Glucose-6-Phosphate Dehydrogenase Deficiency in Taiwan

TING-CHIEN LEE,[1] LING-YU SHIH,[1] PAI-CHI HUANG,[1]
CHI-CHUH LIN,[1] BOON-NAM BLACKWELL,[2]
R. QUENTIN BLACKWELL[2] AND DAVID YI-YUNG HSIA[3]

[1]*Department of Pediatrics, College of Medicine, National Taiwan University, Taipeh, Taiwan*
[2]*Namru-2, Taipeh, Taiwan*
[3]*Genetics Clinic, Children's Memorial Hospital and Department of Pediatrics, Northwestern University Medical School, Chicago, Illinois*

GLUCOSE-6-phosphate dehydrogenase (G-6-P.D.) deficiency is recognized to exist with relatively high frequency among several ethnic groups, notably Negroes and Caucasians of Mediterranean origin including Sardinians and Sephardic Jews (Motulsky, 1960). Relatively few reports have been made concerning the G-6-P.D. deficiency rate among Mongolian peoples (Beutler, Yeh and Necheles, 1959; Vella, 1959; Motulsky, 1960; Smith and Vella, 1960; Weatherall, 1960; Kruatrachue and Harinasuta, 1961). The present paper describes the presence of this enzyme defect among the Chinese residents of Taiwan; the first section deals with the incidence of reactors in the general population and the second with a genetic study of eight affected families. Preliminary reports concerning portions of the present work have appeared in the Chinese literature (Blackwell *et al.*, 1961; Shih and Lee, 1961).

MATERIALS AND METHODS

The current Chinese population of Taiwan may be divided conveniently into three groups on the basis of their earlier mainland China origin and time of migration to Taiwan: Taiwanese Chinese, Hakka Chinese, and Mainland Chinese. Taiwanese Chinese, currently numbering approximately nine million, are descendants of emigrants who left the mainland principally during the seventeenth, and to a lesser extent during the eighteenth and nineteenth centuries. The vast majority of those emigrants were from Minnan County of Fuchien Province which is situated along the southeast coast of mainland China.

The Hakka Chinese people are a much smaller group of several hundred thousand whose ancestors came to Taiwan primarily during the sixteenth and seventeenth centuries. They emigrated from Kwangtung Province along the southern coast of China. The Hakkas were a separate group among the residents of Kwangtung Province and lived primarily in three counties: Chiavin Chou,

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Huei Chou, and Chhau Chou. The present Hakka population of Taiwan springs from emigrants from all three counties. Up to the present time the Hakka people in Taiwan have continued to retain their own dialect and customs as well as to live generally in separate communities. Although the Taiwanese Chinese and Hakka Chinese have lived in Taiwan for more than three centuries, there has been little intermarriage so that the present population retains both distinct groups.

The Mainland Chinese population of Taiwan is composed of people who originally resided in many provinces of the Chinese mainland and who migrated to Taiwan primarily during the period 1948-1950, and in smaller numbers in the following years. This group, combined with their children born since their residence in Taiwan, totals approximately two million.

The remaining important group of Taiwan inhabitants are the aborigine people whose ancestors are believed to have arrived in Taiwan from Malaya and other parts of Southeast Asia more than a thousand years ago. Studies on this population, which is composed of at least eight distinct tribes, currently are in progress.

In the present study attention was directed toward the Chinese inhabitants of Taiwan and particularly toward the Hakka group because an increased incidence of reactors was found among them in a previous preliminary survey (Blackwell, 1961). In a recent study (Shih and Lee, 1961) of families affected by acute hemolytic anemia and showing G-6-P.D. deficiencies, several were from Hakka communities. The eight families used in the present genetic study were chosen from those located in the previous study, but none of the eight families are Hakka, all being either Mainland or Taiwanese Chinese families.

In the population study 3,236 individuals from the three Chinese groups were screened by means of the Motulsky dye test (Motulsky, Kraut, Thieme and Musto, 1959), all specimens failing to discolor after incubation for 55 minutes being considered enzyme deficient. In many cases, the results were confirmed by quantitative measurement of G-6-P.D. levels (Zinkham, Lenard and Childs, 1958).

For the family studies, blood samples were drawn from 46 members of eight affected families and from 62 controls (43 Taiwanese and 19 Mainland Chinese). Determinations were made for glutathione (GSH) concentration as well as glutathione stability in the presence of acetylphenylhydrazine (APH), according to the method of Stevenson, McDonald and Ruston (1960). G-6-P.D. quantitative analyses were made as described by Zinkham *et al.* (1958). The reactor status of each individual was determined by the combined results of these tests. The mean G-6-P.D. level of the controls was 194.1 $\pm$ 34.3 units/100 ml. RBC with a range of 140-322 units/100 ml. RBC. No significant difference was found between the mean levels of the Taiwanese (194.9 $\pm$ 32.8 units/100 ml. RBC) and the Mainlander (192.0 $\pm$ 37.6 units/100 ml. RBC) controls.

All family members whose G-6-P.D. level was below 3 standard deviations from the mean (90 units/100 ml. RBC or less) and whose GSH declined by more than 50 per cent after incubation with APH were classified as reactors. Those whose enzyme level was between 90-140 units/100 ml. RBC and

TABLE 1. FREQUENCY OF REACTORS AMONG VARIOUS POPULATION GROUPS IN TAIWAN

	MALES			FEMALES			ALL		
	No. Tested	No. Abn.	%	No. Tested	No. Abn.	%	No. Tested	No. Abn.	%
I. Mainland Chinese	282	5	1.77	163	2	1.23	445	7	1.57
II. Taiwanese Chinese	343	1	0.29	258	1	0.39	601	2	0.33
III. Hakka Chinese	1535	84	5.47	655	15	2.29	2190	99	4.52
a. Hsin-Pu (Hsin-Chu Hsien)	442	30	6.79	218	3	1.38	660	33	5.00
b. Hu-Kou (Hsin-Chu-Hsein)	242	16	6.61	78	4	5.13	320	20	6.25
c. Mei-Nung (Kaohsiung Hsien)	851	38	4.47	359	8	2.23	1210	46	3.80

whose GSH decreased by more than 50 per cent after incubation with APH were considered intermediate reactors and individuals with G-6-P.D. levels over 140 units/100 ml. RBC and less than 50 per cent GSH decrease after incubation with APH were classified as normal.

RESULTS

Population Studies

Table 1 shows the frequency of G-6-P.D. reactors among the three Chinese populations. It is apparent that there is a relatively low incidence of reactors among the Mainland and Taiwanese Chinese. However, among the Hakka Chinese the incidence of reactors was elevated with levels ranging from 4.5 to near 7 per cent among the males. In comparison, the number of enzyme deficient females detected in this population (2.29 per cent) is lower than might be expected.

It is particularly interesting that there is an increased incidence of glucose-6-phosphate dehydrogenase deficiency among one population group that migrated to Taiwan about 300 years ago, and no such increase in the other. Because it is not possible at the present time to undertake population studies on the Chinese mainland, one can only speculate regarding the cause for this difference. Two hypotheses present themselves. The first is that the Hakka people had an increased incidence prior to the time when they migrated to Taiwan and, because they remained as an isolated population group in Taiwan, their increased incidence has not changed appreciably over the centuries. In the same way, the Taiwanese Chinese came from another part of China where the incidence of reactors presumably was low and it has remained low since migration. The second hypothesis is that there have been selection pressures upon the Hakka people after their migration, whereas no such pressures have existed for the other migrants. This theory is less acceptable for two reasons. First, the period since migration has been relatively short for a significant change in frequency. Second, both the Hakka district in Kwangtung and the three counties where the Hakkas have lived in Taiwan are in low-lying areas, and there is good reason to believe that malaria existed in both areas until very recently. Therefore, it is unlikely that this was a factor in population selection. (Siniscalco, Bernini, Latte and Motulsky, 1961).

Family Studies

The pedigrees of the families investigated are illustrated in Fig. 1 and their erythrocyte G-6-P.D. levels and GSH stability tests in Fig. 2 and 3. Because seven of the 15 parents studied as well as 17 of 31 sibs are affected, a dominant mode of transmission is suggested. Among the parents six mothers and one father are affected, and the most common mating is that permitting the transfer of the gene to the offspring through the mother. This is the pattern expected with a common sex-linked, rather than an autosomal, gene and is demonstrable in families 1 to 6. In family 7, however, the father and one daughter are reactors, whereas the mother and other children are normal, although the female sibling must be a heterozygote. Again, in family 8, two sons are reactors,

the mother is normal, and the father is unavailable for testing. If the gene is sex-linked, the mother in both these families and the female sibling in family 7 must be intermediate reactors; since normal G-6-P.D. activity and glutathione

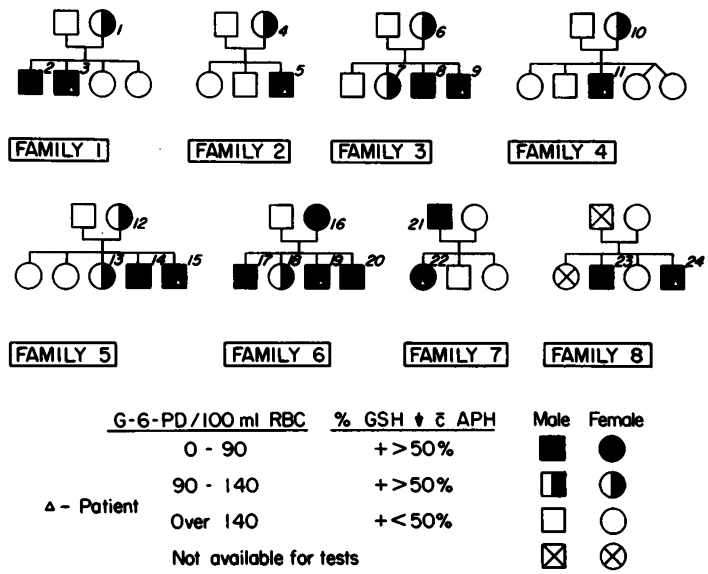

FIG. 1. Pedigrees of eight families of acute hemolytic anemia.

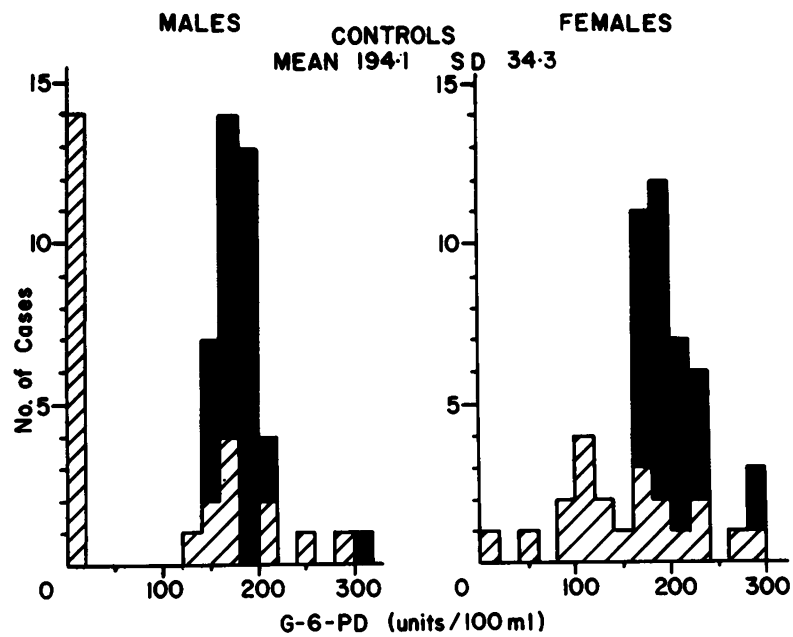

FIG. 2. Activity of glucose-6-phosphate dehydrogenase expressed as units per 100 ml. of packed erythrocytes. Cross hatched bars represent the patients and family members shown in Fig. 1 (eight families) and solid bars represent controls.

stability tests were obtained, variable penetrance in the female must be assumed. These data fit well with the hypothesis that G-6-P.D. deficiency is transmitted by a sex-linked gene showing incomplete dominance and variable expression (Gross, Hurwitz and Marks, 1958).

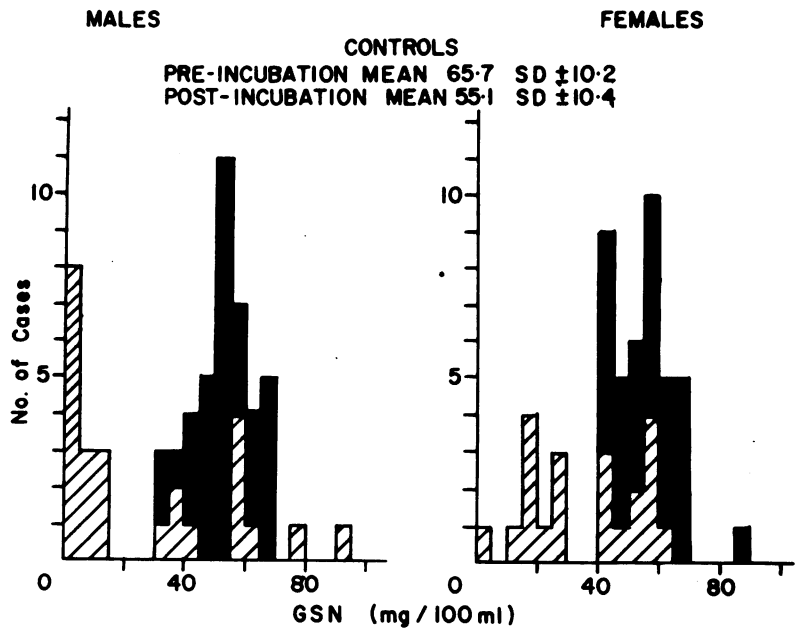

FIG. 3. Glutathione stability test of erythrocytes. Cross hatched bars represent the patients and family members shown in Fig. 1 (eight families) and solid bars represent controls, 31 males and 31 females.

SUMMARY

The present paper describes the presence of glucose-6-phosphate dehydrogenase deficiency among the Chinese residents of Taiwan. A population survey shows an increased incidence of reactors to between 6 and 7 per cent among males of the Hakka Chinese in Taiwan. Family studies have shown that the condition is transmitted by a sex-linked gene showing incomplete dominance and variable expression.

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