Blood Cells, Molecules, and Diseases (1999) 25(2) Jan 31:30-37
Article No. MD990224

Human Hexose-6-Phosphate Dehydrogenase (Glucose 1-Dehydrogenase) Encoded at 1p36: Coding Sequence and Expression

Submitted 01/16/99
(communicated by Ernest Beutler, M.D., 01/18/99)

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ABSTRACT: Using the published protein sequence from a rabbit microsomal glucose-6-phosphate dehydrogenase G6PD we have isolated and sequenced a cDNA clone coding for its human equivalent, which is also known as hexose-6-phosphate dehydrogenase (H6PD) and glucose dehydrogenase. The corresponding genomic sequence is in the databases enabling its localization to chromosome 1p36. The gene spans 37 kb and consists of 5 exons, the fifth of which codes for more than half of the 89kDa protein. The first intron is a 10kb insertion in the 5' untranslated sequence. The predicted mRNA has an exceptionally long (6.5kb) 3' untranslated sequence. The predicted protein shows extensive homology with X-linked G6PD, suggesting the two genes share a common ancestor but no intron positions are conserved between the two genes suggesting the gene duplication was an ancient event. The C-terminal portion of the protein is not homologous with G6PD but shows limited homology with proteins of unknown function found throughout evolution and encoded next to G6PD in various micro-organisms. Intriguingly this C-terminal portion has some homology with the N-terminal sequence of *Plasmodium falciparum* G6PD.
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Keywords: hexose-6-phosphate dehydrogenase gene, glucose 1- dehydrogenase, microsomal G6PD, chromosome 1p36, long 3' untranslated region, devb

INTRODUCTION

Human X-linked G6PD is extremely well characterized; the human gene was cloned and sequenced 12 years ago and 120 disease causing mutations in the coding sequence have been described (1). Recently the enzyme has been crystallized and the tertiary and quaternary structure deduced (2, and S. Au et al manuscript submitted). In contrast very little is known of an autosomally encoded enzyme that catalyses the same reaction as G6PD and has been variously known as salivary G6PD (OMIM entry 138100), microsomal G6PD (3), glucose 1-dehydrogenase (E.C. 1.1.1.47 and OMIM entry 138090) and the name we will use, hexose-6-phosphate dehydrogenase (4). The properties of the enzymes described in these reports are remarkably similar so we believe they are the same entity. Hexose-6-phosphate dehydrogenase is present in most

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ISSN No. 1079-9796/98 $25.00

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tissues but not red cells (4). It shows activity with hexose-6-phosphates other than glucose-6-phosphate especially galactose-6-phosphate and uses NAD as well as NADP as a coenzyme (4). The enzyme is present in the microsomes (5) where its function is thought to be to provide NADH and NADPH to reductases on the lumenal side of the microsomal membrane, where it may be functionally coupled to the microsomal electron transport system (6,7). Electrophoretic polymorphisms of the enzyme have been detected in saliva (8,9), liver and white blood cells (10,11) and the gene has been mapped to chromosome 1, distal to 1p36.13 (12,13). Studies of mouse human somatic cell hybrids indicate the protein is a dimer (12). A 90kDa protein with G6PD activity was purified from rabbit liver microsomes and its amino acid sequence determined and this report represents the only structural information on a mammalian hexose-6-phosphate dehydrogenase (3). We have used this protein sequence to clone and sequence the full length cDNA encoding the corresponding human enzyme and from information in public databases have been able to confirm the assignment of the gene to chromosome 1p36 and deduce the structure of the gene.

MATERIALS AND METHODS

Molecular Biology

Except where detailed all molecular biological procedures were carried out according to standard protocols (14).

Reverse Transcription- PCR

Rabbit liver polyA RNA was obtained from Clontech. Total RNA from HepG2 cells was prepared using an RNeasy™ kit from Qiagen. Conditions for reverse transcription and PCR were as previously described (15). Oligonucleotide primers used were:

1. 5’ A T G G A A/G G G N G T N C C N T T C/T A T 3’
2. 5’ G G N G T C C A A/G A A N A C C C A 3’
3. 5’ A A G C C T T G G A C G A G A G A G T G G G 3’
4. 5’ A G G C G T C G T A G T C C A T G T A C C A 3’

Library Screening

A cDNA library from human bone marrow mRNA in λgt10 was obtained from Clontech and used according to the manufacturers recommendations. Approximately 200,000 plaques were screened with a radioactively labeled probe consisting of the 1.3kb DNA fragment amplified from human cDNA using primers 3 and 4.

DNA Sequencing

Automated sequencing was carried out using as template the 3.3kb cDNA clone and a series of oligonucleotides designed from the completed sequence or using small subclones in pUC or M13 and standard sequencing primers. All the sequence shown in Figure 1 was verified by at least 2 separate sequencing runs and 95% of the sequence was verified by sequencing both strands.

Northern Blotting

A multitissue Northern blot was obtained from Clontech and hybridized with the radioactively labelled 3.3kb cloned cDNA probe. Hybridization and washing conditions were as recommended by the manufacturer.

Databases

Database searching and sequence comparisons were carried out using the programs at the European Bioinformatics Institute at Cambridge at http://www.ebi.ac.uk and sequence information on human chromosome 1 was obtained from the Sanger Centre at http://www.sanger.ac.uk.

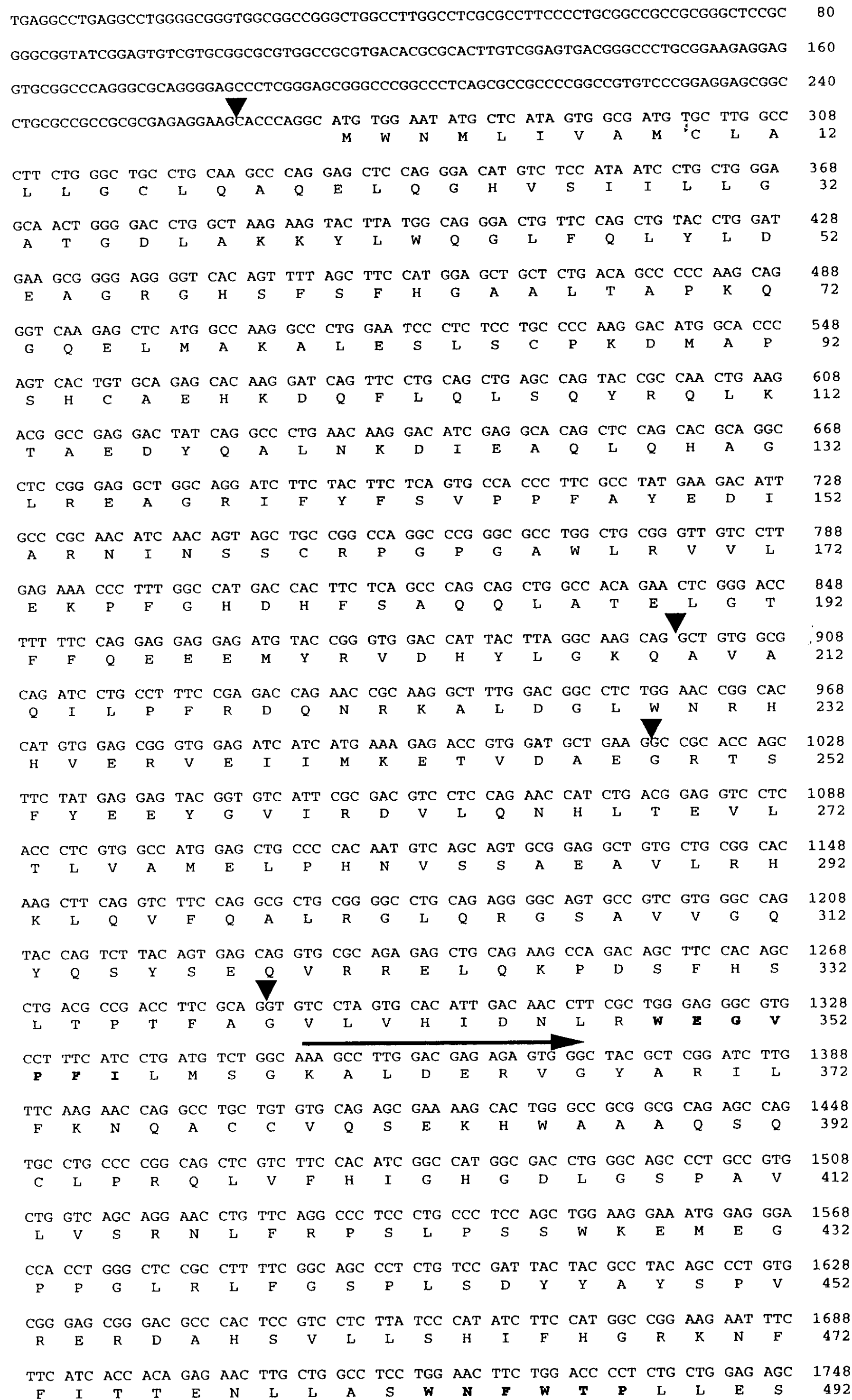

Figure 1. The sequence of H6PD cDNA and the derived amino acid sequence. The N-terminal methionine was chosen as the first methionine of the open reading frame. The corresponding rabbit protein which has been sequenced from the purified protein begins with QEL, amino acid 20 in the above sequence. Residues in bold show the positions of the peptides corresponding to those in the rabbit sequence used to design redundant oligonucleotides. Arrows indicate the oligonucleotides used to amplify a human RNA sequence by RT/PCR. The location of the introns is shown by the filled triangles.

```
CTG GCC CAT AAG GCC CCA CGC CTC TAC CCT GGA GGA GCT GAG AAT GGC CGT CTG TTG GAC  1808
 L   A   H   K   A   P   R   L   Y   P   G   G   A   E   N   G   R   L   L   D    512

TTT GAG TTC AGT AGC GGC CGG TTG TTC TTT TCC CAG CAG CAG CCG GAG CAG CTG GTG CCA  1868
 F   E   F   S   S   G   R   L   F   F   S   Q   Q   Q   P   E   Q   L   V   P    532

GGG CCA GGG CCG GCC CCA ATG CCC AGT GAC TTC CAG GTC CTC AGG GCC AAG TAC CGA GAG  1928
 G   P   G   P   A   P   M   P   S   D   F   Q   V   L   R   A   K   Y   R   E    552

AGC CCG CTG GTC TCC GCC TGG TCC GAG GAG CTG ATC TCT AAG CTG GCT AAT GAC ATC GAG  1988
 S   P   L   V   S   A   W   S   E   E   L   I   S   K   L   A   N   D   I   E    572

GCC ACC GCT GTG CGA GCC GTG CGG CGC TTT GGC CAG TTC CAC CTG GCA CTG TCG GGG GGC  2048
 A   T   A   V   R   A   V   R   R   F   G   Q   F   H   L   A   L   S   G   G    592

TCG AGC CCC GTG GCC CTG TTC CAG CAG CTG GCC ACG GCG CAC TAT GGC TTC CCC TGG GCC  2108
 S   S   P   V   A   L   F   Q   Q   L   A   T   A   H   Y   G   F   P   W   A    612

CAC ACG CAC CTG TGG CTG GTT GAC GAG CGC TGC GTC CCA CTC TCA GAC CCG GAG TCC AAC  2168
 H   T   H   L   W   L   V   D   E   R   C   V   P   L   S   D   P   E   S   N    632

TTC CAG GGC CTG CAG GCC CAC CTG CTG CAG CAC GTC CGG ATC CCC TAC TAC AAC ATC CAC  2228
 F   Q   G   L   Q   A   H   L   L   Q   H   V   R   I   P   Y   Y   N   I   H    652

CCC ATG CCT GTG CAC CTG CAG CAG CGG CTC TGC GCC GAG GAG GAC CAG GGC GCC CAG ATC  2288
 P   M   P   V   H   L   Q   Q   R   L   C   A   E   E   D   Q   G   A   Q   I    672

TAT GCC AGG GAG ATC TCA GCC CTG GTG GCC AAC AGC AGC TTC GAC CTG GTG CTG CTG GGC  2348
 Y   A   R   E   I   S   A   L   V   A   N   S   S   F   D   L   V   L   L   G    692

ATG GGT GCC GAC GGG CAC ACA GCC TCC CTC TTC CCA CAG TCA CCC ACT GGC CTG GAT GGC  2408
 M   G   A   D   G   H   T   A   S   L   F   P   Q   S   P   T   G   L   D   G    712

GAG CAG CTG GTC GTG CTG ACC ACG AGC CCC TCC CAG CCA CAC CGC CGC ATG AGC CTT AGC  2468
 E   Q   L   V   V   L   T   T   S   P   S   Q   P   H   R   R   M   S   L   S    732

CTG CCT CTC ATC AAC CGC GCC AAG AAG GTG GCA GTC CTG GTC ATG GGC AGG ATG AAG CGT  2528
 L   P   L   I   N   R   A   K   K   V   A   V   L   V   M   G   R   M   K   R    752

GAG ATC ACC ACG CTG GTG AGC CGG GTG GGC CAT GAG CCC AAG AAG TGG CCC ATC TCG GGT  2588
 E   I   T   T   L   V   S   R   V   G   H   E   P   K   K   W   P   I   S   G    772

GTC CTG CCG CAC TCC GGC CAG CTG GTG TGG TAC ATG GAC TAC GAC GCC TTC CTG GGA TGA  2648
 V   L   P   H   S   G   Q   L   V   W   Y   M   D   Y   D   A   F   L   G   *    792

GGGCGCCTGTGCCCCTTGCCCGCTTCGCTCCTGTGCTTTCCTTCGCCCGTGTCTTCCCTCCCTTCTCGGCCCCGCCACCT 2728

GCCCAGCGTGCCCTGGCTCTCCAGAACCTTCTATCCCACAGTCAGGCCCCAGAGAGGGCAGGACAAGCCTTGTCCCGATG 2805

CCTTTGACCGGCAGCTCTGTGTATTGGTGGATAGATGCAGAAACA                                    2853
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Figure 1. (Cont'd)

RESULTS

cDNA Cloning

Our strategy to isolate the human cDNA was firstly to use primers designed from the rabbit protein sequence (3) to amplify a portion of rabbit cDNA and then to use this as a probe to isolate the human cDNA by library screening. The rabbit sequence contains the peptides MEGVPFI and WVFWTP (the equivalent peptides in the human sequence are highlighted in Figure 1) separated by 127 amino acids. The corresponding redundant oligonucleotides primers 1 and 2 were synthesized and used to amplify rabbit cDNA by RT/PCR starting with rabbit liver polyA RNA. A fragment of the correct size was obtained and partial sequencing data from this fragment was obtained after cloning restriction enzyme fragments (generated by enzymes Sau3a and Taq1) into phage M13. The resulting sequence encoded the correct amino acid sequence from part of the rabbit protein. The sequence was used to search public databases using a BLAST homology search and was found to have good homology with a human genomic sequence (accession number Z98044) from chromosome 1p36 currently being studied at the Sanger Centre, Hinxton, UK. The coding sequence for part of a protein very similar to the rabbit protein was identified within this genomic sequence and used to design primers (3 and 4) to amplify a 1.3 kb fragment of human cDNA from RNA from the human liver cell line Hep G2. This fragment was used as a probe to screen a human bone marrow cDNA library. 200,000 plaques were screened and 2 clones were obtained which had inserts of about 1.7 and 3.3kb. The 3.3kb clone was

sequenced and found to code for a protein very similar to the rabbit H6PD. The sequence of 2853 nucleotides containing the entire open reading frame and derived amino acid sequence is shown in figure 1.

Characterization of mRNA

Northern blotting (Figure 2) showed a 9kb mRNA present in most tissues examined and strongest in liver, in agreement with the known distribution of enzyme activity. An mRNA of this length, assuming the cDNA clone extends close to the 5' end of the mRNA would imply the 3' untranslated region of the mRNA is 6.5 kb in length. Analysis of the genomic sequence reveals that the first AAUAAA polyadenylation sequence in the 3' untranslated region of the mRNA would occur 6.5 kb after the stop codon, in good agreement with a mRNA size of 9kb. Searching expressed sequence tag (EST) databases with this proposed 3'UTR sequence finds many ESTs with perfect homology from a variety of tissues including several which end 19 bases after this proposed polyadenylation signal. These cDNAs were not identified and many were noted to contain an Alu element. The 3' UTR of the proposed mRNA contains 4 Alu elements.

Gene Structure

By comparing the cDNA sequence with the genomic sequence in the data base entry (accession number Z98044) we were able to deduce the intron/exon organization of the human gene on chromosome 1p36 (Figures 1 and 3). The gene consists of 5 exons and 4 introns and spans 37kb. There is an intron of 9800 bp in the 5' non coding region and the final exon is greater than 7800 bp in length and encodes 453 amino acids, well over half the protein.

DISCUSSION

The sequence codes for a protein of 791 amino acids with a molecular weight of 89 kDa. Comparison with the published rabbit sequence (3) shows the human sequence has 85% identity with its rabbit counterpart (not shown) but there is a stretch of 119 amino acids (610 to 728) that are transposed apart from 13 residues to position 330-435 in the published rabbit sequence. Since the cDNA sequence is in agreement with the genomic sequence we feel the rabbit sequence derived by protein sequencing may have been misaligned. The derived protein sequence has extensive homology with cytosolic G6PD (Figure 4) and in particular the known functional motifs in G6PD are well conserved. These are the coenzyme binding site GAXGDLA (32-38) (2) and the glucose-6-phosphate binding site DHYLGK (203-208) (16). The C-terminal 250 amino acids do not have any homology with cytosolic G6PD. This sequence contains some homology with a diverse family of proteins and derived protein sequences including the devb family (small proteins of unknown function some of which are encoded next to G6PD in certain microorganisms) (17), the N-terminus of *Plasmodium falciparum* G6PD (18) and the yeast SOL 1-3 proteins thought to be involved in tRNA expression or function (19). The C-terminus also contains a good consensus coenzyme binding fold GMGADG at 692-697 which is conserved in all members of these proteins. Elucidating the function of this diverse set of proteins will require further experiments.

The extensive homology between G6PD and H6PD suggests the two proteins share a common ancestor. In the genomic DNA coding for the homologous part of the protein H6PD contains 3 introns and G6PD 12; none of the introns interrupt the sequence in a corresponding position suggesting the duplication event that gave rise to the two genes occured very early in evolution.

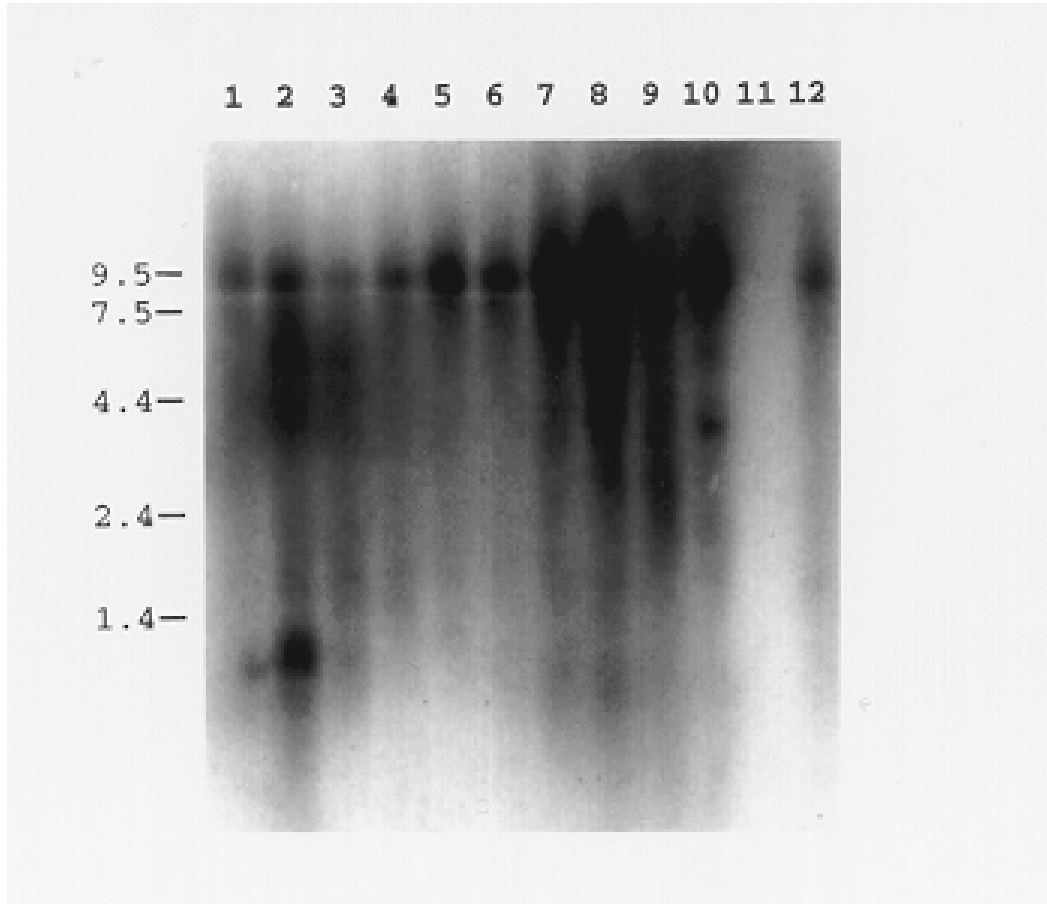

Figure 2. Northern blot. A multitissue Northern blot (Clontech) was hybridized with the 3.3kb cloned cDNA probe. The sizes shown on the left were supplied by the manufacturer. Tracks were 1 brain, 2 heart, 3 skeletal muscle, 4 colon, 5 thymus, 6 spleen, 7 kidney, 8 liver, 9 small intestine, 10 placenta, 11 lung, 12 peripheral blood leukocytes.

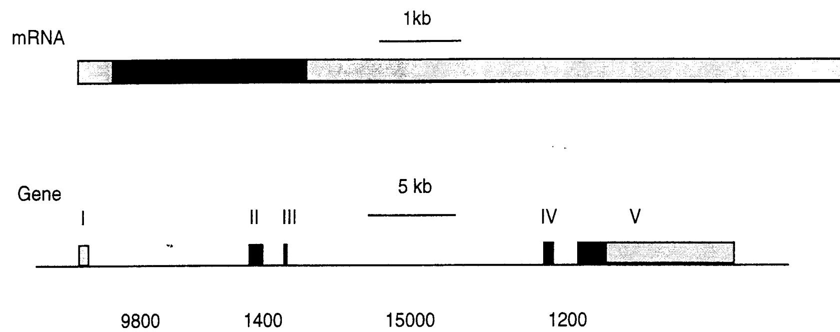

Figure 3. The structure of the H6PD gene at 1q36 derived from the genomic sequence available via accession number Z98044 from the EMBL database. Solid boxes represent coding regions. The sizes of the introns is given in bp below the figure.

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H6PD   MWNMLIVAMCLALLGCLQAQELQG---HVS----IILLGATGDLAKKYLWQGLFQLYLDE 53
G6PD   -MAEQVALSRTQVCGILREELFQGDAFHQSDTHIFIIMGASGDLAKKKIYPTIWWLFRDG 59
         :.     : * *: : :**   * *    :*::**:****** ::  :: *: *

H6PD   AGRGHSFSFHGAALTAPKQGQELMAKALESLSCPKDMAPSHCAEHKDQFLQLSQYR-QLK 112
G6PD   LLPENTFIVG------YARSRLTVADIRKQSEPFFKATPEEKLKLEDFFARNSYVAGQYD 113
          ::* .          :.:  :*.  :. .   . :*..  : :* * : *    * .

H6PD   TAEDYQALNKDIEAQLQHAGLREAGRIFYFSVPPFAYEDIARNINSSCRPGPGAWLRVVL 172
G6PD   DAASYQRLN--SHMNALHLGS-QANRLFYLALPPTVYEAVTKNIHESCMSQIG-WNRIIV 169
        * .** **    . :   * *  :*.*:**:::** .** :::**:.** .   * * *:::

H6PD   EKPFGHDHFSAQQLATELGTFFQEEEMYRVDHYLGKQAVAQILPFRDQNRKALDGLWNRH 232
G6PD   EKPFGRDLQSSDRLSNHISSLFREDQIYRIDHYLGKEMVQNLMVLRFANR-IFGPIWNRD 228
       *****:*  *:::*:..:.::*:*:::**:******: * ::: :*  **  :. :***.

H6PD   HVERVEIIMKETVDAEGRTSFYEEYGVIRDVLQNHLTEVLTLVAMELPHNVSSAEAVLRH 292
G6PD   NIACVILTFKEPFGTEGRGGYFDEFGIIRDVMQNHLLQMLCLVAMEKPASTNSDDVRD-E 287
       ::  * : :**...:*** .:::*:*:****:**** ::* ***** * ...* :.   .

H6PD   KLQVFQALRGLQRGSAVVGQYQS----YSEQVRRELQKPDS-FHSLTPTFAGVLVHIDNL 347
G6PD   KVKVLKCISEVQANNVVLGQYVGNPDGEGEATKGYLDDPTVPRGSTTATFAAVVLYVENE 347
       *::*:::.:  :* ...*:*** .      .* .:  *:.*      * *.***.*:::::*

H6PD   RWEGVPFILMSGKALDERVGYARILFKNQACCVQSEKHWAAAQSQCLPRQLVFHIGHGDL 407
G6PD   RWDGVPFILRCGKALNERKAEVRLQFHDVAGDIFHQ------Q--CKRNELVIRVQP--- 396
       **:****** .****:** . .*: *:: *  :  :       *  *  .:**:::

H6PD   GSPAVLVSRNLFRPSLPSSWKEMEGPPGLRLFGSPLSDYYAYSPVRERDAHSVLLSHIFH 467
G6PD   -NEAVYTKMMTKKPGMFFNPEESE---LDLTYGN----RYKN--VKLPDAYERLILDVFC 446
        . ** ..     :*.:  . :* *        :*.      *     *:  **:. *: .:*

H6PD   GRKNFFITTENLLASWNFWTPLLESLAHKAPRLYPGG-AENGRLLDFEFSSGRLFFSQQQ 526
G6PD   GSQMHFVRSDELREAWRIFTPLLHQIELEKPKPIPYIYGSRGPTEADELMKRVGFQYEGT 506
       * : .*: :::*  :*.::****..:  : *:  *   ...*     *: .    *  :

H6PD   PEQLVPGPGPAPMPSDFQVLRAKYRESPLVSAWSEELISKLANDIEATAVRAVRRFGQFH 586
G6PD   YKWVNPHKL--------------------------------------------------- 515
        : : *

H6PD   LALSGGSSPVALFQQLATAHYGFPWAHTHLWLVDERCVPLSDPESNFQGLQAHLLQHVRI 646
G6PD   ------------------------------------------------------------

H6PD   PYYNIHPMPVHLQQRLCAEEDQGAQIYAREISALVANSSFDLVLLGMGADGHTASLFPQS 706
G6PD   ------------------------------------------------------------

H6PD   PTGLDGEQLVVLTTSPSQPHRRMSLSLPLINRAKKVAVLVMGRMKREITTLVSRVGHEPK 766
G6PD   ------------------------------------------------------------

H6PD   KWPISGVLPHSGQLVWYMDYDAFLG 791
G6PD   -------------------------
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Figure 4. Alignment of human H6PD with human G6PD. The alignment was derived using the Clustal program via the European Bioinformatics Institute, Hinxton. Boxed sequences are the conserved coenzyme and substrate binding sites referred to in the text.

ACKNOWLEDGMENTS

We would like to thank Lisa Lowery for doing the automated sequencing and Nick Cross for help with reverse transcription. This work has made extensive use of the computing facilities at the European Bioinformatics Institute at Cambridge at and has been greatly facilitated by sequencing work done by the chromosome 1 project at the Sanger Centre and their policy of making their data available to the community. This work was supported by the MRC and by the European Community through a fellowship to A.D. The sequence data presented in this paper has been submitted to to the EMBL database and assigned the accession number AJ012590.

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