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$Gm^{3;5,13,14}$ and Type 2 Diabetes Mellitus: An Association in American Indians with Genetic Admixture

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Summary

In a sample of 4,920 Native Americans of the Pima and Papago tribes, there is a very strong negative association between the Gm haplotype $Gm^{3;5,13,14}$ and type 2—or non-insulin-dependent—diabetes mellitus (prevalence ratio = 0.27, 95% confidence interval 0.18–0.40). One might conclude from this observation that the absence of this haplotype—or the presence of a closely linked gene—is a causal risk factor for the disease. It is shown that $Gm^{3;5,13,14}$ is a marker for Caucasian admixture, and it is most likely the presence of Caucasian alleles and the concomitant decrease of Indian alleles that lowers the risk for diabetes, rather than the direct action of the haplotype or of a closely linked locus. This study demonstrates both the potential confounding effect of admixture on the interpretation of disease association studies and the importance of considering genetic admixture (or excluding individuals with genetic admixture) in studies of genetic markers of disease. The relationship between this admixture marker and the prevalence of diabetes also suggests a strong genetic component in the susceptibility to type 2 diabetes in Pima and Papago Indians.

Introduction

Many studies have attempted to find genes associated with either type 1 (insulin-dependent) or type 2 (non-insulin-dependent) diabetes mellitus. The most promising genetic system in recent years has been the HLA system (reviewed by Dausset and Svejgaard 1977; Tiwari and Terasaki 1985). Alleles HLA-DR3 and HLA-DR4 have been found to be strongly associated with type 1 diabetes, whereas modest associations with type 2 diabetes have been reported betweenHLA-A2 and HLA-B40 (Briggs et al. 1980; Serjeantson et al. 1981; Williams et al. 1981). Studies with the Gm allotype system have been inconclusive (Berg et al. 1967; Nakao et al. 1981; Schanfield et al. 1981; Adams et al. 1984; Field et al. 1984).

A number of drawbacks to disease association studies have been recognized for many years (Woolf 1955; Svejgaard and Ryder 1977). The samples of patients and controls are usually small. Antigens or alleles that are associated with the disease are usually only markers and not the disease susceptibility genes themselves. The relation between the gene and the disease is not absolute in that many patients with the disorder do not have the allele that shows the strongest association. The samples of patients and controls need to be drawn from the same ethnic population. These and many other considerations, including questions about how to compensate for multiple tests (Svejgaard et al. 1974; Smouse and Williams 1982), make the interpretation of statistically significant associations difficult.

It will be shown below, using a haplotype from the Gm system of human immunoglobulin G, $Gm^{3;5,13,14}$, that genetic admixture is another variable that can confound a disease association and lead to a false interpretation, even when the sample is very large and the statistical significance high. However, this admixture-marker plays an additional constructive role by suggesting a strong genetic component in the susceptibility to type 2 diabetes in Pima and Papago Indians.

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Subjects and Methods

The Native Americans who are the subjects of this report are participants in a longitudinal study of diabetes begun in 1965 (Bennett et al. 1971). They are drawn primarily from members of the closely related Pima and Papago tribes who live in the Gila River Indian Community in southern Arizona. All members of the study population who were at least 5 years of age were asked to participate in an examination every 2 years. After informed consent, a medical history was taken, medical records were reviewed for documentation of diabetes, and a venous plasma glucose concentration was determined 2 h after ingestion of 75 g of carbohydrate (Dexcola; Custom Laboratories, Baltimore; or Glucola; Ames, Elkhart, IN). Diabetes was diagnosed, according to World Health Organization (1985) criteria, if the 2-h postload plasma glucose was at least 11.1 mmol/liter (200 mg/dl) at any survey examination or if the Indian Health Service hospital serving the community found a fasting, postprandial, or 2-h postload glucose concentration of at least 11.1 mmol/liter during the course of routine medical care (Knowler et al. 1978).

The fraction of Indian heritage (in eighths) was determined for each subject from personal testimony and data on relatives. This index of heritage is probably very accurate, as evidenced by close agreement with admixture estimates based on Gm marker data (Williams et al. 1986). The analysis was restricted to subjects having either (*a*) only Pima, Papago, or non-Indian heritage (*b*) or a heritage that was a combination of only these three groups. Subjects with any known degree of heritage from other tribes were excluded. The non-Indian heritage in this community is almost all of Caucasian origin (Williams et al. 1985).

Gm allotypes were determined by standard methods (Steinberg 1962; Steinberg and Cook 1981). For each subject, the genotype with respect to $Gm^{3;5,13,14}$ was determined. According to the presence of the $Gm^{3;5,13,14}$ phenotype and the presence of any other Gm specification, each subject was classified as having 0, 1, or 2 $Gm^{3;5,13,14}$ haplotypes. The prevalence of diabetes was analyzed in relation to the prevalence of $Gm^{3;5,13,14}$, i.e., the prevalence of persons who had at least one copy of the haplotype. The prevalence rates of diabetes and of $Gm^{3;5,13,14}$ were stratified by age and fraction of Indian heritage; summary statistics for the stratified analysis were computed by the procedure of Mantel and Haenszel (1959). A summary prevalence rate ratio with a 95% confidence interval was computed for an overall estimate of the prevalence rate ratio (prevalence of diabetes in those with $Gm^{3;5,13,14}$ divided by the prevalence in those without this haplotype; Knowler et al. 1978), and the test for homogeneity of Breslow and Day (1980, pp. 173–176) was used to test whether the strength of the association between diabetes and $Gm^{3;5,13,14}$ differed significantly between the different strata. Age-adjusted prevalence rates and their standard errors were computed by the direct method (Knowler et al. 1978), using as the standard the 1980 U.S. Census population aged 15 years and over.

Results

The genotype frequencies of the 4,920 subjects are shown in table 1 according to the fraction of Indian heritage, in eighths. The majority of subjects (99%) were at least half Indian heritage. Only 15 (0.3%) were homozygous for $Gm^{3;5,13,14}$, and all but two of these were in the 0–2-eighths Indian classes. Because of the extremely small size of this homozygous class, and because of the virtual absence of such homozygotes among

Table 1

Distribution of $Gm^{3;5,13,14}$ Haplotype Frequencies According to Indian Heritage in Residents of the Gila River Indian Community

No. of $Gm^{3;5,13,14}$ Haplotypes	Indian Heritage (Eighths)									
	0	1	2	3	4	5	6	7	8	Total (%)
0	11	0	4	19	199	4	72	123	4,195	4,627 (94.0)
1	14	0	8	4	144	0	27	13	68	278 (5.7)
2	7	0	6	0	1	0	0	0	1	15 (.3)
Total	32	0	18	23	344	4	99	136	4,264	4,920 (100.0)

Table 2

Association Between Diabetes and the Haplotype $Gm^{3;5,13,14}$ Among Residents of the Gila River Indian Community—No Restrictions on Age or Fraction of Indian Heritage

$Gm^{3;5,13,14}$	No. of Subjects	No. (%) with Diabetes
Present	293	23 (8)
Absent	4,627	1,343 (29)

NOTE.—Diabetes was inversely associated with the haplotype $Gm^{3;5,13,14}$ (χ^2 = 61.6; df = 1; $P < .001$). Prevalence ratio = 0.27 (95% confidence interval = 0.18–0.40).

the half-to-full-heritage Indians, they were combined with the heterozygous class in subsequent tables and figures. There was a strong inverse association between diabetes and presence of the haplotype $Gm^{3;5,13,14}$ in the sample of 4,920 subjects considered without regard for age or fraction of Indian heritage, as shown in table 2 (prevalence ratio = .27, 95% confidence interval = 0.18–0.40). This association was seen regardless of age, in that in each age group the prevalence of diabetes was lower in those individuals with the $Gm^{3;5,13,14}$ haplotype (fig. 1). Controlled for age, the prevalence of diabetes in subjects with $Gm^{3;5,13,14}$ was 0.53 times (95% confidence interval = 0.39–0.72) that of subjects without the haplotype. The test for homogeneity of the association between strata (χ^2 = 0.7; df = 4; not significant) indicates the results are compatible with a uniform association over all age groups.

The effect of Indian heritage on this association is examined in table 3, in which age-specific and age-adjusted prevalence rates of diabetes are shown in each category of Indian heritage in both those with and those without $Gm^{3;5,13,14}$. The age-adjustment computations for the heritage classes (the columns of table 3) were limited to classes 0, 4, and 8 eighths and for ages 15 years and above, because the computation requires that there be no empty cells for any ages in the set. To avoid creating more empty data cells, the data were not stratified by sex. Sex did not need to be considered as a potential confounding variable, as it was unrelated to Gm type within heritage classes (data not shown). There was a large effect of Indian heritage, with higher age-adjusted prevalence rates in the groups with greater Indian heritage, but virtually no effect of $Gm^{3;5,13,14}$ within Indian heritage strata. Controlled for age and Indian heritage, diabetes and $Gm^{3;5,13,14}$ were not

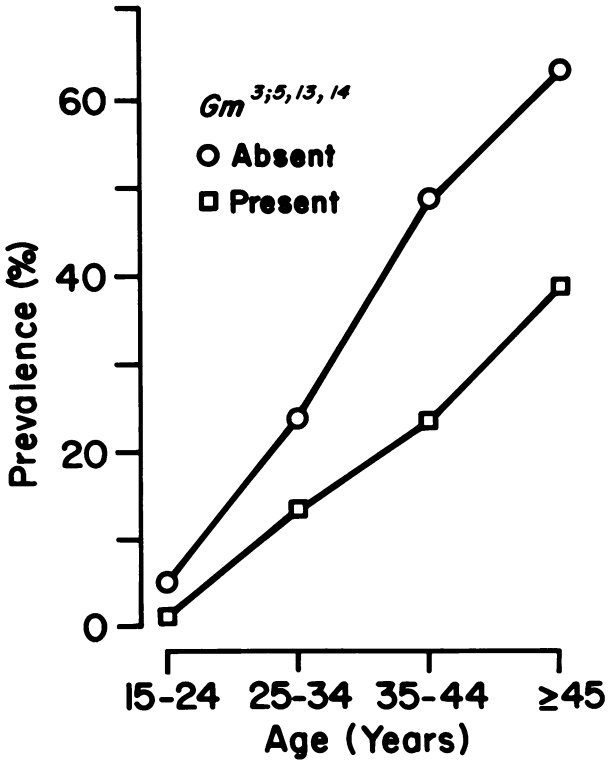

Figure 1 Prevalence of diabetes by age and the presence of the haplotype $Gm^{3;5,13,14}$ among residents of the Gila River Indian Community.

significantly associated (summary χ^2 = 1.08). Comparing those with to those without the haplotype, the age heritage–adjusted prevalence ratio was 0.83 (95% confidence interval = 0.58–1.18). The test for homogeneity of the association between strata (χ^2 = 12.1; df = 15; not significant) indicates the results are compatible with a uniform lack of association over all age-heritage groups. For the three heritage classes with complete data, figure 2 shows the direct relationship of Indian heritage on diabetes prevalence (regardless of Gm phenotype) and the lack of effect of Gm phenotype, within heritage classes, on diabetes prevalence. The lack of association is clearly seen in table 4, which is restricted to subjects of full Indian heritage and of at least 35 years of age. In this group of 1,781 subjects, in whom there was no confounding by Indian heritage or age, diabetes was unrelated to the presence of $Gm^{3;5,13,14}$, occurring in 59% of those with and in 60% of those without the haplotype (χ^2 = 0.01; df = 1; not significantly different).

Table 3

Prevalence of Diabetes (D%) According to Indian Heritage, Age, and Presence of $Gm^{3;5,13,14}$ Haplotype

Age (years) and $GM^{3;5,13,14}$ Status	Indian Heritage (Eighths)															
	0		2		3		4		5		6		7		8	
	N	D%	N	D%	N	D%	N	D%	N	D%	N	D%	N	D%	N	D%
5–14:																
Present	0	–	6	.0	0	–	47	.0	0	–	8	.0	7	.0	19	.0
Absent	0	–	3	.0	5	.0	80	.0	2	.0	20	.0	39	2.6	589	.7
15–24:																
Present	3	.0	8	.0	3	.0	70	2.9	0	–	13	.0	4	.0	20	.0
Absent	1	.0	1	.0	12	.0	92	1.1	0	–	23	.0	46	10.9	1,092	5.3
25–34:																
Present	3	66.7	0	–	1	.0	17	5.9	0	–	2	.0	0	–	13	15.4
Absent	5	.0	0	–	2	.0	15	13.3	2	.0	7	28.6	29	24.1	750	24.5
35–44:																
Present	4	.0	0	–	0	–	6	16.7	0	–	4	.0	1	.0	6	50.0
Absent	1	.0	0	–	0	–	5	20.0	0	–	13	30.8	9	33.3	503	50.3
≥45:																
Present	11	9.1	0	–	0	–	5	60.0	0	–	0	–	1	.0	11	63.6
Absent	4	50.0	0	–	0	–	7	57.1	0	–	9	77.8	0	–	1,261	63.8
Age adjusted:																
Present		17.8		–		–		28.3		–		–		–		35.9
Absent		19.9		–		–		28.8		–		–		–		39.3

Discussion

One might conclude from the data presented in table 1 and figure 1 that the absence of $Gm^{3;5,13,14}$—or the presence of a closely linked gene—was a causal risk factor for type 2 diabetes. This conclusion, however, is probably incorrect, because it ignores the confounding effect of genetic admixture.

Published reports of the distributions of Gm antigens in Pima, Papago, and other Native-American tribes demonstrate that the Gm haplotype $Gm^{3;5,13,14}$ is a very sensitive marker for Caucasian admixture in American Indians (Williams et al. 1985, 1986). The $Gm^{3;5,13,14}$ haplotype has a very low frequency among full-heritage Pima and Papago Indians (.006 in each tribe and .013 among those of mixed Pima-Papago ancestry; Williams et al. 1985) but a frequency of .665 in Caucasians in the United States (Reed 1969). In addition, the utility of $Gm^{3;5,13,14}$ as an admixture marker is supported by its strong correlation with Indian heritage based on personal testimony (table 1; and Williams et al. 1986).

This explains the low prevalence of $Gm^{3;5,13,14}$ when the sample is restricted to full-heritage Indians (table 4). The risk of diabetes varies inversely with the amount of Caucasian admixture, and the $Gm^{3;5,13,14}$ haplotype serves as an indicator of this admixture. This is illustrated in figure 3, which presents data on age-sex-adjusted prevalence of diabetes and $Gm^{3;5,13,14}$ as a function of Indian heritage. As the fraction of Native-American genes increases, the prevalence of diabetes increases while that of $Gm^{3;5,13,14}$ decreases.

The results of disease associations must be interpreted with care, even when the samples are large and the statistical significance is high. In the present case it was possible to define the role of $Gm^{3;5,13,14}$ only because there existed a variable, i.e., admixture, that is not usually considered in population reports. In the absence

Table 4

Association Between Diabetes and $Gm^{3;5,13,14}$ Among Full-Heritage Pima-Papago Indians *Aged* ≥ 35 Years

$Gm^{3;5,13,14}$ Status	No. of Subjects	No. (%) with Diabetes
Present	17	10 (59)
Absent	1,764	1,058 (60)

Note.—Diabetes was not significantly associated with $Gm^{3;5,13,14}$ ($\chi^2 = 0.01$; df = 1; not significant). Prevalence ratio = 0.98 (95% confidence interval = 0.66–1.46).

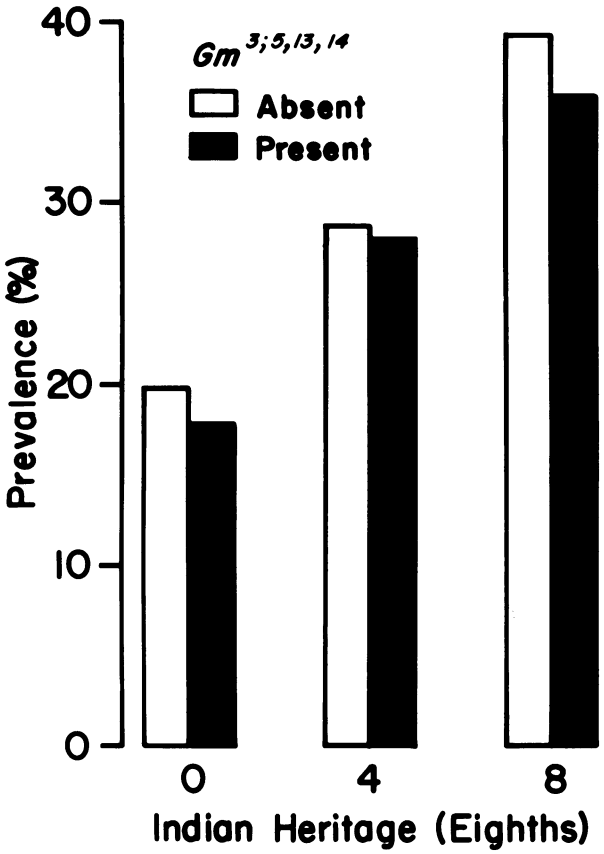

Figure 2 Age-adjusted prevalence of diabetes by the presence of the haplotype $Gm^{3;5,13,14}$, according to Indian heritage, among residents of the Gila River Indian Community.

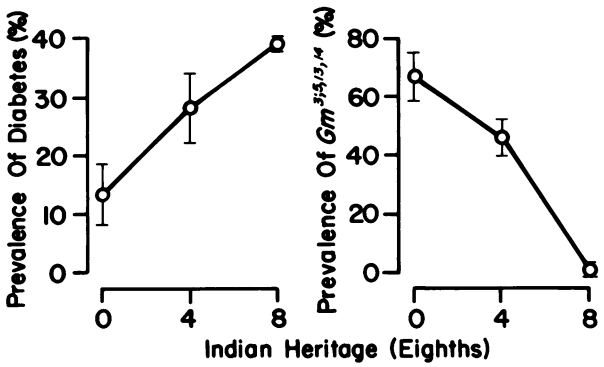

Figure 3 Age-adjusted prevalence (±1 standard error) of diabetes (left) and of $Gm^{3;5,13,14}$ (right), according to Indian heritage, among residents of the Gila River Indian Community.

of additional information such as this, genetic admixture in the sample could confound disease-association studies and lead to an incorrect interpretation of the results. To avoid such errors, either genetic admixture must be considered in genetic marker studies or such studies should be performed in relatively homogeneous populations.

Our conclusions are consistent with previous findings that prevalence rates of several diseases, including type 2 diabetes, vary with ethnicity. Even within a single population of mixed heritage, disease prevalence can vary with the amount of admixture from various sources. This phenomenon was described by Drevets (1965), who determined age-specific prevalence rates of known diabetes in two groups of Choctaw Indians in Oklahoma: 1,993 thought to be of full Choctaw heritage and 1,572 of mixed heritage. From the published age-sex-specific diabetes prevalence rates, we computed the age-sex-adjusted prevalence ratio as 1.9 (95% confidence interval 1.2–3.0) for full-heritage compared with mixed-heritage Choctaws. Similarly, in the Micronesian population of Nauru, genetic factors were thought to play an important role in diabetes, which was much less prevalent in those with foreign admixture detected by HLA typing (Serjeantson et al. 1983). Among Mexican-American residents of San Antonio, the prevalence of diabetes was related to area of residence in the city, which in turn was related to the amounts of American-Indian and Caucasian heritage estimated by skin color (Gardner et al. 1984). However, no direct relationship between the prevalence of diabetes and the amount of American-Indian heritage was demonstrated. Furthermore, individual admixture estimates, derived from typing 16 systems, were not related to the prevalence of diabetes in the study of Mexican-Americans in Starr County, TX (Hanis et al. 1986). The authors of the latter report concluded that unless the genetic markers used for admixture estimates are directly related (such as by linkage) to the disease of interest, the admixture estimates will probably not be related to disease risk.

The possibility that admixture could create a spurious disease-marker association was raised in a report of associations of type 2 diabetes with RH blood group and haptoglobin phenotype distributions in Mexican-Americans in San Antonio (Stern et al. 1986), although the authors of that report believed linkage disequilibrium with a diabetes-susceptibility gene was a more likely explanation for the association. In a subsequent analysis of the data, those authors concluded that the difference in allele frequencies reflected more general genetic diversity between diabetic and nondiabetic sub-

jects, rather than a direct causal association (Chakraborty et al. 1986).

In contrast to the earlier reports, we found a strong association between diabetes and a genetic marker and demonstrated that it arose from genetic admixture. We believe these findings were due to the use of the haplotype $Gm^{3;5,13,14}$, which is an excellent marker for Caucasian admixture in American Indians (Williams et al. 1986).

Although a direct role of Gm type in diabetes susceptibility is very unlikely, the present findings do suggest a strong genetic component in type 2 diabetes in Pima and Papago Indians. On the basis of family data and an association with HLA type, a genetic component in diabetes in the Pima Indians has been postulated (Williams et al. 1981; Knowler et al.1983). The relationship between diabetes and genetic admixture, as measured by the haplotype $Gm^{3;5,13,14}$, argues for the existence of such a component. Although this finding could be due to environmental or cultural effects, we believe a more likely explanation is that subjects with more non-Indian alleles had a lower probability of having the diabetogenic genotype. The results do not indicate the mode of inheritance of diabetes in this population, and, as demonstrated theoretically by Chakraborty and Weiss (1986), the quantitative relationship of disease frequency to amount of admixture in a hybrid population depends on the mode of inheritance and the number of susceptibility genes. Despite the lack of evidence for the location of the diabetogenic gene or genes, the present findings of an association of the disease with genetic admixture provides strong evidence for genetic susceptibility to type 2 diabetes.

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