# Hypothesis:
# The Frequencies of Juvenile Diabetes in American Blacks and Caucasians Are Consistent with Dominant Inheritance

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**SUMMARY**

**A test is described that can be used to distinguish whether a trait (in this case juvenile diabetes) is inherited in an autosomal dominant or a recessive manner. The frequencies of the trait are compared in two populations in which there has been a unidirectional influx of genes from the gene pool of one of the populations into that of the other. Before the racial admixture, the trait should be primarily a characteristic of the first population. If the trait is dominant, its frequency in the second population will be equal to the number of individuals carrying at least one gene causing the trait and thus directly proportional to the overall percentage of its genes received from the first population. If the trait is recessive, its frequency in the second population, relative to that in the first, will be far lower than the overall percentage of its genes received from the first population, because the rate of homozygotes is equal to the square of the gene frequency. The American Caucasian and black populations fulfill the criteria for the test. Racial admixture between the two groups has been entirely from the Caucasian to the black population, and juvenile diabetes was very likely nonexistent in black people before their arrival in North America. About 20% of the American black gene pool is composed of Caucasian genes and the frequency of juvenile diabetes in the American black population is 20%–30% that in American Caucasians. Because juvenile diabetes in American blacks is associated with the same HLA genes as in Caucasians, and these genes are also about 20%–30% as common in American blacks as in Caucasians, the occurrence of juvenile diabetes in American blacks is very likely due to Caucasian genes. If susceptibility to juvenile diabetes is inherited in a recessive manner, its frequency in black Americans should be about $(1/5)^2$ or 1/25 the frequency in Caucasians. However, since the ratio of the frequency of juvenile diabetes in American blacks to that in Caucasians is roughly equal to, or certainly not lower than, the fraction of Caucasian genes in the American black gene pool, the data fit the criterion for dominant better than for recessive inheritance. Because population data are used in the test, factors that confound genetic studies in families, such as incomplete penetrance and recombination should not confound this test.**

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Because the causation of insulin-dependent, juvenile-onset diabetes probably involves environmental as well as hereditary factors,[1–5] it has not been easy to determine its mode(s) of inheritance. In addition, there might be genetic heterogeneity within the syndrome.[6–8] Recently, it was discovered that juvenile diabetes is associated with the HLA complex on chromosome number 6.[9] Several investigators have attempted to use this association to determine whether the susceptibility to juvenile diabetes is inherited in an autosomal recessive or dominant manner by measuring the percentages of pairs of diabetic siblings who shared HLA haplotypes (0, 1, or 2 haplotypes) in families in which more than one offspring was a juvenile diabetic. In all the studies it was found that the frequency of pairs of diabetic siblings with two identical haplotypes was 50%–60%, which was higher than expected by chance.[10–14] (If juvenile diabetes is not linked to the HLA complex, about 25% of the pairs would have shared two haplotypes). Although this result demonstrated that genes associated with juvenile diabetes are indeed linked to genes in the HLA complex, it did not yield clear interpretations about the inheritance of diabetes. If the genes associated with juvenile diabetes are tightly linked to the HLA complex, 100% of the pairs of diabetic siblings should have shared two haplotypes if juvenile diabetes is recessive; if it is dominant, 50% of the pairs should have shared two haplotypes. (See Appendix I.) These proportions do not depend on the penetrance of the genes giving susceptibility to diabetes since, in the cases studied, penetrance was essentially complete, i.e., the subjects studied

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obviously had the genes giving susceptibility to juvenile diabetes. If the genes causing susceptibility to juvenile diabetes are not closely linked to the HLA complex, such that there was recombination between these genes and the HLA complex, the proportion of sibling pairs sharing two haplotypes would have been lower than 100% if diabetes is recessive and lower than 50% if it is dominant. (To determine how much lower, the amount of recombination and the mode of inheritance must be known.) If diabetes is recessive, a high rate of homozygous but unaffected parents could also explain a lower than expected percentage of shared haplotypes, but as noted by Spielman et al.,[14] this explanation is not very plausible. The interpretation involving the fewest assumptions is, of course, that the studies of HLA haplotypes in pairs of diabetic siblings indicate that the inheritance of susceptibility to juvenile diabetes is dominant. However, due to our current lack of knowledge of the genetics of diabetes, other more complex interpretations of these HLA data cannot be excluded.[6]

Besides studies of families, population data can be used to distinguish whether a trait is autosomal dominant or recessive. In the test discussed here the frequency of the trait is compared in two populations in which there has been a unidirectional influx of genes from the gene pool of one of the populations into that of the other. If the disorder was almost nonexistent in the second population before the influx of genes, the test is more rigorous. If the trait is autosomal dominant, its frequency in the second population will be equal to the number of individuals carrying at least one gene causing the trait and thus directly proportional to the overall number of genes received from the first population. If the trait is inherited in an autosomal recessive manner, its frequency in the second population, relative to that in the first, will be far lower than the overall percentage of its genes received from the first population, since the rate of homozygotes is equal to the square of the gene frequency as predicted by the Hardy-Weinberg law. If the trait depends on the simultaneous presence of two or more genes, even if they are dominant, or if the trait is quasicontinuous (multifactorial with a threshold), this would in most cases mimic recessive inheritance by the criterion employed here.* That is, the frequency of the trait will be equal to the product of the frequencies of the individual genes and also far lower in the second population than in the first.

The American Caucasian and black populations fulfill the criteria for this test. Racial admixture between the two groups has been entirely from the Caucasian to the black population and juvenile diabetes was very likely nonexistent in black people before their arrival in North America. The data indicate that most cases of juvenile diabetes are inherited in a dominant manner. The information important to this argument follows:

1. Idiopathic juvenile-onset, insulin-dependent diabetes is extremely rare in blacks in western Africa,[15–21] where 99% of the American black slaves originated,[22] as it is in all populations in which there has been no admixture of genes from Caucasians.[23,24] When insulin-dependent diabetes is found in western Africa, it is often associated with pancreatitis with pancreatic calcifications visible on x-rays,[20,21] characteristics not associated with juvenile diabetes in Caucasians.

2. More than 15 studies of blood groups show that an average of 20% of the genome of black Americans is composed of genes received through racial admixture during the last three and one-half centuries (for a review, see ref. 22).

3. In surveys in which the rates in both ethnic groups were determined concomitantly, the frequency of insulin-dependent, juvenile-onset diabetes among black Americans was no lower than 20%–30% of the frequency of juvenile-onset diabetes among white Americans,[25–29] and estimates ranged as high as 50%.[28,29]

4. The HLA genes DW3 and DW4, which are the ones most strongly associated with juvenile diabetes in Caucasians, are also increased among American black juvenile diabetics. About 50%–60% of Caucasian juvenile diabetics are DW3 and about 40%–50% are DW4.[30,31] About 75% of black juvenile diabetics are DW3 and about 40% are DW4.[32,33] In the general Caucasian population about 20%–30% are DW3 or DW4[30,31] and 7%–14% of the general black American population are DW3 or DW4.[32,33] The frequencies of the HLA genes A1, A2, B8, B15, and CW3 that are in linkage disequilibrium with either DW3 or DW4 in Caucasians[34] have also been found to be increased in black juvenile diabetics,[32,35] but to a lesser extent than DW3 or DW4, as is the case in white juvenile diabetics.[9,13,30,36]

5. The frequencies of the HLA genes A1, A2, B8, B15, DW3, and DW4 in nondiabetic blacks in the United States are about 20%–30% of those in nondiabetic Caucasians.[30,32,37,38] Therefore, these antigens may be in part, or predominately, of Caucasian origin.

The case-finding procedures used in the studies in which almost no juvenile-onset diabetics were found among blacks in western Africa[14–20] seem adequate. There is virtually no juvenile-onset diabetes among blacks in western Africa, but juvenile-onset diabetes occurs among blacks in the United States, whose gene pool has been diluted significantly with Caucasian genes. These findings suggest that the occurrence of juvenile-onset diabetes among black Americans is the result of the admixture of Caucasian genes, which cause a susceptibility to the disease. The associations of juvenile diabetes in blacks with HLA genes that are also associated with the disorder in Caucasians (and that may well be of Caucasian origin) are good evidence that the genetic components of juvenile-onset diabetes in the two ethnic groups are similar.

According to the studies referred to above and the experience of physicians who see juvenile diabetics in areas of the United States where there are large concentrations of blacks, the ratio of the frequency of juvenile-onset diabetes in American blacks to the frequency in American whites is roughly equal to, or certainly not lower than, the fraction of Caucasian genes in the American black gene pool, i.e., about one-fifth to one-third. If susceptibility to juvenile-onset diabetes is inherited in an autosomal recessive manner, the frequency of the disorder in black Americans should be far lower than this, i.e., about $(1/5)^2$ or 1/25 the frequency in whites.

Recent estimates of the frequency of juvenile-onset diabetes in American Caucasian children range from about 1/600 to 1/1,500.[27–29,39] Choosing the average value of about

* This statement is true for most patterns of inheritance except in uncommon types of epistasis, e.g., such that two or more genes are required for the expression of juvenile diabetes and the black genome contained all these genes except one that was a Caucasian gene.

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1/900 for the calculations, then if susceptibility to juvenile diabetes is autosomal recessive, the gene frequency in Caucasians is equal to $\sqrt{1/900} = 1/30$. Assuming that 1/5 of the black American gene pool is composed of Caucasian genes, the frequency of the gene causing diabetes in blacks should be $1/30 \times 1/5 = 1/150$ and the frequency of juvenile-onset diabetics in blacks should be equal to $(1/150)^2$ or about 1 in 22,500 (or 900/22,500 that in whites).

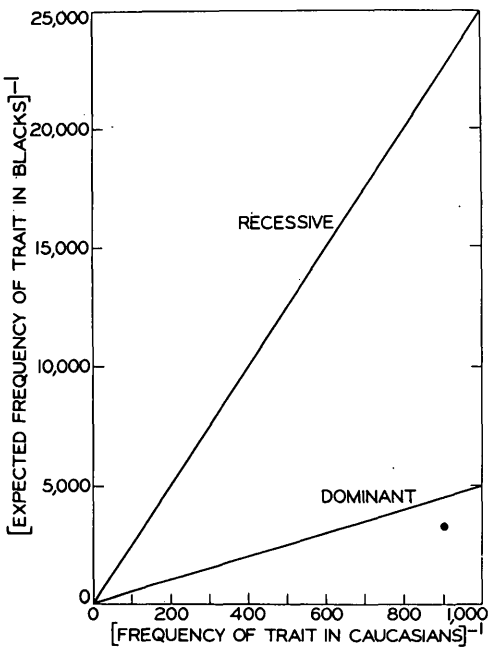
If juvenile-onset diabetes is inherited as an autosomal dominant disorder, the frequency of Caucasians who have a gene that causes the disorder is equal to the frequency of the disorder, and the frequency of the disorder in blacks will be merely one-fifth that in Caucasians or about 1/4,500.

Figure 1 shows the expected frequencies in American blacks of traits inherited from Caucasians should the traits be due to a gene at a single locus and inherited in autosomal dominant or recessive manners. The single point in the figure represents the lowest estimate of juvenile diabetes in American blacks and shows that the frequencies of juvenile diabetes in blacks and Caucasians fit the criterion predicted for dominant far better than that for recessive inheritance.

Contrasting the frequency of juvenile diabetes in blacks with that of cystic fibrosis, a disorder known to be autosomal recessive,[40] supports the idea that juvenile diabetes is not inherited in an autosomal recessive manner. Cystic fibrosis is far less common among American blacks than among American whites. Even though the reporting of cases of cystic fibrosis in blacks has been increasing, it still appears to be 10 to 30 times less frequent among American blacks than among whites.[41,42]

Since the concordance for juvenile diabetes in monozygotic twins is 50% or lower,[2] the gene that causes juvenile diabetes must be incompletely penetrant and therefore environmental factors must play a role in the causation of juvenile diabetes. In the calculations shown above, taking incomplete penetrance into consideration would increase the calculated gene frequencies to the same extent in blacks and whites, but it would not alter the calculated frequencies of the disorder in blacks or whites in either the model for recessive or dominant inheritance. In calculating the frequencies of the disorders, a penetrance factor would be canceled out. For example, if the penetrance was 50%, the calculated frequency of individuals possessing a susceptible genotype would be doubled, but only one-half would have the disorder. If penetrance, for example because of a higher rate of contact with a specific environmental agent that leads to juvenile diabetes, is much higher in the American black than in the American Caucasian population, recessive inheritance might simulate dominant inheritance in the proposed model. Whether this situation might exist is simply unknown at present. The similar frequencies of specific HLA types associated with juvenile diabetics in the two ethnic groups suggest that the amount of genetic influence on the expression of the disorder in both groups is similar. The majority of cases of diabetes in American black children and adolescents are clinically identical to those in whites, with ketosis and an insulin requirement.[26]

**FIGURE 1. Expected frequencies of traits in American blacks inherited from Caucasians should the inheritance be autosomal recessive or dominant. To calculate the expected frequencies of traits in blacks, the frequency of genes of Caucasian origin in the gene pool of American blacks was taken as 20%.[22] The single point represents the frequency of juvenile diabetes in Caucasians (averaged from values given in refs. 27–29 and 39) and the lowest estimate found for the frequency of juvenile diabetes in American blacks, 0.28 that in whites (taken from ref. 26).**




Nerup et al.[30] and Rotter and Rimoin[7] have suggested that there is some evidence for heterogeneity within juvenile diabetes on the basis of different clinical pictures associated with antigens B8 and B15 in Caucasian juvenile diabetes. They find in juvenile diabetics an association of HLA gene B8 with coexistent autoimmune phenomena, such as Hashimoto's thyroiditis or Addison's disease, and antibodies to various endocrine organs, including pancreatic islets. They find another association between HLA B15 in cases of juvenile diabetes not associated with autoimmune phenomena. B8 and B15 are less strongly associated with juvenile diabetes than are DW3 and DW4. It is likely that B8 and B15 are associated with diabetes because, in Caucasians, they are in linkage disequilibrium with DW3 and DW4, respectively.[34,36,43] Even if juvenile diabetes associated with DW3 is considered as a separate disorder from juvenile diabetes associated with DW4, the frequency of cases associated with either antigen in blacks is too high to indicate recessive inheritance.[32,33,43] It should be noted, however, that although many geneticists believe that there could be heterogeneity in the causation of juvenile diabetes, many also regard heterogeneity as currently unproven. Arguments have been advanced that there is no convincing evidence for more than one juvenile diabetes susceptibility allele associated with the HLA complex and that a single susceptibility allele could be associated with both Dw3 and Dw4.[44,45]

To summarize, population data indicate that the gene(s) giving susceptibility to juvenile diabetes is (are) dominantly inherited, so 50% of first degree relatives of juvenile diabetics should be genetically susceptible. The low frequencies (5–15%) of affected first degree relatives of juvenile diabetics[46,47] can be accounted for by incomplete penetrance, possibly caused by lack of contact with, or acquired resistance to, the putative environmental factors that cause juvenile diabetes in genetically susceptible individuals. This concept, even though based on current information,

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is at best an hypothesis. Whether it will eventually be elevated to the status of theory will depend on the outcome of studies with better markers for juvenile diabetes.

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**APPENDIX I**

If the gene for juvenile diabetes is closely linked to the HLA locus, the expectations for HLA types among affected sibs is as shown below. D or d designates the diabetes gene, according to whether it is dominant or recessive; + indicates the normal allele; and w, x, y, and z designate HLA haplotypes.

| | Dominant | | Recessive | |
|---|---|---|---|---|
| Parents | $\frac{D\ w}{+\ x} \times \frac{+\ y}{+\ z}$ | | $\frac{d\ w}{+\ x} \times \frac{d\ y}{+\ z}$ | $\frac{d\ w}{+\ x} \times \frac{d\ w}{+\ z}$ |
| Diabetic offspring | $\frac{D\ w}{+\ y}$ | $\frac{D\ w}{+\ z}$ | $\frac{d\ w}{d\ y}$ | $\frac{d\ w}{d\ w}$ |

If the trait is dominant, half the offspring will have identical HLA types; if recessive, all will have identical HLA types. These proportions will be reduced if there are recombinants, which will be rare if the loci are closely linked. The number of HLA haplotypes is large enough so that almost always all four haplotypes in the two parents will be different. The pattern on the extreme right shows a case in which the parents have one identical haplotype. Note that these expected proportions do not depend on the penetrance of the diabetes gene.

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