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Prevalence of Red Cell Pyruvate Kinase Deficiency: A Systematic Literature Review

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BACKGROUND

- Pyruvate Kinase (PK) deficiency is a rare congenital hemolytic anemia characterized by diminished activity of the PK enzyme in red blood cells (RBC).[1]
- Low PK enzyme activity can lead to lifelong chronic hemolysis with associated symptoms and complications such as anemia, jaundice, gallstones, splenectomy and associated thrombosis, iron overload, and liver cirrhosis.[2]
- PK deficiency is caused by compound heterozygosity or homozygosity for one or more of the >300 known mutations[3] to the *PKLR* gene.
  - These *PKLR* mutations have differing impacts on PK function and likely contribute to the notable clinical heterogeneity in the disorder.[2]
- Reports of PK deficiency prevalence vary by orders of magnitude, likely due to a combination of factors:
  - The extreme rarity of the disorder;
  - Similar phenotype to other RBC disorders leading to misdiagnosis;
  - Heterogeneous clinical presentation;
  - Ethnic and geographic variability; and
  - Different methods used in published reports of prevalence.

OBJECTIVES

The objectives of this systematic literature review were:

- To estimate the prevalence of PK deficiency by critically appraising reported prevalence rates; and
- To better understand factors contributing to the wide range of reported prevalence values.

METHODS

Information Sources

The following sources were queried using PK deficiency and *PKLR* Emtree and Medical Subject Heading (MeSH) terms and keywords combined with epidemiology and gene frequency Emtree/MeSH terms and keywords:

- Embase (1/1/1974 – 1/22/2019) and Medline (1/1/1946 – 1/22/2019);
- A single conference year (2018) of the Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) not indexed by Embase/Medline; and
- Other relevant references encountered over the course of the systematic literature review.

Inclusion Criteria

- Peer-reviewed publications (articles, letters, editorials, or comments) and conference abstracts published (or in press) in English before January 23, 2019;
- Publications describing one of the following:
  - PK deficiency epidemiology defined as one or more of the following among a source population selected without respect to PK deficiency symptoms:
    - Point/period prevalence;
    - Incidence rate/proportion; and/or
    - Survival duration, life expectancy, and mortality rate;
  - Mutant Allele Frequencies (MAFs) for *PKLR* mutations among a general population; or
  - Crude results from which PK deficiency epidemiology or *PKLR* MAFs could be derived.

METHODS *(continued)*

Exclusion Criteria

- Non-human studies;
- Publications that were not the primary report of the data (e.g., literature reviews);
- Studies of PK deficiency prevalence/incidence conducted within a source population of patients with symptoms of PK deficiency such as anemia or jaundice;
- Studies that only reported *PKLR* MAFs among PK deficiency patients; and
- Studies reporting only MAFs for *PKLR* mutations unlikely to cause loss/reduction of PK function as stated by the authors or inferred from amino acid substitution prediction models.

Quality Assessment

- A tailor-made, qualitative quality assessment tool was created. Quality considerations included study generalizability, validity of methods, potential sources of bias, and limitations as reported by the authors.
- The generalizability, quality, and consistency of all outcome statistics were considered collectively to evaluate the weight and associated uncertainty of the evidence of PK deficiency prevalence.

Study Selection Process

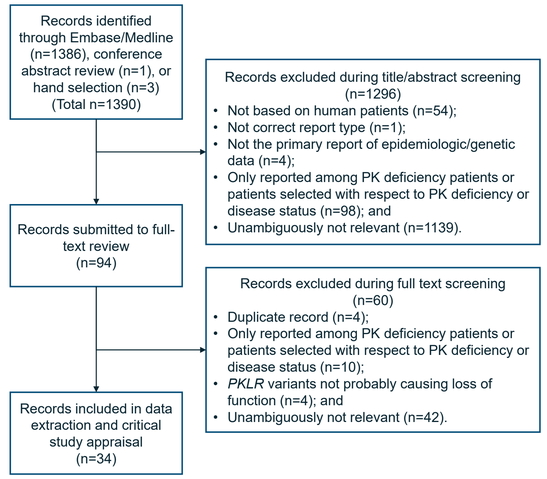
Studies were reviewed by two independent reviewers using the following process:

- Titles and abstracts of all references were screened for eligibility; and
- Data extraction and quality assessment were performed on studies meeting all eligibility criteria after full-text review.

RESULTS

- Of 1390 references screened, 1296 were excluded after title/abstract review and 60 were excluded after full text review (**Figure 1**).

Figure 1. Flow diagram of studies meeting inclusion/exclusion criteria



RESULTS *(continued)*

The remaining 34 studies were grouped based on methods and study population (**Table 1**).

Table 1. Distribution of extracted studies by type of study (n=34)

Type of study	Number of studies
Population-based prevalence	2
Molecular *PKLR* screening in a general population	5
Molecular *PKLR* screening in areas with endemic malaria	4
Molecular *PKLR* screening in other unique population	2
Non-molecular PK deficiency screening in a general population	9
Non-molecular PK deficiency screening in areas with endemic malaria	3
Non-molecular PK deficiency screening in areas with high consanguinity	6
Non-molecular PK deficiency screening in other unique population	3

Potential sources of bias in estimating PK deficiency prevalence were identified in 30 of 34 eligible studies and included:

- A non-generalizable study population (e.g., malaria-endemic areas);
- Use of diagnostic assays of questionable accuracy;
- Consideration of mutations with incomplete penetrance; and
- Consideration of mutations with unclear clinical significance.

The remaining 4 studies were considered high-quality for purposes of estimating overall disease prevalence (**Table 2**).

Table 2. Overview of selected studies estimating overall prevalence of PK deficiency (n=4)

First author (year)[citation]	Study type	*PKLR* genes sequenced	Reported results	Prevalence estimates (per million)
Diagnosed prevalence				
Carey, PJ (2000)[4]	Population-based prevalence study	N/A	Period prevalence: 3.2 per million	3.2*
de Medicis, E (1992)[5]	Population-based prevalence study	N/A	Period prevalence: 1 per 117,206	8.5†
Christensen, R (2010)[6]	Non-molecular pyruvate kinase deficiency screening study in area with high consanguinity	N/A	Incidence for full study population, including polygamist community: 1/30,000	33† (total study population: polygamous and non-polygamous)
			Incidence for polygamist community: 1/250	4,000† (polygamous community)
			Implied incidence for non-polygamous population: 1 per 152,830 births	6.5† (non-polygamous population)
Overall disease prevalence (diagnosed and undiagnosed)				
Beutler, E (2000)[7]	Molecular *PKLR* screening study in a general population	c.1456C>T, c.1468C>T, c.1484C>T, c.1529G>A	Estimated prevalence: 51 per million	51*

* Estimate provided by study authors

† Units converted from authors' estimate

RESULTS (*continued*)

Among these 4 studies, an important distinction was made between studies reporting diagnosed prevalence (n=3) and overall disease prevalence (diagnosed and undiagnosed PK deficiency; n=1).

- Two studies estimated diagnosed PK deficiency prevalence as 3.2 per million[4] and 8.5 per million[5] by identifying diagnosed PK deficiency cases from source populations of known size.
- We estimated the prevalence of diagnosed PK deficiency in a general population to be 6.5 per million[6] using data from another high-quality study that screened newborns for bilirubin and tested jaundiced newborns for PK deficiency.
- These 3 studies are likely underestimates of overall disease prevalence because they only consider diagnosed cases, and, in one study, only diagnosed cases presenting with jaundice.
- In the final study,[7] the authors sought to limit biases related to the Hardy-Weinberg equilibrium assumption, which incorrectly assumes the penetrance of each mutation to be 100%.
  - To address this, the authors identified a mutation known to have high penetrance (c.1529G>A), referred to as the 'index mutation.' They then assumed that the frequency of the index mutation relative to other PK deficiency-causing mutations is the same between the general population and PK deficiency cases, which led to a prevalence estimate (diagnosed and undiagnosed) of 51 per million (standard error: 32.5 per million).

CONCLUSIONS

- The prevalence of diagnosed PK deficiency in a general Western population is probably in the range of 3.2-8.5 per million.
- Overall disease prevalence (diagnosed and undiagnosed) may be as high as 51 per million population.
- Future studies are needed to understand the clinical significance of various mutant alleles. Such studies may inform more accurate, clinically relevant PK deficiency prevalence estimates, identify the degree of and reasons for underdiagnosis, and elucidate PK deficiency heterogeneity between populations.

Disclosures

This study was funded by Agios Pharmaceuticals. MS, KG, LP, ANB: Agios – employment and stockholder. CC, DC: IQVIA – employment. MHS: IQVIA – employment at time of study.

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