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HLA-DR4 in insulin-dependent diabetic parents and their diabetic offspring: A clue to dominant inheritance

(genetics of type I diabetes/HLA-associated diabetes susceptibility determinants)

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ABSTRACT **Insulin-dependent diabetes mellitus (IDDM) susceptibility determinants are known to be associated with both *HLA-DR3* and *-DR4*. We monitored the inheritance of *HLA-DR* alleles in 37 families in which IDDM affected one parent and at least one offspring in order to try to learn more about the modes of inheritance of IDDM determinants. Ninety-seven insulin-dependent diabetics whose parents did not have diabetes and 158 nondiabetics were used as control groups for estimates of *DR* allele frequencies in the overall diabetic and general populations. The proportion of diabetic parents who transmitted *DR4* to diabetic offspring (78%) was significantly higher ($P < 0.001$) than the gene frequency of *DR4* in the overall diabetic population (43%). The proportion of nondiabetic parents who transmitted *DR4* to diabetic offspring (22%) was not significantly different from the gene frequency of *DR4* in the nondiabetic population (16%), but it was significantly lower ($P < 0.05$) than the gene frequency in the overall IDDM population. These proportions suggest that inheritance of the *DR4*-associated IDDM susceptibility determinant is not recessive, because in recessive inheritance expression of a trait depends on each parent contributing a susceptibility determinant. The proportions of diabetic and nondiabetic parents who transmitted the *DR* allele associated with the susceptibility determinant would then equal one another. The transmission of predominantly *DR4* from affected parents to affected offspring suggests that susceptibility to IDDM is inherited primarily via a single dose of a potent determinant associated with *DR4*, as in dominant inheritance. When *DR3* was transmitted at all it was usually by the nondiabetic parent. Only 8% of diabetic parents transmitted *DR3* but 35% of nondiabetic parents transmitted *DR3*. The proportion of nondiabetic parents who transmitted *DR3* was similar to the gene frequency of *DR3* in the overall diabetic population (29%), but it was significantly higher than the gene frequency of *DR3* in the nondiabetic population (15%; $P < 0.005$). The percentage of diabetic offspring with the genotype *DR3DR4* (35%) was identical to the percentage of individuals in the overall IDDM population with this genotype (35%). Numerous population data indicate that the *DR3DR4* genotype carries a higher relative risk for IDDM than any other genotype, which suggests synergism between the *DR3*- and *DR4*-associated determinants. The family data reported here support this synergism but suggest that the *DR4*-associated determinant can give substantial susceptibility independent of the *DR3*-associated determinant and that the *DR3*-associated determinant is often expressed as enhancing susceptibility in the presence of the dominant *DR4*-associated determinant.**

The mode of inheritance of insulin-dependent diabetes mellitus (IDDM) has long been of interest, but recently, after it was discovered that the disorder is associated with the *HLA* complex on chromosome 6, its inheritance has become the subject of lively debate (1, 2). Different *HLA* studies have variously suggested that the inheritance of IDDM is dominant, recessive, and intermediate between dominant and recessive (one dose of an *HLA*-associated allele gives susceptibility to IDDM, but two doses of the allele increases susceptibility markedly) and that there is genetic heterogeneity in IDDM (3–6). There does seem to be general agreement that only susceptibility to IDDM is inherited and that currently unknown environmental factors, either nonspecific or specific, are important in triggering destruction by lymphocytes of the insulin-producing cells in the islets of Langerhans.

The disagreement over the inheritance of susceptibility to IDDM may stem in part from the enormous polymorphism of the *HLA* region and from the complexity of the *HLA* associations in IDDM. The *HLA-DR* locus, which is the *HLA* locus that has shown the strongest association with IDDM, has at least 10 alleles and, unlike most other *HLA*-associated disorders, not one but two *DR* alleles, *DR3* and *DR4*, are associated with IDDM. Most studies show that *DR3* and *DR4* each has a frequency of 20–30% in the general population, whereas 50–60% of subjects with IDDM are *DR3*-positive and 65–80% are *DR4*-positive. In total, >95% of subjects with IDDM are positive for *DR3* and/or *DR4*, and interestingly, the *DR3DR4* genotype has a higher relative risk for IDDM than any other genotype (7, 8). It is now widely appreciated that the *DR3* and *DR4* data are incompatible with any simple form of inheritance. Instead, it is believed that these data suggest that there are two separate diabetes susceptibility determinants—one associated with *DR3* and another associated with *DR4*, and that these determinants often interact to enhance susceptibility to IDDM (4, 7, 8).

To learn more about the modes of inheritance of the *DR3*- and *DR4*-associated determinants in IDDM, we monitored the transmission of *DR* alleles in families with IDDM in one parent and at least one offspring. Despite the many studies of HLA in IDDM, no study has been directed specifically at the inheritance patterns of *DR* alleles in families with a diabetic parent and diabetic offspring.

There should be a high probability that the *DR* allele transmitted to a diabetic offspring by a diabetic parent (and possibly also by a nondiabetic parent) is associated with an IDDM susceptibility allele. If the inheritance of a susceptibility determinant that is associated with a particular *DR* allele is recessive, then the proportions of diabetic and nondiabetic parents transmitting the *DR* allele would be equal. In addition, these proportions should equal the gene frequency of the *DR* allele in the overall IDDM population. Surprisingly, among the *DR* alleles transmitted from the diabetic parents to their diabetic offspring, *DR4* was overrepresented and *DR3* was extremely underrepresented. When *DR3* was transmitted at all, it was usually transmitted

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Abbreviation: IDDM, insulin-dependent diabetes mellitus.

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by the nondiabetic parent. This pattern of inheritance suggests that susceptibility to IDDM is inherited primarily via a single dose of a potent determinant associated with *DR4* as in dominant inheritance of the determinant. The family and population data of the current study support the synergism between the *DR3*- and *DR4*-associated determinants that was previously suggested by population data, but they suggest that the *DR3*-associated determinant is relatively weak and is often expressed as enhancing susceptibility in the presence of the *DR4*-associated determinant.

SUBJECTS AND METHODS

Subjects were typed for all World Health Organization recognized and provisional *HLA-A, -B, -C, -DR, -DQ, -Bw4/Bw6*, and *-DRw52/DRw53* specificities with standard methodology (9). Only the data on *DR* are reported here. The additional data were used to discern parental haplotypes when necessary.

Thirty-seven Caucasian families in which a parent and at least one offspring had typical IDDM were ascertained. Of the 44 diabetic offspring in 37 families, 28 were males, and of the 37 diabetic parents, 29 were fathers. Each diabetic offspring and diabetic parent required and received insulin from diagnosis onward. All families except one were ascertained through an offspring and 10 offspring (nos. 2a, 3, 4, 5, 7b, 9, 15, 19, 30, and 33) were ascertained through the 2-year survey of IDDM described below. The only requirement we imposed was that the families have a parent and at least one offspring with IDDM. These families were all of this type of family known to the first author and every family consented to participate in the study. Because two nondiabetic parents were unavailable (nos. 8 and 29), their DR phenotypes were inferred from the *DR* allele transmitted to their offspring. Each parent was classified as heterozygous for the allele because the probability of homozygosity is low (<5%).

A group of unrelated subjects with IDDM and a group of nondiabetics were HLA typed to obtain estimates of allele frequencies among the overall diabetic and nondiabetic populations. One hundred and seven diabetics were randomly selected for HLA typing from a group of 278 Caucasian subjects reported in a prospective 2-year statewide survey of IDDM in Wisconsin. The criteria for inclusion in this study were that the subjects be Caucasians who were younger than 20 years of age at the diagnosis of IDDM, that they live in the state of Wisconsin, that they were diagnosed as diabetic between July 1, 1982 and June 30, 1984, and that they have signs and symptoms and an insulin requirement typical of IDDM. The age, sex, and geographic distributions of the subjects typed for HLA closely paralleled those of the total reported cases. It was subsequently decided that the 10 subjects with a diabetic parent should not be included in the group of diabetic controls, since data on each of them were used as "family" data. The percentages of subjects with the various DR antigens were very similar whether or not these 10 subjects were included. One hundred and fifty-eight nondiabetic controls were HLA-typed during the years 1982 and 1983.

The distribution of DR antigens among the nondiabetic controls did not differ appreciably from the distribution observed by the Ninth International Histocompatibility Workshop held in West Germany in 1984 or previously observed in 399 Caucasian nondiabetics in Milwaukee (10); and the distribution of DR antigens among the 107 subjects with IDDM did not differ appreciably from data on IDDM reported by others (7, 8, 11–15).

Data on the 97 subjects with IDDM and without diabetic parents were used to estimate the frequencies of the various *DR* alleles in the overall diabetic population and were estimated as follows: 52 subjects were *DR3*-positive, which includes five subjects who typed positive for only *DR3*; 77 subjects were *DR4*-positive, which includes six subjects who typed positive for only *DR4*. Each subject who typed positive for only *DR3* or *DR4* was considered to be homozygous, which may not be the case, but which actually overestimates slightly the frequencies of *DR3* and *DR4* in the diabetic population, making the comparisons with the family data more conservative. The gene frequencies, accordingly, were as follows: *DR3*, 57/194 = 0.29; *DR4*, 83/194 = 0.43; *DRx*, 54/194 = 0.28 (where $x \neq 3$ or 4).

The χ^2 test was used to estimate statistical significance.

RESULTS

Table 1 lists the *DR* type of each diabetic offspring and of his or her diabetic parent, as well as the *DR* allele transmitted from the diabetic parent to the diabetic offspring. A *DR4* allele was transmitted by 29 of 37 diabetic parents (78%) to 36 of 44 diabetic offspring (82%). Three diabetic parents transmitted an allele for *DR3* (8%) and five diabetic parents transmitted an allele that codes for an antigen other than *DR3* or *DR4* (14%) (Table 2). The proportion of diabetic parents who transmitted *DR4* was significantly higher ($P < 0.001$) than the gene frequency of *DR4* in IDDM (43%).

One of the three diabetic parents who transmitted *DR3* (no. 25) has the autoimmune polyendocrine syndrome type II (IDDM in combination with any of the following: adrenal insufficiency, myasthenia gravis, gonadal failure, vitiligo and/or alopecia), which is known to be associated with *DR3*. The daughter received *DR4* from her mother, who does not have diabetes. Of the other two offspring who received *DR3* from a diabetic parent, one received *DR4* from the nondiabetic parent.

Five offspring (nos. 11, 18, 20, 26, and 27) did not have *DR4*. One of these subjects received *DR2*, which is uncommon in IDDM, from both parents. It is noteworthy that this subject (no. 26) was diagnosed as diabetic at age 6 months and her mother was diagnosed as diabetic at age 7 months. The uncommonly young ages of onset, plus the *DR* genotype, raises the question of whether the etiology of the diabetes in this mother and daughter were the same as in the majority of cases of IDDM. Offspring in three families (nos. 3, 22, and 25) received *DR4* from the nondiabetic parent, but not from the diabetic parent, and offspring in five families (nos. 8, 10, 16, 30, and 31) received *DR4* from both parents. Offspring in 11 families who received *DR4* from the diabetic parent also received *DR3* from the nondiabetic parent (nos. 1, 2, 5, 7, 9, 15, 19, 23, 29, 35, and 37).

In contrast to the diabetic parents, only a small proportion of nondiabetic parents transmitted *DR4* (22%), and this proportion was not significantly different from the gene frequency of *DR4* in the nondiabetic controls (16%) (Table 2). However, this proportion (22%) was significantly lower than the gene frequency of *DR4* in IDDM (43%) ($P < 0.05$). The proportion of nondiabetic parents who transmitted *DR3* (35%) was not significantly different from the gene frequency of *DR3* in IDDM (29%). When the proportions of the various *DR* alleles received by the diabetic offspring from the nondiabetic parents were averaged with those received from the diabetic parents, the averages (which are, of course, the same as the gene frequencies among the diabetic offspring) were as follows: *DR3*, 0.22; *DR4*, 0.50; *DRx*, 0.28. Since these gene frequencies were not significantly different from the gene frequencies in the control IDDM subjects (Table 2), this indicates that the diabetic offspring with a diabetic parent were roughly similar, with respect to HLA, to diabetics without a diabetic parent.

The percentages of the diabetic parents who were positive for the various DR antigens were similar to those of the overall population of subjects with IDDM, except that the

Table 1. *HLA-DR* alleles transmitted to diabetic offspring by their parents with IDDM

Subject	*DR* type, sex, and age at diagnosis		*DR* allele transmitted to offspring
	Offspring	Parent	
1	*3,4*; M (3)	*4,4*; M (17)	*4*
2a	*3,4*; F (5)	*4,4*; M (12)	*4*
2b*	*3,4*; F (2)		*4*
3	*3,4*; M (1)	*1,3*; M (1)	*3*
4	*1,4*, F (7)	*1,4*; F (12)	*4*
5	*3,4*; M (7)	*4,5*; F (10)	*4*
6	*1,4*; M (2)	*4,5*; M (21)	*4*
7a	*3,4*; M (4)	*4,4*; M (29)	*4*
7b*	*3,4*; M (8)		*4*
8	*4,4*; F (10)	*4,5*; M (11)	*4*
9	*3,4*; M (3)	*2,4*; M (1)	*4*
10	*4,4*; M (10)	*4,4*; M (10)	*4*
11	*3,7*; M (10)	*3,4*; M (13)	*3*
12	*1,4*; M (1)	*1,4*; M (7)	*4*
13	*1,4*; F (19)	*3,4*; M (39)	*4*
14	*4,5*; M (14)	*1,4*; M (15)	*4*
15	*3,4*; M (13)	*3,4*; F (32)	*4*
16a	*4,4*; M (6)	*4,4*; M (19)	*4*
16b	*4,4*; M (6)		*4*
16c	*4,4*; M (10)		*4*
16d	*4,w6*; M (11)		*4*
16e*	*4,4*; F (14)		*4*
17	*4,w6*; F (6)	*4,4*; M (39)	*4*
18	*1,9*; F (9)	*1,9*; F (27)	*9*
19	*3,4*; M (13)	*3,4*; F (9)	*4*
20	*1,3*; M (6)	*1,3*; M (14)	*1*
21	*1,4*; M (18)	*4,6*; M (23)	*4*
22	*4,5*; M (10)	*3,5*; M (14)	*5*
23	*3,4*; M (3)	*4,8*; M (7)	*4*
24	*4,9*; M (5)	*3,4*; M (4)	*4*
25	*3,4*; F (12)	*1,3*; M (29)	*3*
26	*2,2*; F (6 mo)	*2,7*; F (7 mo)	*2*
27	*3,w6*; F (1)	*3,w6*; M (20)	*w6*
28	*4,7*; F (7)	*4,5*; M (25)	*4*
29	*3,4*; M (3)	*2,4*; M (29)	*4*
30	*4,4*; M (7)	*3,4*; M (13)	*4*
31	*4,4*; F (3)	*4,7*; F (31)	*4*
32	*2,4*; F (7)	*4,4*; M (9)	*4*
33	*4,5*; M (5)	*4,7*; M (46)	*4*
34	*4,7*; F (2)	*3,4*; M (35)	*4*
35	*3,4*; M (12)	*1,4*; F (31)	*4*
36a	*4,w6*; M (11)	*3,4*; M (4)	*4*
36b	*1,4*; F (17)		*4*
37	*3,4*; M (11)	*1,4*; M (36)	*4*

Numbers in parentheses indicate age in yr unless specified otherwise.

*These offspring received a haplotype containing *DR4* from the diabetic parent that is different from the one received by the other sibling(s).

percentage of *DR3*-positive diabetic parents and those with the *DR3DR4* genotype were decreased relative to the overall diabetic population [35% versus 54% *DR3*-positive ($P < 0.05$) and 22% versus 35% with the *DR3DR4* genotype ($P < 0.05$)]. The percentage of diabetic parents that were possibly homozygous for *DR4* was increased (19% versus 6%; $P < 0.02$). The frequency of homozygosity of *DR4* was also higher among the diabetic offspring of diabetic parents than among the IDDM controls (14% versus 6%; not significant) (Table 3).

The percentage of nondiabetic parents who were *DR3*-positive (38%) was intermediate between that of the general population (28%) and that of the overall IDDM population (54%), but it was not statistically different from that of either group. The percentage of *DR4*-positive nondiabetic parents (35%) was similar to that in the general population (30%). The percentage of nondiabetic parents who were neither *DR3*- nor *DR4*-positive (30%) was much higher than that in the overall IDDM population (2%), and the percentage of nondiabetic parents who were *DR4*-positive was much lower than that in the overall IDDM population (79%) ($P < 0.0001$).

DISCUSSION

The increased homozygosity for *DR4* among the diabetic parents may explain a small part of the high frequency of diabetic parents who transmitted *DR4* to their diabetic offspring, since the homozygous *DR4* individual could, of course, transmit only *DR4*. It is possible that some of these parents may have two doses of the *DR4*-associated susceptibility determinant. This idea is supported by the fact that in three of the four families with multiple affected offspring, the diabetic parent happened to be homozygous for *DR4* and transmitted different *DR4*-containing haplotypes to different offspring.

The increased homozygosity for *DR4* among the diabetic offspring (14% versus 6% of IDDM subjects) may be an indication that two doses of a *DR4*-associated determinant give greater susceptibility to IDDM than a single dose of the determinant. On the other hand, since neither the proportion of nondiabetic parents who transmitted *DR4* (22%) nor the percentage of *DR4* homozygous diabetic offspring (17%) was significantly greater than the gene frequency of *DR4* in the overall nondiabetic population (16%), it is possible that some or most of the *DR4* alleles received from the nondiabetic parents were not in linkage with a susceptibility determinant for IDDM. This idea is supported by *HLA-B* data. Both our population data and published data (16) show that "extended" *DR4* haplotypes containing *Bw60* or *Bw62* (which are also in linkage disequilibrium with *DR4* in the general population) are associated with IDDM. None of the five diabetic offspring who received *DR4* from both parents received *Bw60* or *Bw62* from the nondiabetic parent. However, 16 of the 29 diabetic parents who transmitted *DR4* to their diabetic offspring also transmitted *Bw60* or *Bw62*.

A predominance of diabetic fathers versus diabetic mothers with diabetic offspring, as was seen in the present study, has been previously noticed and discussed thoroughly (17, 18). Our data do not suggest that the transmission of *DR4* is primarily limited to diabetic fathers. Six of the eight diabetic mothers transmitted *DR4* to their diabetic offspring—a proportion that is similar to that of diabetic fathers who transmitted *DR4*.

The only slightly higher ratio of *DR4* in IDDM than *DR3* to their respective frequencies in the general population does not suggest that the mode of inheritance of the *DR3*-associated susceptibility gene is any different from that of the *DR4*-associated susceptibility gene. However, the high proportion of diabetic parents who transmitted *DR4* (78%) and the low proportion who transmitted *DR3* (8%) (Table 2) probably indicates that a single dose of a gene associated with *DR4* is capable of giving susceptibility to IDDM, as in dominant inheritance. If the inheritance of the HLA-related susceptibility to IDDM were simple recessive, it would be necessary for the nondiabetic parent to transmit the same susceptibility gene to the diabetic offspring as that transmitted by the diabetic parent. Therefore, the proportions of nondiabetic parents and diabetic parents who transmitted the *DR* allele associated with the susceptibility determinant would be similar. Since this did not occur, simple recessive inheritance can be ruled out. As mentioned above, only 22% of the nondiabetic parents transmitted *DR4*, and this proportion was not significantly different from the gene frequency of *DR4* in the nondiabetic population (16%). The fact that the

Table 2. Frequencies of *DR3* and *DR4* alleles in the general nondiabetic and IDDM populations and proportions of *DR* alleles transmitted from diabetic and nondiabetic parents to a diabetic offspring in 37 families

Allele	Allele frequency: General population (n = 158)	Allele frequency: IDDM population (n = 97)	Proportions of alleles transmitted by parents to diabetic offspring: From diabetic parent (n = 37)	From nondiabetic parent (n = 37)	Averages from parents or allele frequency in offspring (n = 37)
DR3	0.15	0.29	0.08*	0.35†	0.22
DR4	0.16	0.43	0.78‡	0.22§	0.50
DRx	0.69	0.28	0.14	0.43	0.28

*$P < 0.02$ vs. IDDM; not significant vs. general population.
†P = not significant vs. IDDM; $P = 0.02$ vs. from diabetic parent; $P < 0.005$ vs. general population.
‡$P < 0.001$ vs. IDDM; $P = 0.0001$ vs. from nondiabetic parent.
§P = not significant vs. general population.

percentage of diabetic parents who transmitted *DR4* to a diabetic offspring (78%) was very close to the percentage of subjects in the overall IDDM population who have at least one *DR4* allele (79%) is also consistent with a single dose of a *DR4*-associated susceptibility determinant being sufficient to give susceptibility to IDDM.

It is noteworthy that when *DR3* was transmitted to the diabetic offspring it was usually transmitted by the nondiabetic parent. The proportion of nondiabetic parents who transmitted *DR3* (35%) was about equal to the gene frequency of *DR3* in the overall diabetic population (29%) (Table 2). The transmission of *DR3* primarily by the nondiabetic parent and the transmission of *DR4* primarily by the diabetic parent raises the question of what is the relationship between the *DR3*-associated and the *DR4*-associated susceptibility determinants. The percentage of diabetic offspring who were positive for both *DR3* and *DR4* (35%) was identical to that of the overall IDDM population (35%), but each of these percentages was much higher than the percentage of the *DR3DR4* genotype in the overall nondiabetic population (5%) (Table 3). Since the *DR3DR4* genotype is associated with a higher relative risk for IDDM than any other phenotype (7, 8, 11–15), it is tempting to speculate that the role of the *DR3*-associated determinant is often to augment the susceptibility conferred by the *DR4*-associated determinant.

Studies of families with multiple siblings with IDDM have shown that two *HLA* haplotypes are shared by affected siblings much more often than expected (19–21). Until recently, the increased *HLA* haplotype identity in these families was taken as evidence by many investigators that a dose of an *HLA*-linked allele from each parent (which suggests classical recessive inheritance) was necessary to give susceptibility to IDDM.

Several models to explain the apparent dominant and recessive characteristics of the inheritance of IDDM have been developed (1–6, 22). The idea of dominant-like inheritance of a *DR4*-associated allele and a recessive-like and "risk-enhancing" effect of a *DR3*-associated allele partially fits some of these models. A model termed the intermediate inheritance model makes the assumption that individuals who have one dose of a diabetes susceptibility allele, as in classical dominant inheritance, are less susceptible than individuals who have two doses of the susceptibility allele as in classical recessive inheritance (23, 24). This model predicts that the inheritance of IDDM should appear to be dominant on a population basis but recessive in families with multiple affected siblings, as the increased frequency of two *HLA* haplotypes shared by affected siblings previously seemed to suggest. If one dose of a *DR4*-associated determinant is sufficient to give susceptibility to IDDM, this should resemble classical dominant inheritance on a population basis. Although two doses of either the *DR3*-associated determinant or the *DR4*-associated determinant may increase susceptibility, current evidence suggests that most individuals who have two doses of susceptibility alleles have the *DR4*-associated susceptibility determinant plus the *DR3*-associated determinant—a situation similar to recessive inheritance except that the susceptibility alleles are not identical. In fact, a study by Anderson and co-workers (25) on multiple affected siblings supports this suggestion. Their results show that the frequency of the *DR3DR4* genotype is increased among diabetic siblings who share two *HLA* haplotypes, but not among those sharing only one haplotype. Furthermore, the same study suggests that when only one *DR*-associated determinant was shared by siblings, it was the one associated with *DR4*. Neither the DR3DRx phenotype (where $x \neq 3$ or

Table 3. Percentages of subjects with a DR phenotype

Phenotype	General population (n = 158)	IDDM subjects (n = 97)	Diabetic parents (n = 37)	Nondiabetic parents (n = 37)	Diabetic offspring (n = 37)*
DR3	28	54 ($P = 10^{-4}$)†	35 ($P < 0.05$)‡	38	43
DR4	30	79 ($P = 10^{-9}$)†	81	35 ($P < 10^{-4}$)‡	86
DR3DR4	5	35 ($P = 10^{-9}$)†	22 ($P < 0.05$)‡	5	35
DR3DR3	3	5	0	3	0
DR4DR4	4	6	19 ($P < 0.02$)‡	3	14

*Only oldest offspring counted.
†Significance vs. general population.
‡Significance vs. IDDM.

4) nor the *DR3DR4* genotype was increased among sibling pairs sharing only one haplotype, but the DR4DRx phenotype was increased in this type of sibling pair.

It is noteworthy that Thomson (6) has found that when the population data on IDDM from the Eighth Histocompatibility Workshop held in 1980 are analyzed separately with respect to *DR3* and *DR4*, the *DR3* data are in agreement with recessive expectations, whereas the *DR4* data are compatible with dominant expectations. Although the *DR3*-associated determinant appears to show recessive characteristics, a single dose of *DR3* is undoubtedly associated with some risk for IDDM because, as in family 25 of the present study, *DR3* appears to be associated with the autoimmune polyendocrine syndrome type II (26, 27). IDDM in this syndrome may represent a small subset (<5%) of all cases of IDDM (27). Although the etiology is autoimmune, it may differ in some way from that of the majority of cases of IDDM.

If it is accepted that *DR3* is associated with a risk for IDDM, independent of *DR4*, then the three-allele or heterogeneity model of Rotter and co-workers (28, 29) partially fits with the current hypothesis. They proposed that there are three forms of IDDM—a form associated with *DR3*, a form associated with *DR4*, and a form associated with both alleles. Our results suggest that the two latter forms, if they are indeed very different from each other, are numerically the major forms of IDDM, which is in keeping with the predictions of Rotter and co-workers. However, since *DR3* is more often than not associated with *DR4* in IDDM and the *DR4*-associated determinant is apparently independently capable of giving susceptibility to IDDM, it is possible that the so-called form of IDDM associated with both the *DR3*- and the *DR4*-related genes should be viewed as a subset of a major form determined primarily by the *DR4*-associated susceptibility gene.

In summary, our data on families with diabetes in two generations indicate that a major IDDM susceptibility determinant is associated with *DR4* and was usually transmitted by the diabetic parent, and that another susceptibility determinant is associated with *DR3* and was usually transmitted by the nondiabetic parent, when it was transmitted at all. The determinant associated with *DR4* appears to give susceptibility independently of other susceptibility determinants, as in dominant inheritance. In light of population data and the family data reported here as well, the determinant associated with *DR3* appears to often require a second determinant for expression—either a second dose of the *DR3*-associated determinant (6) or, more often, a *DR4*-associated determinant. The *DR3*-associated determinant seems to be synergistic with the *DR4*-associated determinant (7, 8). In these respects, the *DR3*-associated determinant shows recessive characteristics. The increased expression of a disease in a mixed heterozygote (versus either single heterozygote), as in an individual with both the *DR3*- and the *DR4*-associated determinants, is reminiscent of certain genetic anemias, such as sickle thalassemia. The difference between the *DR3*- and *DR4*-associated determinants is undoubtedly one of degree and might be difficult to define with classical genetic terminology.

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