A fine control of the blood glucose level is essential to avoid hyper- or hypoglycemic shocks associated with many metabolic disorders, including diabetes mellitus and type I glycogen storage disease. Between meals, the primary source of blood glucose is gluconeogenesis and glycogenolysis. In the final step of both pathways, glucose-6-phosphate (G6P) is hydrolyzed to glucose by the glucose-6-phosphatase (G6Pase) complex. Because G6Pase (renamed G6Pase-α) is primarily expressed only in the liver, kidney, and intestine, it has implied that most other tissues cannot contribute to interprandial blood glucose homeostasis. We demonstrate that a novel, widely expressed G6Pase-related protein, PAP2.8/UGRP, renamed here G6Pase-β, is an acid-labile, vanadate-sensitive, endoplasmic reticulum-associated phosphohydrolase, like G6Pase-α. Both enzymes have the same active site structure, exhibit a similar $K_m$ toward G6P, but the $V_{max}$ of G6Pase-α is 6-fold greater than that of G6Pase-β. Most importantly, G6Pase-β couples with the G6P transporter to form an active G6Pase complex that can hydrolyze G6P to glucose. Our findings challenge the current dogma that only liver, kidney, and intestine can contribute to blood glucose homeostasis and explain why type Ia glycogen storage disease patients, lacking a functional liver/kidney/intestine G6Pase complex, are still capable of endogenous glucose production.

Blood glucose homeostasis between meals is maintained by endogenous hepatic and renal glucose production via gluconeogenesis and glycogenolysis. In the terminal stages of both pathways, glucose-6-phosphate (G6P) is hydrolyzed to glucose by the glucose-6-phosphatase (G6Pase) complex embedded in the membranes of the endoplasmic reticulum (ER) (reviewed in Refs. 1 and 2). This complex is composed of a G6P transporter (G6PT) that transports G6P from the cytoplasm into the lumen of the ER and a G6Pase catalytic subunit that hydrolyzes the G6P to glucose. Disruption of either component disturbs glucose homeostasis and results in glycogen storage disease type Ia (GSD-Ia, G6Pase deficiency) or type Ib (GSD-Ib, G6PT deficiency). The G6PT and G6Pase activities are co-dependent (3, 4), and both GSD-Ia and GSD-Ib patients manifest the symptoms of failed G6P hydrolysis, namely hypoglycemia, growth retardation, hepatomegaly, nephromegaly, hyperlipidemia, hyperuricemia, and lactacidemia (1, 2).

Despite disruption of the G6Pase complex in GSD-I patients, several studies (5–7) indicate that these patients are still capable of producing glucose, implying there are alternative pathways for endogenous glucose production. G6PT is expressed ubiquitously (8), but G6Pase expression is considered to be restricted to the liver, kidney, and intestine (9, 10). Therefore, we searched the ENSEMBL data base for a G6Pase homolog expressed outside of the liver, kidney, and intestine. We identified a theoretical phosphatidic acid phosphatase, PAP2.8, encoded within locus 92579 (accession number XM.045901) on chromosome 17q21.31, which, by electronic analysis, manifested significant amino acid sequence identity with human G6Pase. Sequence-similarity search of human G6Pase identified this as a ubiquitously expressed G6Pase catalytic subunit-related protein (UGRP) lacking phosphohydrolase activity.

Human PAP2.8/UGRP is a hydrophobic protein sharing 36% amino acid sequence identity with human G6Pase. Sequence-identity analysis of H6Pase predicts that it should contain nine transmembrane helices and an active hydrolytic site lying on the luminal side of the ER (12–15). Therefore, the reported absence of phosphohydrolase activity was unexpected. The activity assays used by Martin et al. (12) were performed on cell lysates in which PAP2.8/UGRP had been expressed transiently using a plasmid-based vector. We wondered whether the low level of UGRP expression in this system limited the sensitivity of the phosphohydrolase assay. In this study, we adopted a recombinant adenoviral vector-mediated expression system to increase the level of expression of PAP2.8/UGRP and enhance the sensitivity of the G6P hydrolysis assay. We demonstrate that PAP2.8/UGRP is a phosphohydrolase that can couple with G6PT to form an active G6Pase complex. We now propose naming PAP2.8/UGRP as G6Pase-β, to differentiate it from the liver/kidney/intestine G6Pase that we rename G6Pase-α. Our results provide new insights into glucose homeostasis and explain why patients genetically deficient in the G6Pase-α complex are still capable of endogenous glucose production.

**EXPERIMENTAL PROCEDURES**

**Isolation of Human G6Pase-β cDNA and Construction of Mutants**—The entire coding region of human PAP2.8/UGRP (G6Pase-β) was isolated by PCR amplification of human full-length cDNA obtained from Panomics (Redwood City, CA) using oligonucleotide primers derived from nucleotides 217–237 (5'-ATGAGTCCACGCTGGCCGCG-3').

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1The abbreviations used are: G6P, glucose-6-phosphate; G6Pase, glucose-6-phosphatase; ER, endoplasmic reticulum; G6PT, G6P transport; UGRP, ubiquitously expressed G6Pase catalytic subunit-related protein; TRITC, tetramethylrhodamine isothiocyanate.
**G6Pase-β Is a Functional Phosphohydrolase**

**A** G6Pase-β is a G6P phosphohydrolase. A, G6P phosphohydrolase activity assayed at pH 6.5 and 30 °C and Western blot analysis of COS-1 lysates infected with Ad-G6Pase-β-3FLAG and Ad-G6Pase-α. The background activity of mock-infected cultures (4.6 ± 0.2 nmol/mg/min) has been subtracted from the data presented. Ad-G6Pase-β had equivalent activity. MOI, multiplicity of infection. B, characteristics of G6P phosphohydrolase activity in Ad-G6Pase-β or Ad-G6Pase-α-infected COS-1 microsomes assayed at pH 6.5 and 37 °C for G6Pase-β and pH 6.5 and 30 °C for G6Pase-α. Acid stability was determined by assaying G6P phosphohydrolase activity in deoxycholate-disrupted (0.2%) microsomes before and after pre-incubation at pH 5.0 for 10 min at 37 °C. Latency, assessed by phosphohydrolysis of mannose-6-phosphate in intact (I) versus detergent-disrupted (D) microsomes, is defined as (1 - I/D) x 100.

| MOI  | G6Pase-β Activity (nmol/mg/min) | G6Pase-α Activity (nmol/mg/min) |
|------|---------------------------------|---------------------------------|
| 0    | 0                               | 0                               |
| 5    | 20.8 ± 2.5                      | 0                               |
| 10   | 30.2 ± 1.2                      | 307.6 ± 27.3                    |
| 50   | 57.4 ± 4.9                      | 422.8 ± 37.6                    |

Statistical analysis using the unpaired t test was performed with the GraphPad Prism program (GraphPad Software, San Diego, CA). Data are presented as the mean ± S.E.

**Immunofluorescence Microscopy**—COS-1 cells (5 × 10^4/chamber) in a 2-well chambered coverglass (Nalge Nunc International Co., Naperville, IL) were transfected with 2 μg of pSVL-G6Pase-β-3FLAG or pSVL-G6Pase-α-3FLAG using SuperFect transfection reagent according to the manufacturer’s protocol (Qiagen, Valencia, CA). After incubation at 37 °C for 2 days, the transfected cells were fixed for 10 min at 25 °C in 3.7% formaldehyde in PBS.

For intracellular staining, the cells were blocked with 2% normal horse serum in PBS for 20 min at room temperature, incubated with a monoclonal anti-G6Pase antibody in PBS containing 0.1% saponin for 1 h, followed by goat fluoroscein isothiocyanate-conjugated anti-mouse IgG (Sigma) in PBS containing 0.1% saponin for 1 h. After washing in PBS containing 0.1% saponin, the cells were mounted with an anti-fade, water-based mounting medium (Vector Lab, Burlingame, GA) and analyzed under a laser scanning confocal fluorescence microscope (Leica TCS-4D DMIRE, Heidelberg, Germany). Staining of the calretulin ER marker was performed similarly using rabbit anti-calretulin antibody (Affinity BioReagents, Golden, CO) and TRITC-conjugated goat anti-rabbit IgG (Sigma). Excitation wavelengths of 488 (for fluorescein isothiocyanate) and 568 (for TRITC) nm were used to generate fluorescence emission in green and red, respectively. Co-localization of green fluorescent G6Pase-α or G6Pase-β and red fluorescent calretulin is reflected by yellow fluorescence.

**RESULTS**

**G6Pase-β Is a Phosphohydrolase**—To improve the transient expression assay of G6Pase-β, we used an adenoviral-based expression system. Because an antibody against G6Pase-β is not available, we incorporated a FLAG epitope into our construct to monitor expression. This choice of protein tag was based on our previous experience that FLAG epitopes have no effect on the expression or activity of G6Pase-α (13). Stocks of Ad-G6Pase-β virus and Ad-G6Pase-β-3FLAG virus, a carboxy-terminal FLAG-tagged recombinant G6Pase-β were used to infect the monkey kidney cell line COS-1. Phosphohydrolase assays of Ad-G6Pase-β-3FLAG-infected COS-1 lysates, analyzed at the optimal conditions for the hepatic/renal/intestinal G6Pase-α (pH 6.5, 30 °C), show a dose-dependent G6P hydrolytic activity ranging from 20.8 ± 2.5 nmol/min/mg (at a multiplicity of infection of 5 pfu/cell) to 57.4 ± 4.9 nmol/min/mg (at a multiplicity of infection of 100 pfu/cell) (Fig. 1A). Ad-G6Pase-β has identical activity to the Ad-G6Pase-β-3FLAG (data not shown). In contrast to G6Pase-β, the G6Pase-α is consistently eight times more active, Ad-G6Pase-α-infected COS-1 lysates yielding 307.6 ± 27.3 and 422.8 ± 37.6 nmol/mg/min at a multiplicity of infection of 25 and 50 pfu/cell, respectively (Fig. 1A). Western analysis showed that the ex-
pression of G6Pase-β and G6Pase-α proteins correlates with enzymatic activity (Fig. 1A).

Hepatic/renal/intestinal G6Pase-α has a characteristic profile of acid lability, pH and temperature dependence, and vanadate inhibition (10) that differs from other phosphatases. G6Pase-β shows a similar profile. Analysis of adenoviral-directed G6Pase activity in infected COS-1 microsomes shows that like G6Pase-α, G6Pase-β is acid-labile. Incubating either Ad-G6Pase-β- or Ad-G6Pase-α-infected COS-1 microsomes at pH 5.0 for 10 min at 37 °C led to a loss of over 98% of G6P hydrolytic activity (Fig. 1B). Both G6Pase-β and G6Pase-α have a temperature-independent pH optimum of 6.5 (Fig. 2A), although the temperature optimum of each activity differs. G6Pase-α activity is similar at 30 °C and 37 °C, with an optimum at 30 °C, whereas G6Pase-β activity is significantly higher at 37 °C than at 30 °C (Fig. 2A).

Under the optimal conditions defined above, the $K_m$ values for G6P hydrolysis are similar, namely 2.22 mM for G6Pase-β and 1.82 mM for G6Pase-α (Fig. 1B). However, consistent with the earlier observation, G6Pase-α has a higher $V_{max}$ for G6P (667.7 nmol/mg/min), compared with G6Pase-β (108.7 nmol/mg/min). Assuming similar efficiencies of infection and expression, G6Pase-β appears less active, possessing −12% of the activity of hepatic G6Pase-α (Fig. 1A). G6Pase-β is also vanadate-sensitive, but more readily inhibited than G6Pase-α, G6Pase-β showing 50% inhibition of activity at 1.4 mM vanadate compared with a [vanadate]$_{0.5}$ of 3.1 mM for G6Pase-α (Fig. 2B).

**G6Pase-β Is Localized in the Endoplasmic Reticulum—**

G6Pase-α is a nine-transmembrane domain protein embedded in the ER membrane, oriented with its active site facing into the lumen (13, 14). The protein contains a carboxyl-terminal KKKK motif, responsible for the retention of type I transmembrane proteins in the ER (18), and has a latent activity that is released upon disruption of the microsomes (10). In contrast, G6Pase-β lacks any apparent ER retention motif (19, 20), although Ad-G6Pase-β-infected microsomes do exhibit latency similar to Ad-G6Pase-α (Fig. 1B). To confirm the ER retention of G6Pase-β, FLAG-tagged constructs of pSVL-G6Pase-β or pSVL-G6Pase-α were transfected into COS-1 cells and visualized by double immunostaining for the FLAG-tag and ER-marker protein calreticulin (21). As expected from the microscopic localization of the activities, both G6Pase-α and G6Pase-β co-localize with calreticulin (Fig. 3), confirming their retention within the ER.

The **Active Site Residues Are Conserved between G6Pase-β and G6Pase-α**—Functional analysis of missense and codon deletion mutations in the G6Pase-α gene of GSD-1a patients (22) as well as active site analysis (14) has identified 43 amino acid residues essential for G6Pase catalysis (Fig. 4). Thirty-five of these residues, including three active site residues, are conserved between mammalian G6Pase-α and G6Pase-β (Fig. 4). The active site of G6Pase-α is composed of residues Arg$^{83}$, His$^{119}$, and His$^{176}$ (14), and the analogous residues in G6Pase-β appear to be Arg$^{79}$, His$^{114}$, and His$^{167}$ (Fig. 4). To demonstrate the importance of these residues in G6Pase-β, mutations known to disrupt the active site in G6Pase-α (14) were introduced into G6Pase-β. Mutants R79A, H114A, or H167A were constructed in Ad-G6Pase-β-3FLAG, expressed transiently in COS-1 cells, and assayed for expression by Western blot and G6P phosphohydrolase activity (Fig. 5). Each mutant is expressed as efficiently as the wild-type G6Pase-β protein but is devoid of G6P hydrolytic activity. Therefore, Arg$^{79}$, His$^{114}$, and His$^{167}$ are components of the active site of G6Pase-β.

G6Pase-β Couples with G6PT to Form an Active G6Pase Complex—In the liver and kidney, G6P transport and hydrolysis are tightly coupled (3). The uptake and accumulation of G6P in the ER lumen is stimulated dramatically when G6PT and G6Pase (G6Pase-α) are co-expressed (4). G6Pase-β demonstrates a similar functional coupling to G6PT (Fig. 6). COS-1 cells co-infected with Ad-G6PT/Ad-G6Pase-α or Ad-G6PT/Ad-G6Pase-β have identical time courses for microsomal G6P accumulation (Fig. 6A) although the maximal accumulation mediated by G6Pase-β is −25% of that for G6Pase-α (Fig. 6B), consistent with the decreased phosphohydrolase activity of G6Pase-β. The pH profile of the uptake activity (Fig. 6C) shows G6Pase-β has a broader pH

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**Fig. 2.** The dependence of G6P hydrolase activity on temperature, pH, and vanadate. A, the pH dependence of G6P phosphohydrolase activity of deoxycholate-disrupted microsomes isolated from Ad-G6Pase-β- or Ad-G6Pase-α-infected COS-1 cells assayed at 37 °C (○) or 30 °C (●). B, vanadate inhibition of G6P phosphohydrolase activity of deoxycholate-disrupted microsomes isolated from Ad-G6Pase-β-infected (○) or Ad-G6Pase-α-infected (●) COS-1 cells assayed at pH 6.5 and 37 °C for G6Pase-β and pH 6.5 and 30 °C for G6Pase-α.

**Fig. 3.** G6Pase is localized in the endoplasmic reticulum. Double immunofluorescence staining for recombinant G6Pase-β (green fluorescence), recombinant G6Pase-α (green fluorescence), and endogenous calreticulin (red fluorescence) in pSVL-transfected COS-1 cells expressing human G6Pase-β-3FLAG or human G6Pase-α-3FLAG. Note the intracellular colocalization of G6Pase-β or G6Pase-α with the ER-marker calreticulin, indicated by yellow in the merged image.
optimum than G6Pase-\(\alpha\). Unlike G6P hydrolysis, increasing the assay temperature to 37 °C does not increase G6P uptake for either the G6Pase-\(\alpha\)/G6PT or G6Pase-\(\beta\)/G6PT co-infected micro-
somes (data not shown), which is consistent with the finding that G6PT is the rate-limiting activity in the coupled G6PT/G6Pase system in vitro (10).
G6Pase-β Is a Functional Phosphohydrolase

In humans, blood glucose levels must be maintained between 70–110 mg/dl to avoid the complications of hyper- and hypoglycemia. Although insulin plays major roles in regulating blood glucose levels (23), blood glucose homeostasis between meals depends on gluconeogenesis and glycogenolysis. In the terminal step common to both pathways, G6P is hydrolyzed to glucose by the G6Pase complex, which is composed of a G6P transporter coupled to a G6P phosphohydrolase (1, 2). Deficiencies in the G6Pase complex disrupt glucose production via gluconeogenesis and glycogenolysis, resulting in the metabolic disorder GSD-I, which is characterized by hypoglycemia, growth retardation, hepatomegaly, nephromegaly, hyperlipidemia, hyperuricemia, and lactic acidemia (1, 2). Currently, only the liver, kidney, and intestine are considered to be involved in inter-prandial glucose homeostasis. This view is based on the absence of G6Pase-α, an activity essential to the final stage of gluconeogenesis and glycogenolysis, outside of these organs. We now show that other tissues may be able to contribute to blood glucose homeostasis through the activity of PAP2.8/UGRP (11, 12), a G6Pase-related protein expressed ubiquitously, that we rename G6Pase-β.

An initial report on G6Pase-β ascribed no phosphohydrolase activity to the protein (12). By improving the transient expression of the gene with an adenovirus-based expression system, we have demonstrated that, like the hepatic/renal/intestinal phosphohydrolases, both G6Pase-α and G6Pase-β are acid-labile. They are also inhibited readily by vanadate, although nonspecific phosphatases are not able to contribute to glucose homeostasis. Both G6Pase-α and G6Pase-β are localized in the ER. When G6Pase-β is co-expressed with G6PT, the proteins couple to transport G6P from the cellular cytoplasm into the ER lumen. Although the rate of G6P accumulation mediated by the G6Pase-β/G6PT complex is 25% of that of the G6Pase-α/G6PT complex, it is still a significant accumulation, showing a broader pH optimum but a similar temperature dependence as G6Pase-α/G6PT.

Although G6Pase-β has only ~12% of the activity of G6Pase-α, the demonstration of a significant, specific G6P hydrolytic activity that can couple to G6PT outside of the liver raises interesting questions about the ability of other tissues to cycle glucose and contribute to blood glucose homeostasis. Of particular interest is the muscle, which expresses an elevated level of G6Pase-β (12). Although the liver stores the largest reservoir of body glycogen, storing about 300 g of glycogen per 70-kg male (24, 25), the muscle, by its sheer mass (40–45% of the wet body weight) (24–27), is the largest reservoir of body glycogen, storing about 90 g in a 70-kg male. It is interesting to speculate that some of this glycogen reservoir may be cycled into blood glucose by G6Pase-β. Without further study, it is difficult to judge how important this might be to glucose homeostasis, because in muscle, cytoplasmic G6P has multiple fates, which include hydrolysis to glucose, glycogenesis, energy production via glycolysis, entry into the pentose phosphate pathway, and lipid synthesis. Studies of G6Pase-α-deficient patients or mice (3) may hold interesting clues.

Monitoring of GSD-Ia patients, who lack a functional G6Pase-α, clearly demonstrates that there is a significant supply of endogenous glucose production from an unknown source. Young GSD-Ia patients show significant hypoglycemia, but with age, the endogenous glucose production rate improves, starting from 50% of normal in young GSD-Ia patients to 67–

DISCUSSION

FIG. 5. G6P phosphohydrolase activity and Western blot analysis of deoxycholate-disrupted COS-1 lysates infected with wild-type and active site mutants of Ad-G6Pase-β-3FLAG. Phospho-
hydrolase activity was assayed at pH 6.5 and 37 °C, and the results are given as mean ± S.E.

FIG. 6. G6Pase-β couples with G6PT to mediate microsomal G6P uptake. A, time course of microsomal G6P uptake activity. B, microsomal G6P uptake activity in COS-1 cells infected with Ad-G6Pase-β (25 pfu/cell), Ad-G6Pase-α (25 pfu/cell), Ad-G6PT (50 pfu/cell), or co-infected with 25 pfu/cell of either Ad-G6Pase-β or Ad-G6Pase-α and 50 pfu/cell of Ad-G6PT. C, pH dependence of microsomal G6P uptake activity. For both the time course and pH-dependence, the cells were co-infected at the same time with 50 pfu/cell of Ad-G6PT and either 25 pfu/cell of Ad-G6Pase-β or 25 pfu/cell of Ad-G6Pase-α. G6P uptake was performed at pH 6.5 and 30 °C. The results are given as mean ± S.E.
100% of normal in adult GSD-Ia patients (5–7). Because the muscle mass is only ~20% of the body weight of a newborn but improves through adolescence (38% muscle mass) to adulthood (40–45%) (27), it is reasonable to suggest that the muscle G6Pase-β/G6PT complex may be the source of some or all of the extra blood glucose. Indeed preliminary experiments examining the G6Pase activity in muscle derived from G6Pase-β-deficient (3) and G6PT-deficient (28) mice are promising in this respect. Because G6Pase-β is well expressed in kidney (12), another potential source of the glucose is the kidney, although this seems less significant because the kidney weighs only ~17% of the wet weight of the liver (25) and has a significantly lower glycerol content weight for weight.

Our findings with G6Pase-β challenge the current dogma of glucose homeostasis and suggest that glucose recycling through glycerol or other G6P-mediated pathways may take place in a much wider range of tissues than previously envisaged. The proof of this rests in detailed in vivo measurements of glucose recycling, which are currently in progress. The importance of such a finding depends on the physiological impact of the loss of G6Pase-β activity. We are currently addressing the physiological importance of this through the use of knock-out and over-expression mouse strains.

REFERENCES

1. Chou, J. Y., Matern, D., Mansfield, B. C., and Chen, Y.-T. (2002) Curr. Mol. Med. 2, 121–143
2. Chen, Y.-T. (2001) in The Metabolic and Molecular Bases of Inherited Disease (Scriver, C. R., Beaudet, A. L., Sly, W. S., Valle, D., Childs, B., Kinzler, K. W., and Vogelstein, B., eds) 8th Ed., pp. 1521–1551, McGraw-Hill Inc., New York
3. Lei, K.-J., Chen, H., Pan, C.-J., Ward, J. M., Mosinger, B., Lee, E. J., Westphal, H., and Chou, J. Y. (1996) Nat. Genet. 13, 203–209
4. Hiraiwa, H., Pan, C.-J., Lin, B., Moses, S. W., and Chou, J. Y. (1999) J. Biol. Chem. 274, 5532–5536
5. Powell, R. C., Wentworth, S. M., and Brandt, I. K. (1981) Metabolism 30, 443–450
6. Tsaklikian, E., Simmons, P., Gerich, J. E., Howard, C., and Haymond, M. W. (1984) Am. J. Physiol. 247, E513–E519
7. Collins, J. R., Bartlett, K., Leonard, J. V., and Aynsley-Green, A. (1990) J. Inherit. Metab. Dis. 13, 195–206
8. Lin, B., Annabi, B., Hiraiwa, H., Pan, C.-J., and Chou, J. Y. (1998) J. Biol. Chem. 273, 31656–31670
9. Pan, C.-J., Lei, K.-J., Chen, H., Ward, J. M., and Chou, J. Y. (1998) Arch. Biochem. Biophys. 358, 17–24
10. Nordlie, R. C., and Sukalski, K. A. (1985) in The Enzymes of Biological Membranes (Martensoni, A. N., ed) 2nd Ed., pp. 349–398, Plenum Press, New York
11. Rebbian, M., Chalifa-Caspi, V., Prilusky, J., and Lancet, D. (1997) GeneCards: Encyclopedia for Genes, Proteins and Diseases, Weizmann Institute of Science, Bioinformatics Unit and Genome Center, Rehovot, Israel
12. Martin, C. C., Oser, J. R., Svitvick, C. A., Hunter, S. I., Hutton, J. C., and O’Brien, R. M. (2002) J. Mol. Endocrinol. 29, 205–222
13. Pan, C.-J., Lei, K.-J., Annabi, B., Hemrika, W., and Chou, J. Y. (1998) J. Biol. Chem. 273, 6143–6148
14. Ghosh, A., Shieh, J.-J., Pan, C.-J., Sun, M.-S., and Chou, J. Y. (2002) J. Biol. Chem. 277, 32937–32942
15. Hoffman, K., and Stoffel, W. (1995) Biol. Chem. Hoppe-Seyler 374, 166–170
16. Hardy, S., Kitamura, M., Harris-Stansil, T., Dai, Y., and Phipps, M. L. (1997) J. Biol. Chem. 272, 1842–1849
17. Chen, L.-Y., Pan, C.-J., Shieh, J.-J., and Chou, J. Y. (2002) Hum. Mol. Genet. 11, 3199–3207
18. Jackson, M. R., Nilsson, T., and Peterson, P. A. (1990) EMBO J. 9, 3153–3162
19. Sigrist, C. J., Cerutti, L., Hulo, N., Gattiker, A., Falquet, L., Pagni, M., Bairoch, A., and Bucher, P. (2002) Brief Bioinform. 3, 265–274
20. Puntervoll, P., Linding, R., Gemund, C., Chabanis-Davidson, S., Mattingdale, M., Cameron, S., Martin, D. M., Aussiello, G., Brannetti, B., Costantini, A., Ferre, F., Maselli, V., Via, A., Cesareni, G., Diella, F., Superti-Furga, G., Wywicz, L., Ramu, C., McGuigan, C., Gudavalli, R., Letunic, I., Bork, P., Rychlewski, L., Kuster, B., Helmer-Cutercher, M., Hunter, W. N., Aasland, R., and Gibson, T. J. (2003) Nucleic Acids Res. 31, 3625–3630
21. Pozzan, T., Rizzuto, R., Volpe, P., and Meldolesi, J. (1994) Physiol. Rev. 74, 595–636
22. Shieh, J.-J., Terzioğlu, M., Hiraiwa, H., Marsh, J., Pan, C.-J., Chen, L.-Y., and Chou, J. Y. (2002) J. Biol. Chem. 277, 5047–5055
23. Taylor, S. I. (2001) in The Metabolic and Molecular Bases of Inherited Disease (Scriver, C. R., Beaudet, A. L., Sly, W. S., Valle, D., Childs, B., Kinzler, K. W., and Vogelstein, B., eds) 8th Ed., pp. 1433–1469, McGraw-Hill Inc., New York
24. Baynes, J., and Dominiczak, M. H. (1999) in Medical Biochemistry (Baynes, J., ed) pp. 129–155, Mosby, London
25. Snyder, W. S., Cook, M. J., Nasset, E. S., Karhausen, L. R., Howells, G. P., and Tipton, I. H. (1975) in Report of the Task Group on Reference Man (International Commission on Radiological Protection, ed) Pergamon Press, Oxford
26. Janssen, I., Heymsfield, S. B., Baumgartner, R. N., and Ross, R. (2000) J. Appl. Physiol. 89, 465–471
27. Gallagher, D., Steven, B., Heymsfield, S. B., and Wang, Z. M. (1999) The Role of Protein and Amino Acids in Sustaining and Enhancing Performance, pp. 255–277, National Academy Press, Washington, D. C.
28. Chen, L.-Y., Shieh, J.-J., Lin, B., Pan, C.-J., Gao, J.-L., Murphy, P. M., Roe, T. F., Moses, S., Ward, J. M., Westphal, H., Lee, E. J., Mansfield, B. C., and Chou, J. Y. (2003) Hum. Mol. Genet. 12, 2547–2558

2 J.-J. Shieh, C.-J. Pan, B. C. Mansfield, and J. Y. Chou, unpublished data.
A Glucose-6-phosphate Hydrolase, Widely Expressed Outside the Liver, Can Explain Age-dependent Resolution of Hypoglycemia in Glycogen Storage Disease Type Ia

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