Notes

Human Glucose-6-Phosphate Dehydrogenase Variants*

by AKIRA YOSHIDA,[1] ERNEST BEUTLER [2] & ARNO G. MOTULSKY [3]

So many glucose-6-phosphate dehydrogenase (G6PD) variants have been described that it has become very difficult to determine whether or not a newly discovered variant is distinct from any other. This difficulty can be partially overcome by performing a number of physicochemical tests and comparing the results with those already reported for the known variants. The purpose of this communication is to provide an up-to-date table summarizing the currently available data on G6PD variants. For purposes of convenience, the variants described in the accompanying table are somewhat arbitrarily divided into five classes, in accordance with their activity in red cells and their associated clinical manifestations:

Class 1: Severe enzyme deficiency with chronic non-spherocytic haemolytic anaemia.

Class 2: Severe enzyme deficiency (<10% of normal)

Class 3: Moderate to mild enzyme deficiency (10-60% of normal)

Class 4: Very mild or no enzyme deficiency (60–100% of normal)

Class 5: Increased enzyme activity (more than twice normal).

The distinction between these classes is not always clear. For example, G6PD Mediterranean has been placed in class 2, but has been reported to be associated with non-spherocytic congenital haemolytic anaemia. Furthermore, some of the variants listed in class 1, because of the severe functional lesions they cause, actually have higher enzyme activities *in vitro* than some of the variants with " moderate to mild enzyme deficiency " (class 3). Within the classes, the variant enzymes are arranged in order of their electrophoretic mobility—i.e., the fastest one is first.

The variants of each class are also subdivided into four groups according to the degree of their characterization, as tabulated in the report of the WHO Scientific Group on the Standardization of Procedures for the Study of Glucose-6-Phosphate Dehydrogenase (1967).

Group I: Variants have been fairly completely characterized, and appear to be distinctive.

Group II: Insufficient information is available to be reasonably certain that it is unique. These variants are shown with quotation marks around the name of the variant.

Group III: Variants have been described, but insufficient data have been given to warrant their inclusion in the tabulation.

Group IV: Variants have been characterized, but seem to be idential to one of the variants listed in the table.

The data in the table are the raw values given in the reports; no critical judgement of their dependability or accuracy has been made. In general, values of the Michaelis constant (K_m) for NADP, particularly those of deficient variants, may not be accurate. Therefore, differences of K_m for NADP alone cannot be used as a critical factor in distinguishing variants.

In order to distinguish closely similar variants, parallel comparisons under the same conditions should be performed. Unfortunately, many blood samples having the crucial G6PD phenotypes are no longer available or are difficult to obtain. To complicate the problem, several variants, particularly those reported earlier than 1967, were not characterized by the standard methods recommended by the WHO Scientific Group (1967). More extensive characterization by improved methods is now required. For example, comparison of the utilization of deamino-NADP has been very useful for

* This work is supported by a grant from the World Health Organization (International Reference Center for G6PD Variants) and by US Public Health Service grants GM 15253 and HE 07449 from the National Institutes of Health.

[1] Research Professor, Department of Medicine (Division of Medical Genetics), University of Washington, Seattle, Wash., USA.

[2] Chairman, Division of Medicine, City of Hope National Medical Center, Duarte, Calif., USA.

[3] Professor of Medicine and Genetics, University of Washington, Seattle, Wash., USA.

Glucose-6-phosphate dehydrogenase variants

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility [b] (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
				Normal							
	B[1-3]	Various	100	100	50–70	2.9–4.4	<4	55–60	normal	normal (truncate)	usual
				Class 1. Severe enzyme deficiency associated with chronic non-spherocytic haemolytic anaemia							
I	Ohio [4]	Italy	2–16	110 (trisglycine)	slightly increased	slightly increased	< 4		very low		rare
	Torrance [5]	USA	2.4	103 (ph)	48–60	2.4			very low	8.0–8.5	reversibly inactivated at pH 8
	Bat-Yam [6]	Iraq–Jewish	0	100 (TEB)	27		40–45		very low	biphasic	rare
	Albuquerque [7]	USA–white	1	100 (TEB, tris, ph)	115	11	0		very low	sharp peak at 8.5	rare

[a] Sources of data:

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Glucose-6-phosphate dehydrogenase variants (*continued*)

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility [b] (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
Class 1. Severe enzyme deficiency associated with chronic non-spherocytic haemolytic anaemia (*continued*)											
I (*cont.*)	Bangkok [8]	Thailand	5	100 (TEB, tris ph)	60	5.3	8.4		very low	8–8.5	
	Oklahoma [9, 10]	Western Europe	4–10	100 (tris)	127–200	20	<4		low	narrow peak at 8.2	rare
	Duarte [7]	USA–white	8.5	100 (TEB, tris, ph)	58	5	5.4		very low	7.0	rare
	Hong Kong [11]	China	0–15	100 (TEB, pH 8.0)	½ normal	normal	slightly increased		normal	normal	
	Chicago [12]	Western Europe	9–26	100 (tris)	58–76	3.1–3.7	<4		very low	normal	rare

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[b] Tris = tris (hydroxymethyl) aminoethane buffer; TEB = tris–EDTA–boric acid buffer; ph = phosphate buffer.

Glucose-6-phosphate dehydrogenase variants (*continued*)

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility [b] (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
Class 1. Severe enzyme deficiency associated with chronic non-spherocytic haemolytic anaemia (*continued*)											
I (*cont.*)	Tripler [13]	USA–white	35	97 (TEB) 97 (tris) 90 (ph)	30		3.7	62.4	very low	slightly biphasic	
	Alhambra [14]	Finland Sweden	9–20	96 (TEB) 95 (tris) 85 (ph)	55	2.6	2		low	rare	
	Milwaukee [15]	Puerto Rico–white	0.5	92 (tris)	224		3.7			8.0	rare
	Ramat-Gan [6]	Iraq–Jewish	0	90–92 (TEB)	35		40		very low	biphasic	rare
	Ashdod [6]	Jewish–N. Africa	10	90–92 (TEB)	100		40		slightly low	biphasic	rare
	Freiburg [16, 16a]	Germany	10–20	85 (TEB) 90 (ph)	87–118	4				biphasic	rare
	Worcester [17]	USA–white	0	86 (TEB, pH 7.6) 70 (TEB, pH 9.1 cellulose acetate)	11.2	61	<2	21	very low	sharp peak at 8.0	
II	" Beaujon " [18]	France	0	fast acrylamide–tris–glycine, pH 8.6)	182					peak at 9.5	rare
	" Clichy " [18]	Greece	2	100 (acrylamide–tris-glycine, pH 8.6)	178					abnormal plateau 9–10	rare
	" Strasbourg " [19]	France	6	100 (cellulose acetate, pH 8.6)	96	13			low	peak at pH 9.0	
	" Paris " [18]	Western Europe	4	?	280				very low	sharp peak at 9.5	rare
III	The following G6PD variants of this group have been described, but insufficient data have been given to warrant their inclusion in the tabulation: Eyssen [2], Fulham [20], Nashville 1 [21], Berlin [22].										
IV	The following G6PD variants of this group have been characterized, but they seem to be identical to one of the variants given in the table: Nashville 2 [21], similar to Chicago.										

Glucose-6-phosphate dehydrogenase variants (*continued*)

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility [b] (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
	Class 2. Severe enzyme deficiency										
	Hualien-Chi [23]	Taiwan	1	110 (tris) 120 (ph)	10.1		42		normal	biphasic (6.28–10.0)	
	San Juan [24]	Puerto Rico	10	110 (tris) 105 (ph)	16.2 ±0.7		21.6		very low	biphasic (7.0 & 9.5)	rare
	Markham [25]	New Guinea	1.5–10	105–108 (tris)	4.4–6.3		162–222		low	biphasic	common—uses NAD as cofactor
	Taiwan-Hakka [26]	Hakka-Chinese	2–9	110 (ph) 105 (tris)	10.7–12.2		9.8–21.1		normal to slightly low	biphasic (7.0 & 9.5–10.0)	common—uses NAD as cofactor
	Union [27]	Philippines	<3	107 (TEB, ph)	8–12	3.6–5.2	180	400	low	very biphasic (5.5 & 9.0)	common—does not use NAD as cofactor
	Teheran [23]	Iran	<1	100 (tris) 110 (ph)	46.8		<4		normal	biphasic (5.5 & 10.0)	
	Hualien [23]	Taiwan	0	105 (tris)	8.7		72.2		very low	biphasic (6.5 & 9.75)	
	Indonesia [28]	Indonesia	<5	100 (tris)	25–52	4–9			normal to slightly low	slightly biphasic	
	Camplellpur [29]	Pakistan	2–7	100 (tris) 100 (ph)	11.4–13.9		5.6–16.4		very low	biphasic (7.5 & 9.5)	common; 2% in this population
	Mediterranean [30, 34]	Greece Sardinia Sephardic Jews Asiatic Indians Asian, N.W. Ind.	0–7	100 (TEB, tris, ph)	19–26	1.2–1.6	23–27	350	low	biphasic	common; sometimes associated with favism or NSHA; may be heterogeneous (see below)
	Corinth [35]	Greece Mediterranean S.E. Asia	0–7	100 (TEB, tris, ph)	19–26	1.2–1.6	23–27	55–60	low	biphasic	may be common

Glucose-6-phosphate dehydrogenase variants (*continued*)

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility [b] (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
				Class 2. Severe enzyme deficiency (*continued*)							
I (*cont.*)	Panay [36]	Philippines	5	96 (tris, ph)	30	4.7	normal		slightly low	biphasic	may be common
	Orchomenos [37]	Greece	0–7	92–94 (ph) 100 (TEB, tris)	11	2.1	105	350		biphasic	
	Lifta [6]	Iraq–Jewish	0	87–90 (TEB)	25		60		very low	no clear optimum	rare
	Carswell [38]	Ireland	10	78 (TEB) 92 (tris) 78 (ph)	44	6.4	3.5		normal	normal or slightly displaced	rare
II	" Taiwan-Ami 6 " [23]	Taiwan	1	105 (tris) 110 (ph)	30.2		29.0		very low	biphasic (6.5 & 10.0)	
	" Taiwan-Ami 5 " [23]	Taiwan	0	105 (tris)	35.3		52.8			biphasic (7.0 & 9.5)	
	" Zähringen " [39]	Germany	1–4	105 (ph)	28	4.7	30		low	7.5 & 8.5	Rare. Associated with favism. Similar to San Juan
III	The following G6PD variants of this group have been described, but insufficient data have been given to warrant their inclusion in the tabulation: São Paulo 3 [21]; Joliet 3 [40].										
IV	The following G6PD variants of this group have been characterized, but they seem to be identical to one of the variants given in the table: Athens-like [37], similar to Athens; " U-M " [37], similar to Markham or Union; Taiwan-Ami 1 [23], similar to Markham or Union; Taiwan-Ami 2 [23], similar to Taiwan-Hakka; Johnstown [41], similar to A–; Panay-like [26], similar to Panay; El Morro [24], similar to Mediterranean; New Guinea II [25], similar to Mediterranean; Hong Kong 2 [11], similar to Canton; Singapore [42], similar to Canton; Joliet 1 [40], similar to Columbus.										

Glucose-6-phosphate dehydrogenase variants (*continued*)

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility [b] (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
				Class 3. Moderate to mild enzyme deficiency							
I	Barbieri [31]	Italy	24–40	135 (tris, pH 7.6)	increased	increased			normal		rare
	Puerto Rico [43]	Puerto Rico	38	112 (tris)	18.6		2.7		slightly low	normal	rare
	A– [2, 10, 44, 45]	Negro	8–20	110 (TEB, tris) 115 (ph)	normal	normal	<4	50–60	normal	normal	common
	Debrousse [46] (formerly Constantine)	Arab	20	113 (ph) 110 (tris)	19–29	1.9–3.3	4–11		normal	normal	common
	Taipei-Hakka [26]	China	6–9	105 (tris) 110 (ph)	27.7–43.4	3.3–5.4			slightly low	truncate (9.75–10.0)	
	Kabyle [47]	Algeria	14–36	104 (TEB) 110 (ph)	68		normal		normal	normal	
	Chibuto [48]	Negro Bantu	20	108 (TEB) 109 (ph)	30	8.2	<4		slightly low	normal	rare
	Melissa [37]	Greece	25	107 (TEB) 105 (tris) 105 (ph)	18.1–22.0	3.1–3.7	3.7	59–65	truncate		
	Canton [49]	South China	4–24	105 (tris) 105 (ph)	17.7–38.3		1.2–20.8		low	biphasic (6.5–7.0 & 9.0–9.5)	may be heterogeneous
	Columbus [4]	Negro	36	100 (tris)	normal	normal	normal				rare
	Athens [50]	Greece	20–25	98 (TEB)	16–19	2.5–6.5	10–15	126	slightly low	slightly biphasic	common
	Washington [43]	Negro	16–33	95 (tris)	49–57.4		1.6		normal	normal	
	Benevento [41]	Italy	13	93 (tris)	4.6		245		low	biphasic (5.5 & 9.75)	

Glucose-6-phosphate dehydrogenase variants (*continued*)

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility [b] (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
Class 3. Moderate to mild enzyme deficiency (*continued*)											
I (*cont.*)	West Bengal [51]	Asiatic India	9	90 (TEB) 82 (tris)	31	6.6	4		normal	normal	rare
	Mexico [52]	Mexico	10–22	85–88 (TEB) 91 (tris) 90 (ph)	32–40	2–3	26–33	130–160		truncate	
	Seattle [53, 54]	Wales Scotland	8–21	80 (TEB) 90 (tris)	15–25	2.4–2.8	7–11		normal	slightly biphasic	rare
	Kerala [51]	Asiatic, S.E. India	50	75 (TEB) 90 (tris)	23	1.5	7.4		normal	biphasic	rare
	Tel Hashomer [55, 56]	Tunisia–Jewish	25–40	60–70 (TEB)	30–40		normal		normal	slightly biphasic	rare
	Capetown [57]	Cape (coloured Norwegian)	53–80	55–65 (TEB) 76–88 (tris) 35–48 (ph)	11–14	0.2–1	7–16		normal	biphasic	
	Port-Royal [58]	Sicily	50–75	85 (TEB)	20		7.5	10	low		probably rare
II	"Attica" [59]	Greece	50	105 (Cellogel, pH 7.5)	40.7	4.7	1.8		normal	normal	
III	The following G6PD variants of this group have been described, but insufficient data have been given to warrant their inclusion in the tabulation: Madison [60]; Andhra Pradesh [61]; São Paulo [21]; Joliet 2 [40].										
IV	The following G6PD variants of this group have been characterized, but seem to be identical to one of the variants given in the table: Loyola (D–) [53, 62], identical to Seattle; and Seattle-like [59, 63].										

Glucose-6-phosphate dehydrogenase variants (*continued*)

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility [b] (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
				Class 4. Very mild or no enzyme deficiency							
I	Inhambane [48]	Africa–Bantu	100	112 (TEB) 115 (ph)	38	4.7	<4		normal	slightly biphasic	rare
	Steilacoom [64]	Negro	100	>110 (TEB) 107 (ph)	62	3	<4		normal	normal	
	A+ [2,10,65]	Negro	80–100	110 (TEB, tris) 115 (ph)	normal	normal	<4	50–60	normal	normal	common
	Levadia [66]	Greece	100	107 (TEB) 104 (tris) 108 (ph)	40.6	3.5	2.6	60		normal	
	Lourenzo Marques [48]	Africa–Bantu	100	106 (TEB) 106 (ph)	66	4.3	<4		normal	normal	rare
	King County [35]	Negro	100	105 (TEB)	61	4	6			normal	rare
	Thessaly [67]	Greece	100–110	98 (TEB) 105–105 (tris) 98 (ph)	28.5	12.3	9.7	70		normal	
	Karditsa [37]	Greece	85	95 (TEB, tris) 91–92 (ph)	24.7	6.5	6.5	52.4		normal	
	Western [68]	Greece	60	95 (TEB, ph)	38	2.2	3.6	42		normal	
	Manjacaze [48]	Africa–Bantu	100	90 (TEB) 90 (ph)	141	3.8	<4		normal	normal	rare
	Baltimore-Austin [69,73]	Negro	75	90 (tris)	65	3.1	<4		normal	normal	rare
	Ijebu-Ode [70]	Negro	100	85 (TEB)	60	24			low	biphasic	rare

Glucose-6-phosphate dehydrogenase variants (*concluded*)

Group	Variant (source of data [a] in brackets)	Population origin	RBC enzyme activity (% of normal)	Electrophoretic mobility (% of normal)	K_m G6P (μM)	K_m NADP (μM)	2dG6P utilization (% of G6P rate)	Deamino-NADP utilization (% of NADP rate)	Heat stability	pH optima	Population frequency or comment
Class 4. Very mild or no enzyme deficiency (*continued*)											
I (*cont.*)	Minas Gerais[71]	Brazil	>70	82 (ph)	41	4	9			normal	rare
	Tacoma[68]	Negro	100	94 (TEB) 80–82 (ph)	66	4	2.6	69		normal	can be distinguished from Ibadan-Austin, Madrona & Minas Gerais by side-by-side comparison.
	Madrona[72]	Negro	70–80	80 (ph)	32	3.5	Normal			normal	rare
	Ibadan-Austin[69,73]	Negro	72	80 (tris)	62–72	3.3	<4		normal	normal	rare
	Ita-Bale[69]	Negro	100	65 (TEB)	91	11			slightly low	normal	rare
Class 5. Increased enzyme activity											
I	Hektoen[74–77]	USA–white	400	100 (TEB, tris) 120 (ph, pH 6.5)	51	3.0	3	44	normal	normal	rare
III	The following G6PD variants of this group have been described, but insufficient data have been given to warrant their inclusion in the tabulation: Hartford[78].										

differentiating between G6PD variants not otherwise distinguishable. Determination of the precise amino acid substitutions of the G6PD variants could provide unambiguous evidence of their identity. Thus far, amino acid substitutions have been determined in only two G6PD variants (G6PD A+ and G6PD Hektoen), but technical improvements will facilitate such structural study of all variants in the future. Until that goal can be accomplished, the only recourse is a descriptive register. The accompanying table includes all the published and unpublished variants known to the authors up to August 1970. We hope to prepare annual supplementary tables as further variants are described. In compiling the type and quantity of data included in the present tabulation, we have undoubtedly made errors both in interpretation and in transcription and we shall welcome having such errors called to our attention.

ACKNOWLEDGEMENTS

We are grateful to Dr P. McCurdy and Dr G. Stamatoyannopoulos for making their results known to us before publication.

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Prevalence of α1-Antitrypsin Deficiency in Japan*

by KAZUO NOMIYAMA,[1] HIROKO NOMIYAMA[2] & HISAO MATSUI[3]

A high prevalence of pulmonary emphysema or chronic obstructive pulmonary disease has been found in people with a hereditary α_1-antitrypsin deficiency (α_1-ATD) (Eriksson 1965, Ganrot et al., 1967). Emphysema with α_1-ATD is characterized by familial prevalence, a relatively early onset, exacerbation in winter, and panlobular emphysema without clinical chronic bronchitis (Eriksson 1964, Talamo et al, 1966). Irritation due, for example, to smoking, air pollution, or occupational exposure may lead to the onset of the clinical disease.

A very high prevalence of the condition among α_1-antitrypsin (α_1-AT) deficient heterozygotes has been reported from Sweden and the USA (Table 1). The α_1-ATD test has already been recommended in the USA for screening workers who might be exposed to irritant gases.

Because apparently healthy people with α_1-ATD may develop emphysema upon continuous exposure to low concentration of air pollutants, a screening survey for α_1-ATD was carried out in the Shibukawa and Maebashi districts of Gunma Prefecture, Japan, in early 1970.

* From the Department of Hygiene, Gunma University School of Medicine, Maebashi, Japan.

[1] Associate Professor.

[2] Research Associate.

[3] Postgraduate Student.

Methods

Sera were collected at random from 433 residents over 40 years of age in the Shibukawa district and from 377 students 15–25 years of age and 150 pupils 14 years of age in the Maebashi district. Total antitrypsin activity was determined by a slight modification of the gelatin-film test (James et al., 1966). The gelatin film test for detecting α_1-ATD was a little less accurate than the photometric procedure (coefficient of variation in photometry 8.6%, compared with 22.5% for the gelatin-film test). The gelatin-film test, however, was found to be a simple and inexpensive procedure and was appropriate for screening large populations.

Results

As seen in Table 1, no α_1-ATD could be detected in 433 apparently normal individuals, and 1 and 2 presumed heterozygous individuals for α_1-ATD were found in other groups of 377 students and 150 pupils, respectively.

The mean α_1-AT levels were 1.90 mg $\pm$0.24 mg (mean $\pm$ standard deviation) and 1.79 mg $\pm$0.21 mg of trypsin inhibitor per millilitre of serum for the adults and the young people, respectively. The α_1-AT level seemed to increase with age, although this increase was not significant (see Fig. 1). No