

Hematologically Important Mutations: Red Cell Pyruvate Kinase (2nd update)

Submitted 06/29/98

(communicated by Ernest Beutler, M.D., 07/06/98)

Luciano Baronciani, Paola Bianchi, Alberto Zanella

Pyruvate kinase (PK) deficiency is known to be the most common cause of chronic nonspherocytic hemolytic anemia (CNSHA). Two PK genes are present in mammals, *PKLR* and *PKM*, but only the former codes for the isoenzyme normally expressed in the red cell (R-type).

A total of 117 mutations in the *PKLR* gene associated with CNSHA are here reported in Table 1, whereas Table 2 provides the polymorphic sites identified in the gene. Mutations and polymorphisms are designated using the cDNA sequence of the R-type isoenzyme and genomic DNA sequence of the *PKLR* gene, with the A of the initiation ATG being assigned number +1. The GenBank accession numbers are D10326 D90465 for the cDNA, U47654 for the genomic DNA and D13232 for the putative promoter region. The

numbering system in the tables varies from that of GenBank and in order to designate the initiated A as +1 it is necessary to subtract 39 from the sequences D10326 or U47654. The following discrepancies are present between sequence D10326 and U47654: nt 1 t→c, 324 T→G, 330 T→A, 342 T→G, 427 A→T, 432 A→C, 733 A→G, 774 G→C, 1458 A→G (numbers according to sequence D10326). Moreover, in sequence D13232 the following discrepancies have been reported (1): nt 244G→GG, 251G→GA, 265A→AAA. These nucleotide changes are in progress to be updated. Additional information can be found in the published reviews (2,3) and a continuously updated review is reported on the World Wide Web in OMIM at: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?266200>. © 1998 Academic Press

Table 1. Mutations reported in the *PKLR* gene

Variant Name ^a	cDNA Nucleotide Substitution	Genomic Nucleotide Substitution	Amino Acid Substitution	Exon	Reference
*	-284 t→a -44 g→c	-284 t→a -44 g→c	Promoter		(4)
*	IVS2(-1) g→a	1105a	Splice Site	IVS2	(5)
*	110 G→A	1115A	37 Gly→Gln	3	(6)
"Essen"	183 16bp 184 ins	1188 16bp 1189 ins	Frameshift	3	(7)
*	227-231 TGGAC _{del}	1232-1236 del	Frameshift	3	(8)

Divisione di Ematologia, I.R.C.C.S. Ospedale Maggiore, Milano

Reprint request to: Luciano Baronciani, Ph.D., Divisione di Ematologia and Centro Trasfusionale e di Immunologia dei Trapianti, I.R.C.C.S. Ospedale Maggiore, Via F. Sforza, 35 Milano 20122 Italy, phone 39 2 55033471, fax 39 2 55033425, email: l.baronciani@agora.stm.it

Variant Name ^a	cDNA Nucleotide Substitution	Genomic Nucleotide Substitution	Amino Acid Substitution	Exon	Reference
*	238 T→C	1243C	80 Ser→Pro	3	(9)
*	257 G→C	1262C	86 Arg→Pro	3	(10)
*	269 T→A	1274A	90 Ile→Asn	3	(4)
*	283 G→T	1288T	95 Gly→Arg	3	(4)
*	IVS3(-2) a→c	2467c	Splice Site	IVS3	(8)
"Aomori"	IVS3(-2) a→t	2467t	Splice Site	IVS3	(11)
*	307 C del	2492 del	Frameshift	4	(12)
*	320 T→C	2505C	107 Met→Thr	4	(1)
*	331 G→A	2516A	111 Gly→Arg	4	(4)
"Val de Marne"	343 G→C	2528C	115 Ala→Pro	4	(13)
"Beaujon"	359 C→T	2544T	120 Ser→Phe	4	(13)
Conakry	389 C→A	2670A	130 Ser→Tyr	5	(14)
*	391-393 ATC del	2672-2674 del	131 Ile del	5	(15)
*					(1)
*	401 T→A	2682A	134 Val→Asp	5	(15)
*					(4)
Beppu	434 C del	2715 del	Frameshift	5	(16)
*	464 T→C	2745C	155 Leu→Pro	5	(15)
*	475 G→T	2756T	159 Gly→Val	5	(17)
Linz	487 C→T	2768T	163 Arg→Cys	5	(18)
*	IVS5(+1) g→a	2789a	Splice Site	IVS5	(4)
Sassari	514 G→C	2928C	172 Glu→Gln	6	(8)
Shimane	520 G→T	2934T	174 Glu→End	6	(19)
*	603 G→A	3017A	201 Trp→End	6	(1)
*	628-629 GT del	3042-3043 del	Frameshift	6	(20)
*	663 GAC 664 ins	3077 GAC 3078 ins	221 Asp 222 ins	6	(16)
"Katsushika"	665 G→C	3079C	222 Gly→Ala	6	(21)
*	IVS6(-2) a→t	3469t	Splice Site	IVS6	(22)
*	721 G→T	3497T	241 Glu→End	7	(15)
"Bukarest"					(23)
*					(1)
*					(12)
*					(8)
*					(13)
*					(4)
*	787 G→A	3563A	263 Gly→Arg	7	(20)
"Torre Annunziata"	787 G→T	3563T	263 Gly→Trp	7	(8)
*	808 C→T	3584T	270 Arg→End	7	(12)
*	823 G→C	3599C	275 Gly→Arg	7	(1)
*	823 G→A	3599A	275 Gly→Arg	7	(8)
*	841 G→A	3617A	281 Asp→Asn	7	(16)
*	859 T→G	3635G	287 Phe→Val	7	(16)
"Moriguchi"	862 G→T	3638T	288Val→Leu	7	(21)
*	884 C→T	3660T	295 Ala→Val	7	(17)
"Dordrecht"	929 T→A	3705A	310 Ile→Asn	7	(24)
Hong Kong	941 T→C	3717C	314 Ile→Thr	7	(25)
*	943 G→A	3719A	315 Glu→Lys	7	(17)
Kowloon	IVS7(+1) g→t	3742t	Splice Site	IVS7	(11)

Variant Name ^a	cDNA Nucleotide Substitution	Genomic Nucleotide Substitution	Amino Acid Substitution	Exon	Reference
*	991 G→A	3863A	331 Asp→Asn	8	(7)
"Parma"	993 C→A	3865A	331 Asp→Glu	8	(12) (8)
*	994 G→A	3866A	332 Gly→Ser	8	(5)
*					(8)
*					(26)
*					(20)
*	1006 G→T	3878T	336 Ala→Ser	8	(5)
*	1010 G→C	3882C	337 Arg→Pro	8	(27)
*	1010 G→A	3882A	337 Arg→Gln	8	(20)
*	1022 G→C	3894C	341 Gly→Ala	8	(12)
*	1022 G→A	3894A	341 Gly→Asp	8	(17)
*	1024 A→T	3896T	342 Ile→Phe	8	(26)
"Brescia"	1042-1044 AAG del	3914-3916 del	348 Lys del	8	(22)
"Kamata"	1044 G→T	3916T	348 Lys→Asn	8	(11)
*	1055 C→A	3927A	352 Ala→Asp	8	(7)
*	1060-1062 AAG del	3932-3934 del	354 Lys del	8	(5)
*					(20)
"Aomori"	1075 C→T	3947T	359 Arg→Cys	8	(16)
*	1076 G→A	3948A	359 Arg→His	8	(15)
*	1081 A→G	3953G	361 Asn→Asp	8	(5)
*					(20)
*	1089 G 1090 ins	3961 G 3962 ins	Frameshift	8	(12)
Tjaereborg	1091 G→A	3963A	364 Gly→Asp	8	(28)
"Osaka"	1102 G→T	3974T	368 Val→Phe	8	(29)
*	1127 G→T	4643T	376 Ser→Ile	9	(20)
Tokyo	1151 C→T	4667T	384 Thr→Met	9	(30)
Beirut					(18)
Nagasaki					(31)
Mosul					(23)
*					(22)
*	1160 A→G	4676G	387 Glu→Gly	9	(22)
"Mantova"	1168 G→A	4684A	390 Asp→Asn	9	(8)
*	1174 G→A	4690A	392 Ala→Thr	9	(5)
*	1178 A→G	4694G	393 Asn→Ser	9	(12)
"Paris"					(13)
*					(4)
*	1179 T→A	4695A	393 Asn→Lys	9	(12)
*	1181 C→A	4697A	394 Ala→Asp	9	(22)
*	1181 C→T	4697T	394 Ala→Val	9	(22)
Mondor	1195 G del	4711 del	Frameshift	9	(32)
*	1203 AGC 1204 ins	4719 AGC 4720 ins	401 Cys 402 ins	9	(5)
"Hirosaki"	1222 A→G	4738G	408 Thr→Ala	9	(21)
Fukushima	1261 C→A	4777A	421 Gln→Lys	9	(31)
Maebashi					(31)
Sendai					(25)
"Kamata"	1269 G→A	4785A	Splice Site	9	(16)
*					(4)

Variant Name ^a	cDNA Nucleotide Substitution	Genomic Nucleotide Substitution	Amino Acid Substitution	Exon	Reference
"Torre Annunziata"	1269 G-C	4785C	Splice Site	9	(8)
*	IVS9(+3)a-g	4788g	Splice site	IVS9	(10)
Naniwa *	1276 C-T	4886T	426 Arg-Trp	10	(16) (1)
Sapporo	1277 G-A	4887A	426 Arg-Gln	10	(33)
"Katsushika"	1280 A-C	4890C	427 Glu-Ala	10	(21)
*	1281 G-T	4891T	427 Glu-Asp	10	(20)
*	1373 G-A	4983A	458 Gly-Asp	10	(12)
*	1376 C-T	4986T	459 Ala-Val	10	(1)
*	1378 G-A	4988A	460 Val-Met	10	(12)
*					(1)
Hadano	1403 C-T	5013T	468 Ala-Val	10	(25)
*	1403 C-G	5013G	468 Ala-Gly	10	(10)
"Sakurajima"	1429 A-G	5039G	477 Thr-Ala	10	(21)
Amish Shinshu	1436 G-A	5046A	479 Arg-His and Splice Site	10	(34) (25)
Gypsy	1437-1618 del	5768-6905 del	Frameshift	11	(12)
*	1454 C-T	6303T	485 Ser-Phe	11	(20)
*	1456 C-T	6305T	486 Arg-Trp	11	(15)
*					(27)
*					(12)
"Soresina"					(8)
Milano					(8)
"Parma"					(8)
*					(20)
*					(4)
"Brescia"					(22)
*	1462 C-T	6311T	487 Arg-End	11	(4)
*	1463 G-A	6312A	488 Arg-Gln	11	(10)
*	1468 C-T	6317T	490 Arg-Trp	11	(16)
*					(9)
"Tama"					(35)
"Gifu"					(35)
"Yamagata"					(36)
*	1483 G-A	6332A	495 Ala-Thr	11	(7)
*					(22)
*	1484 C-T	6333T	495 Ala-Val	11	(15)
*					(12)
*					(1)
"Rouen"	1488 C del	6337 del	Frameshift	11	(13)
*	1492 C-T	6341T	498 Arg-Cys	11	(27)
*					(4)
*	1493 G-A	6342A	498 Arg-His	11	(12)
*					(5)
*	1501 C-T	6350T	501 Gln-End	11	(1)
*	1511 G-T	6390T	504 Arg-Leu	11	(17)
*	1523 T-G	6372G	508 Leu-End	11	(27)
*	1528 C-T	6377T	510 Arg-End	11	(17)

Variant Name ^a	cDNA Nucleotide Substitution	Genomic Nucleotide Substitution	Amino Acid Substitution	Exon	Reference
* * "Hamburg" "Köln" Aprica * * * * * *	1529 G-A	6378A	510 Arg→Gln	11	(15) (5) (23) (23) (8) (27) (12) (1) (13) (37) (20) (4)
"Nichinan"	1531 G-A	6380A	511 Gly→Arg	11	(21)
"Soresina" "Yamagata"	1552 C-A	6401A	518 Arg→Ser and Splice Site	11	(8) (36)
*	1574 G 1575 ins	6423 G 6424 ins	Frameshift	11	(1)
*	1591 C-T	6440T	531 Arg→Cys	11	(21)
* "Bukarest" *	1594 C-T	6443T	532 Arg→Trp	11	(5) (23) (8)
*	1641 A 1642 ins	7555 A 7556 ins	Frameshift	12	(10)
* *	1654 G-A	7568A	552 Val→Met	12	(1) (4)
*	1675 C-G	7589G	559 Arg→Gly	12	(1)
*	1675 C-T	7589T	559 Arg→End	12	(22)
*	1698 C-A	7612A	566 Asn→Lys	12	(16)

^a The variants reported in quotes have been found to be heterozygous for the corresponding mutation.

* The variant has no name.

Table 2. Polymorphisms in the *PKLR* gene

Polymorphic Site cDNA Number	Polymorphic Site Genomic Number	Exon	Reference
IVS5(+51)C/T	2838 C/T	IVS5	(38) (8) (39)
T _{10/19} ^b	5972-5981 (T ₁₀)	IVS11	(40)
Microsatellite ATT	7181-7222 (14 ATT)	IVS12	(41)
1705 A/C	7619 A/C	Exon 12	(31)
1738 C/T	7652 C/T	Exon 12	(8) (24)
1992 C/T	7906 C/T	Exon 12	(40)

^b T-stretch occurring in the two forms (T)₁₀ and (T)₁₉

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