data, such as the excess of DR3/DR4 heterozygotes. Risch,[30] using a combined linkage and segregation approach on DR-typed families with IDDM, also rejects all two-allele models in favor of a three-allele model. Our analysis of patterns for several three-allele models shows that they can be distinguished under certain circumstances and that the IDDM HLA-DR data are most consistent with one of the three types of models analyzed here, i.e., the case in which the disease-predisposing allele associated with DR3 is recessive and the DR4-associated allele is additive when they are not in the presence of each other.

The use of the single-allele recessive hypothesis for distinguishing complex models is valid and robust. Expectations are simple to derive and test. If there is population substructuring in the data, the number of observed DR3/DR4 heterozygotes will be less than Hardy-Weinberg expectations even if IDDM is a simple recessive disease, making the test of the recessive hypothesis conservative. The fact that different three-allele models yield distinguishable patterns when compared to recessive expectations makes this test useful.

When the restriction on associations is relaxed, the patterns of the three models analyzed here overlap. For example, if one antigen is positively associated with both predisposing alleles, then the model in which both alleles are recessive in the absence of the other can exhibit the A_1/a and A_2/a pattern observed in the IDDM data; however, in this case the a/a class should be less than expected, yet no significant trend in this direction is observed in the data. The restrictions imposed in our report are biologically relevant and realistic given the strong associations of both DR3 and DR4 with IDDM. If the IDDM-predisposing components increased in frequency because of a hitchhiking phenomenon, then the expectation is that each would be positively associated with only one antigen at a given locus.

Misclassifications of homozygosity due to blanks or cross-reacting sera can affect the patterns described above (Table 3). The simulated data sets were submitted to various degrees of artificial misclassification of one or both of the A_1/a and A_2/a classes as homozygotes. These perturbed data sets were then reanalyzed by applying the recessive test. Misclassifying A_1/a heterozygotes as A_1/A_1 homozygotes results in an increase in the estimate of k_1 and a decrease of $k_3 = 1 - k_1 - k_2$ in the application of the test of the recessive hypothesis. In all three models, this results in the a/a class always being greater than expected under the recessive hypothesis, and there is no significant trend in this direction observed in the data. The effects on the A_1/a and A_2/a patterns may differ for the three models. For the recessive-recessive model, misclassification involving only one of the two antigens does result in the misclassified heterozygous class being less than expected, whereas the other heterozygous class is greater than expected. This superficially mimics the observed pattern in the data; yet as mentioned before, the a/a class is also affected and this is not observed in the data. The degree and type of misclassification would have to be consistent throughout all the data sets to yield the observed patterns of DR3/DRX and DR4/DRX classes. The additive-additive model can also superficially mimic the observed patterns if only one heterozygous genotype class is misclassified and the degree of misclassification is extreme. As before, the a/a class would not be consistent with the observed data. If both A_1/a and A_2/a classes are misclassified, then the patterns for the recessive-recessive and additive-additive models do not mimic those patterns observed in the data. Misclassification in the mixed additive-recessive model either increases or decreases the amount of deviation from recessive expectations without altering the pattern, except for the a/a class. The frequency of blanks in the population and the proportion of DRX antigens (not DR3, not DR4) in these data that are typed makes the possible effects of misclassification negligible for this analysis and for the conclusions drawn.

TABLE 3
Deviations from single-allele recessive expectations for three different three-allele synergistic models

	Antigen genotype					
Model	A_2/A_2	A_2/A_1	A_1/A_1	A_2/a	A_1/a	a/a
Recessive-recessive	↓	↑	↓			
Additive-additive	↓	↑	↓	↑	↑	
Additive-recessive	↓	↑	↓	↓	↑	

Arrows indicate direction of deviation for each antigen class under each model (blanks mean no deviation expected). Models analyzed here assume that each HLA antigen, A_1 and A_2, is positively associated with only one of two synergistically interacting IDDM-predisposition alleles ("a" represents all other antigens at the locus). First model states that each of predisposition alleles is recessive in absence of the other, second states that each allele is additive in absence of the other, and third states that allele in positive association with A_1 is additive and other allele (in positive association with A_2) is recessive. Genotypes are ordered for ease in comparison to results of Table 1.

The recent finding that DR1 is also associated with IDDM[9,31-34] and that there is an excess of DR1/DR4 heterozygotes in some populations,[9,32] analogous to the DR3/DR4 excess, suggests that there are more than two predisposing components linked to HLA. It is not yet possible to distinguish between the possibility that the DR1- and DR3-associated components are identical (and therefore consistent with the model presented here) or whether a third component is necessary to explain the data (making a four-allele model).

In the affected-sib methods, a three-allele synergistic model yields expectations consistent with the observed haplotype-sharing distribution among sib pairs and trios with IDDM.[35,36] Furthermore, the observed haplotype sharing in affected-sib trios is closer to the mixed recessive-additive and recessive-recessive expectations than to the additive-additive expectations (E. J. Louis, H. Thomson, and H. Payami, unpublished observations).

Different populations that have different frequencies of these two predisposing components would be expected to have different antigen genotype frequencies among patients. A population with a high frequency of the additive DR4-as-

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sociated component and a low recessive DR3-associated component may appear to be consistent with an additive or dominant mode of inheritance, whereas the data presented here are not. MacDonald[37] has shown that IDDM data of American Blacks is most consistent with a dominant mode of inheritance. Rotter and Hodge[38] suggest that this observation can be explained with a three-allele synergistic model.

As well as providing further confirmation for a three-allele synergistic (DR3/DR4) model for IDDM predisposition, our results indicate heterogeneity in the modes of inheritance of the DR3- and DR4-associated predisposing components.

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