A New Inherited Enzymatic Deficiency of Human Erythrocytes: 6-Phosphogluconate Dehydrogenase Deficiency

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DURING A STUDY of the relationship between glucose-6-phosphate dehydrogenase (G6PD) deficiency and types of schizophrenia (Dern, Glynn, and Brewer, 1963), a Negro female patient was detected who exhibited about half-normal activity of another erythrocytic enzyme, 6-phosphogluconate dehydrogenase (6PGD). All available relatives of this patient were subsequently studied, and the results indicate that the decreased activity of 6PGD is inherited as if due to a simple autosomal dominant gene. A preliminary report of a portion of this work has been published (Brewer and Dern, 1964).

MATERIALS AND METHODS

The proposita is an adult Negro woman with schizophrenia. The members of the kindred were typed for ABO, Rh, and MN blood groups (Table 1). In one case paternity was excluded. The individuals whose red cell enzyme assays were used as controls were all healthy male and female Negroes, unrelated to the members of this kindred or to each other. All of the family members included in this study had hemoglobin values above 11.0 g/100 ml.

The activities of G6PD and 6PGD in hemolyzates were measured by a modification of the method of Glock and McLean (1953) similar to that used by Zinkham and Lenhard (1959). Over a period of years we have noted considerable fluctuation of 6PGD activities of hemolyzates. This appears to be caused by variation in the 6-phosphogluconate used as substrate. To eliminate this variable, the same lot of 6-phosphogluconate (Lot #42B-653, Sigma Chemical Company, St. Louis, Missouri) was used in all assays reported here.

RESULTS

The Activity of 6PGD in Erythrocytes

The biological relatives of the prosita could be classified into two groups with respect to 6PGD activity (Fig. 1). Part of the 6PGD values fell within

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TABLE 1. HEMOLYZATE 6PGD AND G6PD ACTIVITIES AND BLOOD TYPES OF THE TESTED MEMBERS OF THE KINDRED

Pedigree number*	Enzyme activities (μmoles TPNH/g Hb/hour)		Blood types		
	6PGD	G6PD	ABO	MN	Rh
I-1	155	213	B	M	CcDee
I-2	75	198	A	MN	ccDEe
II-1	168	303	O	–	CcDEe
II-2	69	170	B	MN	ccDEe
II-3	178	274	O	M	ccDee
II-4	86	217	B	MN	ccDee
III-1	75	263	O	M	CcDee
III-3	173	11	O	–	CcDee
III-5	78	240	B	MN	ccDEe
III-6	80	12	O	M	CcDee
III-7	150	206	–	–	–
III-8	145	205	–	–	–
III-9	180	33	O	MN	ccDee
III-10	129	221	–	–	–
III-12	174	243	B	MN	ccDee
III-13	113	258	O	–	ccDee
III-14	68	225	B	MN	ccDee
III-15	152	10	–	–	–
III-16	156	261	B	M	ccDEe
III-17	85	297	O	MN	ccDee
III-18	69	235	O	M	ccDee
IV-4	139	267	–	–	–
IV-5	128	263	–	–	–
IV-8	146	11	–	–	–
IV-15	63	248	O	M	ccDee
Control values (Mean ± SD)	136 ± 24 (59)†	233 ± 36 (60)†			

*See Fig. 2.

†Number in parenthesis is the number of individuals tested.

the control range; the others were definitely low. Each of the latter values was two or more standard deviations below the mean of control subjects, and the individuals with these values have been classified 6PGD deficient. The mean 6PGD activity of the 6PGD deficient family members was 75 μmoles of triphosphopyridine nucleotide reduced per gram of hemoglobin per hour. This value was approximately one-half the mean activity of the nondeficient family members (155) and slightly greater than one-half the mean activity of the control subjects (136).

Pedigree of the Kindred

The pedigree of the kindred is shown in Fig. 2. The sex-linked trait, G6PD deficiency (Carson *et al.*, 1956), was present in the kindred, as well as 6PGD deficiency (Table 1), and both traits are indicated in the pedigree.

The women II-2 and II-4 are double heterozygotes. Six of the 12 offspring at risk for 6PGD deficiency in generation III have this deficiency. The same 12 offspring were also at risk for G6PD deficiency and five are affected. The

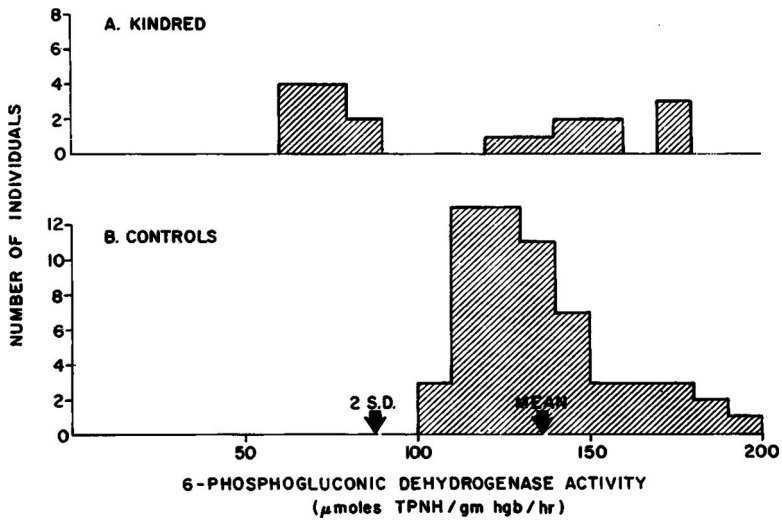

FIG. 1. The distribution of the 6PGD activities of the erythrocytes of the proposita and her biological relatives (above) and of 59 controls (below). The arrows indicate (1) the mean of the control distribution and (2) a point two standard deviations below the mean.

segregation of the two traits in the 12 offspring excludes close linkage between the two genes. Thus, five of these offspring have 6PGD deficiency alone, four have G6PD deficiency alone, two have neither deficiency, and one has both. Close linkage of the 6PGD deficiency gene with the ABO and MN blood group genes is also excluded.

DISCUSSION

The 6PGD deficient members of this kindred are presumably heterozygous for an autosomal mutant gene affecting the activity of 6PGD in erythrocytes. In generation III of the pedigree, 12 offspring have resulted from matings of 6PGD deficient females with normal males; 50% of the children are affected, strengthening the concept of simple dominant genetic control. The probable location of the 6PGD deficiency gene on an autosome can be adduced from the biochemical and genetic evidence. Men and women with 6PGD deficiency have approximately equal enzyme activities, i.e., activities about one-half normal. If the gene were sex-linked, it is unlikely that hemizygous males and heterozygous females would have similar half-normal values. Furthermore, analysis of the pedigree excludes close linkage of the 6PGD deficiency gene with the gene for G6PD deficiency, which is known to be sex-linked (Childs and Zinkham, 1959). Thus, the evidence suggests that the mutant gene is located on an autosome. Demonstration of male to male transmission of the 6PGD deficiency gene would prove an autosomal mode of inheritance. However, none of the affected males had male offspring.

Fildes and Parr (1963) recently reported an autosomally-controlled electrophoretic variant of erythrocytic 6PGD. The variant described by them is distinct from the one reported here, i.e. the electrophoretic variant is associated with quantitatively normal 6PGD activity.

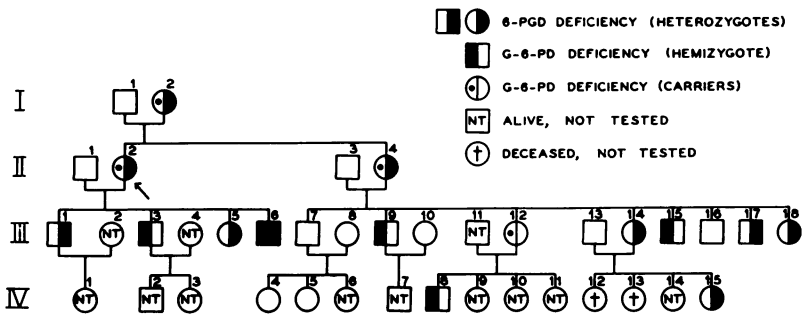

FIG. 2. The pedigree of the kindred. In addition to 6PGD deficiency, G6PD deficiency was present in this family. The expression of G6PD deficiency is quite variable in heterozygotes, but it is possible under some circumstances to establish by pedigree analysis that a woman is heterozygous for G6PD deficiency in the presence of normal G6PD activity. II-2, II-4, and III-12, all of whom are women with normal G6PD activity, have been designated G6PD deficient heterozygotes on this basis. Also I-2, whose G6PD activity was normal, is probably heterozygous. She has two heterozygous G6PD deficient daughters, and her husband (I-1) is not G6PD deficient.

The probable autosomal location of the gene or genes affecting 6PGD is of interest since this enzyme, like G6PD, reduces triphosphopyridine nucleotide and catalyzes a reaction in the pentose phosphate pathway of carbohydrate metabolism. Despite this close metabolic relationship of 6PGD and G6PD, the genes controlling the activity of these enzymes appear to be on different chromosomes.

Porter *et al.* (1963) have reported another, possibly related, entity. They described a family in which the activity of both 6PGD and G6PD in the erythrocytes was one-half normal in affected members (mother and three sons), even in affected males (Porter, personal communication).

Heterozygosity for the 6PGD deficiency gene results in enzyme activity approximately 50% normal. The relative uniformity of the expression of the mutant gene in 6PGD deficient heterozygotes suggests that the gene is fully penetrant; this is in agreement with the incidence of the trait in the family members who were at risk, e.g., of 14 persons in the kindred who were at risk and tested (excluding the proposita and her parents), eight were affected, which is close to the 50% expectation. This is in contrast to the sex-linked trait G6PD deficiency, in which expressivity in heterozygotes is extremely variable, resulting in incomplete penetrance.

We do not have a good estimate of the frequency of 6PGD deficiency in the American Negro and Caucasian populations, but the frequency is probably low (less than 1%). However, it is possible that this gene is present in higher frequencies in some populations. Screening tests for G6PD deficiency which have been used in studying many populations would not reveal 6PGD deficient heterozygotes. The methemoglobin reduction test (Brewer, Tarlov, and Alving, 1960, 1962), the glutathione stability test (Beutler, Robson, and Buttenweiser, 1957), and the dye decolorization test (Motulsky *et al.*, 1959) were normal in 6PGD deficient heterozygotes (in the absence of G6PD deficiency). All of these tests ultimately depend upon a relative decrease in

the rate of reduction of triphosphopyridine nucleotide in G6PD deficient cells. A deficiency of 6PGD activity should also decrease this rate, but apparently the tests are not sufficiently sensitive to detect this in the presence of normal activity of G6PD, which acts in the metabolic sequence preceding 6PGD.

SUMMARY

An inherited deficiency of the enzyme 6-phosphogluconate dehydrogenase in erythrocytes has been described in a Negro kindred. The enzyme deficiency appears to be due to a simple autosomal dominant gene which, in this kindred, is fully penetrant. Only individuals heterozygous for the gene have been identified, and these persons have approximately 50% normal enzyme activity. Glucose-6-phosphate dehydrogenase deficiency is also present in the kindred and segregates independently. The probable autosomal location of the gene regulating 6-phosphogluconate dehydrogenase activity is of interest in view of the close metabolic relationship of this enzyme with glucose-6-phosphate dehydrogenase, known to be controlled by a gene on the X chromosome.

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