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Review

Red blood cell PK deficiency: An update of *PK-LR* gene mutation database

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ABSTRACT

Pyruvate kinase (PK) deficiency is known as being the most common cause of chronic nonspherocytic hemolytic anemia (CNSHA). Clinical PK deficiency is transmitted as an autosomal recessive trait, that can segregate neither in homozygous or in a compound heterozygous modality, respectively. Two *PK* genes are present in mammals: the pyruvate kinase liver and red blood cells (*PK-LR*) and the pyruvate kinase muscle (*PK-M*), of which only the first encodes for the isoenzymes normally expressed in the red blood cells (R-type) and in the liver (L-type). Several reports have been published describing a large variety of genetic defects in *PK-LR* gene associated to CNSHA. Herein, we present a review of about 250 published mutations and six polymorphisms in *PK-LR* gene with the corresponding clinical and molecular data. We consulted the PubMed website for searching mutations and papers, along with two main databases: the Leiden Open Variation Database (LOVD, https://grenada.lumc.nl/LOVD2/mendelian_genes/home.php?select_db=PKLR) and Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/gene.php?gene=PKLR) for selecting, reviewing and listing the annotated *PK-LR* gene mutations present in literature.

This paper is aimed to provide useful information to clinicians and laboratory professionals regarding overall reported *PK-LR* gene mutations, also giving the opportunity to harmonize data regarding PK-deficient individuals.

Contents

1. Introduction

PK deficiency, an autosomal recessive disorder, is the most known and frequent enzyme abnormality of the glycolytic pathway, and together with Class I Glucose-6-Phosphate Dehydrogenase mutations [1,2] represents the most common cause of hereditary non-spherocytic hemolytic anemia (CNSHA). The prevalence of PK deficiency has been estimated to be 1:20000 in the general white population [3]. Since the first detection in the early '60s, many cases have been described.

Although abnormalities in *PK-LR* gene may result in alterations of both erythrocyte and liver enzyme, clinical symptoms are confined to red blood cells (RBCs). The severity of clinical picture is variable, ranging from mild or fully compensated forms to life-threatening neonatal anemia that requiring exchange transfusions and subsequent continuous transfusion support. It is worth noting that the anemia may be surprisingly well tolerated in PK deficient patients because of the increased RBCs 2,3-BPG content, resulting in decreased hemoglobin oxygen affinity.

The hematological tests for PK deficiency are common to other CNSHA diseases: variable severity of anemia, reticulocytosis and biochemical signs of hemolysis (lactate dehydrogenase, haptoglobin, serum total bilirubin, hemoglobin, hematocrit). Splenectomy usually

Abbreviations: PK-LR, pyruvate kinase liver and red blood cells; PK-M, pyruvate kinase muscle; CNSHA, chronic nonspherocytic hemolytic anemia; RBCs, red blood cells; LOVD, Leiden Open Variants Database; HGMD, Human Gene Mutation Database.

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Table 1
All variants of the *PK-LR* gene reported in the literature.

cDNA nucleotide substitution	Aminoacid substitution	Exon	Type of mutation	Origin	Comments	References
1. *Point missense mutations*						
92 C > T	A31V	3	S	North Africa	Heterozygote	[14]
107 C > G	p.A36G	3	S	Central Italy	Heterozygote	[15]
110 G > A	p.G37Q	3	S	Netherlands	NA	[16]
118 C > T	p.R40W	3	S	Netherlands	Heterozygote	[17]
119 G > A	p.R40Q	3	S	China	NA	[18]
218 T > C	p.L73P	3	S	Czech	Compound heterozygote for 1060_1062delAAG	[17]
238 T > C	p.S80P	3	S	Japan	Compound heterozygote for 1468 C > T	[19]
245 C > A	p.P82H	3	S	Italy	Compound heterozygote for 1456 C > T	[20]
257 G > C	p.R86P	3	S	Japan	NA	[21,22]
269 T > A	p.I90N	3	S	Netherlands	Compound heterozygote for 331 G > A	[17,23]
278 C > T	p.T93I	3	S	Central Italy	Compound heterozygote for 1456 C > T	[15]
283 G > A	p.G95R	3	S	Netherlands	NA	[23]
320 T > C	p.M107T	4	S	USA black	Compound heterozygote for 1529 G > A	[24]
331 G > A	p.G111R	4	S	Netherlands	Compound heterozygote for 929 T > A; compound heterozygote for 1456 C > T; compound heterozygote for 1492 C > T	[17,23]
343 G > C [PK Val-de-Marne]	p.A115P	4	S	France	Heterozygote	[25]
359 C > T [PK Beaujon]	p.S120F	4	S	France	Heterozygote	[25]
363 C > A	p.H121Q	4	S	France	Compound heterozygote for IVS4-1 G > A	[26]
388 T > C	p.S130P	5	S	France	NA	[18]
389 C > A [PK Conakry]	p.S130Y	5	S	Guinea	Homozygote	[27]
401 T > A	p.V134D	5	S	USA	Compound heterozygote for 1456 C > T	[28]
403 C > T	p.R135D	5	S	Pakistan	Compound heterozygote for 1190 A > T	[15]
409 G > A	p.A137T	5	S	Australia	Compound heterozygote for 283 + 1914_1436del5006bp	[15]
427 G > A	p.G143S	5	S	India	Compound heterozygote for 1436 G > A	[29]
458 T > C	p.I153T	5	S	Germany/Turkia	Compound heterozygote for 238 T > C	[30]
460 G > A	p.A154T	5	S	Czech	Heterozygote	[17]
464 T > C	p.L155P	5	S	USA	Compound heterozygote for 1529 G > A	[28]
476 G > T	p.G159V	5	S	Caucaso	Compound heterozygote for 1529 G > A	[31]
487 C > T [PK Linz]	p.R163C	5	S	Turkia	Homozygote	[32]
488 G > T	p.R163L	5	S	Turkia	Homozygote	[17]
491 C > A	p.T164N	5	S	Portugal	NA	[18]
494 G > T	p.G165V	5	S	Netherlands	Compound heterozygote for 142_159delACCCAGGAGCTGGGCACT	[17]
499 C > A	p.L167M	5	S	India	Compound heterozygote for 992 A > G	[29]
507 G > A	p.G169G	5	Splicing	Northern Italy	Compound heterozygote for 721 G > T	[15]
514 G > C [PK Sassari]	p.E172Q	6	S	Italy	Homozygote	[33]
601 T > C	p.W201R	6	S	France	Compound heterozygote for −248 delT	[26,34,35]
656 T > C	p.I219T	6	S	Germany/Turkia	Compound heterozygote for 359 C > T	[30]
661 G > T	p.A221Y	6	S	Italy	Compound heterozygote for IVS4 + 10G > T	[36]
661 G > A	p.D221N	6	S	Central Italy	Compound heterozygote for 1209 G > A	[15]
665 G > C [PK Katsushika]	p.G222A	6	S	Japan	NA	[22,37]
671 T > C	p.I224T	6	S	France	Compound heterozygote for 1168 G > A	[26,34]
694 G > T	p.G232C	6	Hypothetical splicing and stop downstream	France	NA	[26]
757 A > G	p.N253D	7	S	Netherlands	NA	[13,38]
787 G > A	p.G263R	7	S	Germany	Heterozygote	[39]
787 G > T [PK Torre Annunziata]	p.G263W	7	S	Italy	Compound heterozygote for 1269 G > C	[33]
796 G > A	p.E266K	7	S	France	Heterozygote	[26]
805 G > C/A	p.V269F	7	S	Pakistan	Heterozygote	[14]
814 C > G	p.L272V	7	S	Netherlands/Ghana	Heterozygote	[17,38]
815 T > C	p.L272P	7	S	Portugal	NA	[40]
823 G > C	p.G275R	7	S	Ireland	Compound heterozygote for 1484 C > T	[24]

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