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.

The remaining 34 studies were grouped based on methods and study type (Table 2).

RESULTS (continued)

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

• Embase (1/1/1974 – 1/2/2019) and Medline (1/1/1946 – 1/2/2019);

• 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; and

• 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:
    \[\text{Point prevalence}
  \]
    \[\text{Incidence rate/proportion; and/or}
  \]
    \[\text{Survival duration, life expectancy, and mortality rate;}
  \]
    \[\text{Mutant Allele Frequencies (MAFs) for PK deficiency patients; and}
  \]
    \[\text{Prevalence based on population in the north of England.}
  \]

Exclusion Criteria

• 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-of-function as stated by the authors or inferred from amino acid substitution prediction models.

Quality Assessment

• A tailor-made, qualitative assessment tool was created. Quality considerations included study generalizability, validity of methods, potential sources of bias, and limitations as reported by the authors.

• Of 1390 references screened, 1296 were excluded after title/abstract review (n=94); full-text review (n=940); and critical text review (n=32). Studies were reviewed by two independent reviewers using the tailored, qualitative quality assessment tool. Quality Assessment.

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

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population-based prevalence</td>
<td>2</td>
</tr>
<tr>
<td>Molecular PKLR screening in a general population</td>
<td>5</td>
</tr>
<tr>
<td>Molecular PKLR screening in areas with endemic malaria</td>
<td>2</td>
</tr>
<tr>
<td>Non-molecular PKLR screening in a general population</td>
<td>9</td>
</tr>
<tr>
<td>Non-molecular PKLR screening in areas with endemic malaria</td>
<td>3</td>
</tr>
<tr>
<td>Non-molecular PKLR screening in areas with high consanguinity</td>
<td>6</td>
</tr>
<tr>
<td>Non-molecular PKLR screening in other unique population</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Overview of selected studies estimating overall prevalence of PK deficiency (n=44)

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Study type</th>
<th>PKLR genes sequenced</th>
<th>Reported results</th>
<th>Prevalence estimations (per million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camp, PJ (2004)</td>
<td>Population-based prevalence study</td>
<td>N/A</td>
<td>Period prevalence: 3.2†</td>
<td>N/A</td>
</tr>
<tr>
<td>de Medicis, E (1992)</td>
<td>Population-based prevalence study</td>
<td>N/A</td>
<td>Period prevalence: 8.5*</td>
<td>1 per 117,206</td>
</tr>
<tr>
<td>Christiansen, R (2010)</td>
<td>Non-molecular pyruvate kinase deficiency screening study in a general population</td>
<td>N/A</td>
<td>Incidence for full study population, including non-polyglobulism population: 33†</td>
<td>0.0002 (polyglobulism)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>non-polyglobulism population: 4.0002 (polyglobulism)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>community: 130,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Incidence for non-polyglobulism population: 4.0002 (polyglobulism)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Impaired incidence for non-polyglobulism population: 6.5† (non-polyglobulism population)</td>
</tr>
</tbody>
</table>

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 million and 8.5 per million 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 8.5 per million using data from another high-quality study that screened newborns for bilirubin and tested jaundiced newborns for PK deficiency.

• These 3 studies are likely underestimated of overall disease prevalence because they only consider diagnosed cases, and, in one study, only diagnosed cases presenting with jaundice.

• In the final study, the authors sought to limit bias related to the Hardy-Weinberg equilibrium assumption, which incorrectly assumes the prevalence of each mutation to be 100%.

To address this, the authors identified a mutation known to have high frequency (c.1520G>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 Inc., MS, KG, LP, AMB – employment; and UpToDate – employment. MS, KG, LP, AMB, UpToDate – employment at time of study.

References