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Recessive Inheritance of the Adult Type of Intestinal Lactase Deficiency

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The question of adaptive versus genetic etiology of the adult type of intestinal lactase deficiency seems to be fairly well answered by Sahi et al. [1] who present good evidence favoring the genetic hypothesis. We describe here the results of family studies performed in Mexico which corroborate that the inheritance of this enzyme deficiency is controlled by a single recessive autosomal gene. This corroboration is particularly important because the studies were performed in an ethnic group where lactase deficiency is frequent [2, 3], which was not the case in the previous report.

MATERIALS AND METHODS

A total of 61 families with 177 children over 6 years of age were investigated. They were studied in Mexico City and several neighboring villages. All volunteered for the study and were not informed of its objective until completion of the tests so that milk drinking habits or intolerance symptoms would not influence the decision to cooperate in the investigation. The requisite to enter the study was that both parents participate and that they have at least one child older than 6 years of age. Children under 6 were excluded. Care was taken to omit individuals with chronic or acute diarrhea at the time of the test.

To detect the presence of lactase deficiency, the lactose tolerance test was performed after an overnight fast. Each subject was given a dose of lactose, equal to 2 g/kg of body weight, except that those over 25 kg received a standard dose of 50 g. Lactose was dissolved in a glass of water. Capillary samples were taken for blood glucose estimation before and 15 and 30 min after the lactose load. The criterion for lactase deficiency was a maximum blood glucose rise of less than 20 mg/100 ml. When the blood glucose rise was between 20 and 25 mg/100 ml (found in six subjects), the presence of explosive diarrhea within 6 hr of performing the test was taken as indicative of deficiency. The usefulness of this technique has been studied previously [2, 4, 5]. Snyder's ratios [6] were used to analyze the data.

RESULTS

Table 1 shows observed and expected numbers for each mating type under the assumption that the deficient state represents homozygosity for an autosomal recessive gene *a* with a frequency of .8777 in this population. This figure is the

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TABLE 1

OBSERVED AND EXPECTED NUMBERS UNDER ASSUMPTION OF AUTOSOMAL RECESSIVE GENE

MATING	No. FAMILIES	THEORETICAL GENOTYPES (♂ × ♀)	OFFSPRING: Normal Obs.	Normal Exp.	Deficient Obs.	Deficient Exp.	χ^2	P (1 df)
Normal × normal	3	*AA* × *AA* *AA* × *Aa* *Aa* × *AA* *Aa* × *Aa*	7	7.1	2	1.9	0.01	>.9
Normal × deficient or deficient × normal	22	*AA* × *aa* *Aa* × *aa* *aa* × *AA* *aa* × *Aa*	30	38.3	42	33.7	3.84	~.05
Deficient × deficient	36	*aa* × *aa*	4	0.0	92	96.0	...	...
Total	61	...	41	45.4	136	131.5	0.54	>.3

NOTE.—See text for method of calculating expected numbers.

square root of the proportion of deficient individuals (94/122 = 77.0%) found in the parental population. The expected numbers were calculated using the above gene frequency and considering all possible genotypes present in each of the matings (table 1). Comparison was made between observed and expected individuals among the offspring using the χ^2 test, except for the deficient × deficient matings, where the test cannot be applied because the expected number of normal individuals is zero.

DISCUSSION

Data supporting the adaptive etiology of the adult type of lactase deficiency are mainly based on animal experiments [7], while data supporting a genetic etiology are based on (1) differences in its prevalence in different population groups [8]; (2) similarities in its prevalence in the same ethnic group living in different habitats [8]; (3) results from a study of three isolated families [9, 10]; and (4) the recent work of Sahi et al. [1] in which genetic analysis of several families gave strong evidence that this deficiency is due to homozygosity for a single recessive autosomal gene. The data here presented, showing no significant differences between observed and expected phenotypes among the offspring (table 1), except for the deficient × deficient matings, support the hypothesis that the deficient state is controlled by an autosomal gene pair.

It may be argued that the gene frequency used to estimate the expected phenotypes is not correct, since the group studied is not really a single population. However, when gene frequencies obtained for other groups in Mexico [2, 3] are used, the results are essentially identical. A major discrepancy is that in the deficient ×

deficient matings four of 96 individuals were found to have adequate enzyme levels. Two explanations are possible: (1) the technique used may, for several reasons, not be sensitive enough to properly classify all individuals; and (2) nonpaternity is a possibility. The first explanation is a likely one since glucose measurements were made using a field reflectometer, and we have shown previously [2] that this gives up to 5% false positive results compared to those obtained using the autoanalyzer. Thus four false positive cases among the 96 offspring of deficient × deficient matings is within this range. Similarly, the excess of deficient individuals from normal × deficient matings could be partially due to misclassification of some deficient parents as normal in this group. The possibility of misclassification or nonpaternity in the four critical cases was not investigated because the individuals involved, all living in a very small village 60 miles from Mexico City, refused further participation. In spite of this drawback, we feel that the data support the contention that this trait is inherited in a simple Mendelian fashion.

SUMMARY

In order to investigate the genetic control of the adult type of intestinal lactase deficiency, 61 families with 177 children over 6 years of age were investigated. The results strongly suggest that this deficiency is inherited as a simple Mendelian recessive trait.

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