Comorbidities and complications across genotypes in adult patients with pyruvate kinase deficiency: Analysis from the Peak Registry

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Andreas Glenthøj, MD,[1] Rachael F Grace, MD,[2] Eduard J van Beers, MD,[3] Joan-Lluis Vives Corrons, MD,[4] Bertil Glader, MD, PhD,[5] Kevin H M Kuo, MD,[6] Carl Lander, RN,[7] Dagmar Pospíšilová, MD,[8] Jean Williams, MPH,[9] Yan Yan, MS,[9] Bryan McGee, PharmD,[9] Paola Bianchi, BSc, PhD[10]

[1]Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [2]Dana-Farber/Boston Children's Cancer and Blood Disorder Center, Boston, MA, USA; [3]Van Creveldkliniek, Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Institute for Leukaemia Research Josep Carreras ENERCA Coordinator, University of Barcelona, Barcelona, Spain; [5]Stanford University School of Medicine, Palo Alto, CA, USA; [6]Division of Hematology, University of Toronto, Toronto, ON, Canada; [7]Metabolic Support UK, Wrexham, UK; [8]Department of Pediatrics, Palacky University and University Hospital, Olomouc, Czech Republic; [9]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [10]UOC Ematologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, congenital, glycolytic enzymopathy caused by mutations in the *PKLR* gene, which leads to lifelong hemolytic anemia and may result in complications such as iron overload, pulmonary hypertension, and gallstones[1]
- PK deficiency has wide genetic heterogeneity, with >300 mutations reported, and previous data suggest that disease complications may be common regardless of genotype[2]
- To better understand the characteristics and disease burden of patients diagnosed with PK deficiency, the observational PK Deficiency Natural History Study (NHS; NCT02053480) was initiated in 2014 at 31 sites across 6 countries, and followed patients for 2 years[1,3]
- The Peak Registry (NCT03481738) was initiated in 2018 as a global retrospective and prospective observational study of patients diagnosed with PK deficiency to continue and expand on the PK Deficiency NHS and the understanding of PK deficiency, with a targeted enrollment of approximately 500 adult and pediatric patients at ~60 sites in up to 20 countries[4]

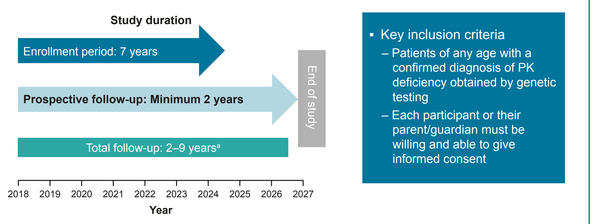
OBJECTIVE

- **To further characterize comorbidities and complications across genotypes in adult patients with PK deficiency enrolled in the Peak Registry**

METHODS

- The Peak Registry is a global retrospective and prospective observational study of adult and pediatric patients diagnosed with PK deficiency (**Figure 1**)

Figure 1. Peak Registry study design and duration



[a]Participants in the Peak Registry who were originally included in the NHS and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years; NHS, Natural History Study; PK, pyruvate kinase

- Adult patients (≥18 years) were eligible for inclusion in this analysis if they had available age at enrollment and complete genotype information as of the data cut-off date of 29June2021
- For this analysis, adults with complete *PKLR* genotype data were grouped into 3 cohorts: missense/missense (M/M), missense/non-missense (M/NM), and non-missense/non-missense (NM/NM):
  - NM mutations included nonsense, frameshift, in-frame small indels, large deletions, and splicing variants (including R479H)
  - Genotype classifications were aligned with those previously reported from the PK Deficiency NHS[2]
- Data on demographics, laboratory values, and medical history inclusive of comorbidities and complications at enrollment were summarized descriptively
- Comorbidities and complications common in patients with PK deficiency were identified in collaboration with Peak Registry Steering Committee members and based on evidence previously reported in the literature[1,2,5]
  - Categories of comorbidities and complications with high clinical significance to the adult PK deficiency population were included in this analysis (supplemental material [QR code] contains the full breadth of comorbidities and complications)

RESULTS

Baseline characteristics

- As of the 29June2021 data cut-off date, 90/103 (87.4%) adult patients in the registry had complete *PKLR* genotype data (**Table 1**)
- Of these 90 patients, 57 (63.3%) were classified as M/M, 28 (31.1%) as M/NM, and 5 (5.6%) as NM/NM
- The distribution of the 3 classes of genotypes from patients with available data in each Peak Registry enrollment country is shown in **Figure 2**

Medical history

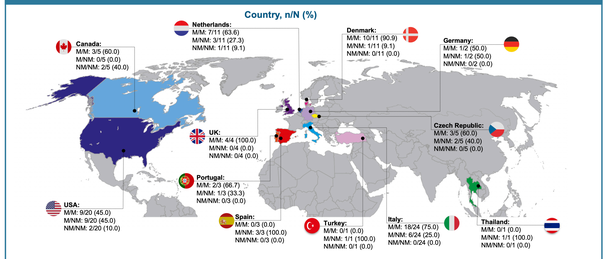
- Median age (range) of PK deficiency diagnosis was 16.0 years (0–68) for the overall adult population (all genotypes), 21.0 years (0–68) for M/M patients, 12.0 years (0–40) for M/NM patients, and 0.0 years (0–0) for NM/NM patients (**Table 1**)
- Among the 87 patients with known transfusion status, 36.8% had never been transfused (M/M: 44.4%; M/NM: 28.6%; NM/NM: 0.0%)
- Splenectomy had been performed in almost half of M/M patients (47.3%), the majority of M/NM patients (60.7%), and all NM/NM patients (100.0%)

Table 1. Baseline characteristics and medical history

	All adult patients	Genotype subgroups		
	All genotypes N=90	M/M N=57	M/NM N=28	NM/NM[a] N=5
Baseline characteristics				
Age at enrollment, median (range), yrs	33.5 (18.0–77.0)	36.0 (18.0–77.0)	25.5 (18.0–77.0)	42.0 (20.0–50.0)
Female, n/N' (%)	55/90 (61.1)	35/57 (61.4)	16/28 (57.1)	4/5 (80.0)
Medical history				
Age at PK deficiency diagnosis[b], N'	87	56	27	4
Median (range), yrs	16.0 (0–68)	21.0 (0–68)	12.0 (0–40)	0.0 (0–0)
Never transfused, n/N' (%)	32/87 (36.8)	24/54 (44.4)	8/28 (28.6)	0/5 (0.0)
Regularly transfused (≥6 transfusions in the 12 months prior to enrollment), n/N' (%)	7/74 (9.5)	4/47 (8.5)	3/23 (13.0)	0/4 (0.0)
# of transfusions over the 12 months prior to enrollment, mean (SD)	10.4 (4.2)	11.5 (5.2)	9.0 (2.7)	NA
Non-regularly transfused (0–5 transfusions in the 12 months prior to enrollment), n/N' (%)	67/74 (90.5)	43/47 (91.5)	20/23 (87.0)	4/4 (100.0)
# of transfusions over the 12 months prior to enrollment, mean (SD)	0.3 (0.9)	0.2 (0.8)	0.5 (1.2)	1.0 (0.8)
Unknown transfusion frequency, n	16	10	5	1
Ever had splenectomy, n/N' (%)	48/88 (54.5)	26/55 (47.3)	17/28 (60.7)	5/5 (100.0)
Age at splenectomy, N'	48	26	17	5
Median (range), yrs	6.5 (1–27)	9.0 (2–27)	4.0 (1–18)	4.0 (1–8)
Ever had chelation therapy, n/N' (%)	30/84 (35.7)	15/51 (29.4)	12/28 (42.9)	3/5 (60.0)

The number of patients with known results (denoted as N') was used as the denominator in calculation of percentage. Patients with data missing, or with response as "Not Reported" or "Not Done" were excluded from the denominator; [a]Low NM/NM patient numbers make the true prevalence of complications difficult to assess; [b]Age at PK deficiency diagnosis=year of PK deficiency diagnosis−year of birth; M/M, missense/missense; M/NM, missense/non-missense; NA, non-applicable; NM/NM, non-missense/non-missense; PK, pyruvate kinase; SD, standard deviation; yr, year

Figure 2. Genotype distribution by enrollment country



N represents the total number of adult patients from each country with available age at enrollment and complete *PKLR* genotype data in the Peak Registry as of June 2021; n represents the number of adult patients with each PK deficiency genotype enrolled in each country; M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense; PK, pyruvate kinase

Baseline hematologic and iron markers

- At registry enrollment, median (range) hemoglobin in the M/M, M/NM, and NM/NM cohorts was 9.9 g/dL (7.1–14.2), 9.1 g/dL (6.7–14.1), and 7.3 g/dL (6.9–8.1), respectively (**Table 2**)
- Although all (n=5; 100.0%) NM/NM patients had been splenectomized, median hemoglobin levels in this subgroup were numerically lower than in the M/M and M/NM subgroups

Table 2. Baseline hematologic and iron markers

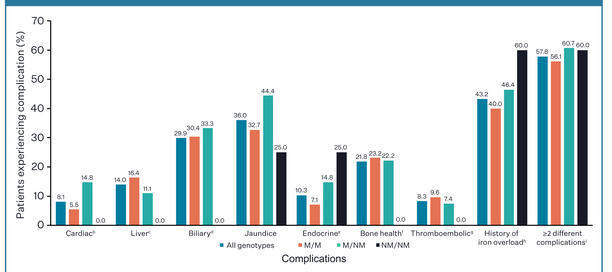
Variable	All adult patients	Genotype subgroups		
	All genotypes N=90	M/M N=57	M/NM N=28	NM/NM[a] N=5
Hemoglobin, N'	51	37	9	5
Median (range), g/dL	9.3 (6.7–14.2)	9.9 (7.1–14.2)	9.1 (6.7–14.1)	7.3 (6.9–8.1)
Percent reticulocyte count, N'	21	16	3	2
Median (range), %	6 (0–40)	5 (0–40)	27 (10–30)	25 (20–30)
Indirect bilirubin, N'	29	20	6	3
Median (range), µmol/L	43.0 (13.7–155.5)	37.3 (13.7–108.1)	54.8 (15.1–155.5)	69.0 (41.6–94.1)
Lactate dehydrogenase, N'	34	26	7	1
Median (range), U/L	225 (133–849)	224 (133–849)	222 (186–324)	239 (239–239)
Ferritin, N'	36	29	6	1
Median (range),µg/L	404 (19–2263)	317 (19–2263)	769 (160–1164)	926 (926–926)

The number of patients with known results (denoted as N') was used as the denominator in calculation of percentage. Patients with data missing, or with response as "Not Reported" or "Not Done" were excluded from the denominator; [a]Low NM/NM patient numbers make the true prevalence of complications difficult to assess; M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense

Comorbidities and complications

- Jaundice was common for patients across genotypes (M/M: 32.7%; M/NM: 44.4%; NM/NM: 25.0% [**Figure 3**])
- Biliary events (M/M: 30.4%; M/NM: 33.3%; NM/NM: 0.0%) and bone health problems (M/M: 23.2%; M/NM: 22.2%; NM/NM: 0.0%) were also commonly reported
- Endocrine complications occurred in around 10% of patients with PK deficiency, although the occurrence varied between genotype subgroups (M/M: 7.1%; M/NM: 14.8%; NM/NM: 25.0%)
- History of iron overload was observed in substantial numbers of patients, regardless of genotype: 40.0% in M/M patients, 46.4% in M/NM patients, and 60.0% in NM/NM patients
- Overall, 57.8% of patients experienced ≥2 of the complications shown in **Figure 3** (M/M: 56.1%; M/NM: 60.7%; NM/NM: 60.0%)

Figure 3. Percentage of patients experiencing complications in each genotype group[a]



[a]Low NM/NM patient numbers make the true prevalence of complications difficult to assess; [b]Pulmonary hypertension, arrythmia, left ventricular hypertrophy, cardiac failure congestive; [c]Non-alcoholic steatohepatitis, non-alcoholic fatty liver, hepatic cirrhosis, hepatomegaly; [d]Cholecystisis, cholangitis, asymptomatic gallstones, bile duct stone; [e]Hypothyroidism, growth hormone deficiency, hypoparathyroidism, secondary hypogonadism, diabetes mellitus, nocturia, microalbuminuria, hyperthyroidism, Hashimoto's disease, Basedow's disease, thyroid mass; [f]Fracture, osteoporosis, osteopenia, bone pain; [g]Deep vein thrombosis, pulmonary embolism, 2 events classified as "other"; [h]History of iron overload defined as ever having received: 1) chelation therapy or 2) phlebotomy for removal of iron; or within 3 months of enrollment had any of: 3) ferritin >1000 ng/mL, 4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight, or 5) cardiac T2* MRI ≤20 ms; [i]Complications included in the calculation of "≥2 different complications" were cardiac, biliary, liver, jaundice, endocrine, bone health, thromboembolic events, and history of iron overload; M/M, missense/missense; M/NM, missense/non-missense; MRI, magnetic resonance imaging; NM/NM, non-missense/non-missense

- The most common cardiac complication in the overall adult population was arrhythmia (5.8%) and was observed in 5.5% of M/M patients, 7.4% of M/NM patients, and 0.0% of NM/NM patients (**Supplemental table 2** [QR code])
- At least 1 thromboembolic event was reported in 7 patients; of the patients who experienced thromboembolic events, the timing of the events relative to splenectomy was known for 6 patients, and in all 6 patients the 13 thromboembolic events occurred after splenectomy (**Supplemental table 3** [QR code])
  - Details of the thromboembolic event(s) in a 7th patient were unspecified
- Of patients with a history of iron overload, 25.0% of M/M patients and 12.5% of M/NM patients had never been transfused (**Table 3**)

Table 3. Number of patients with a history of iron overload by transfusion status

Variable	All adult patients		Genotype subgroups					
	All genotypes N=90		M/M N= 57		M/NM N=28		NM/NM[a] N=5	
	Never transfused n=32	Ever transfused n=55	Never transfused n=24	Ever transfused n=30	Never transfused n=8	Ever transfused n=20	Never transfused n=0	Ever transfused n=5
History of iron overload,[b,c] n/N' (%)	7/32 (21.9)	31/53 (58.5)	6/24 (25.0)	16/28 (57.1)	1/8 (12.5)	12/20 (60.0)	NA	3/5 (60.0)

The number of patients with known results (denoted as N') was used as the denominator in calculation of percentage. Patients with data missing, or with response as "Not Reported" or "Not Done" were excluded from the denominator; [a]Low NM/NM patient numbers make the true prevalence of complications difficult to assess; [b]History of iron overload defined as ever having received: 1) chelation therapy or 2) phlebotomy for removal of iron; or within 3 months of enrollment had any of: 3) ferritin >1000 ng/mL, 4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight, or 5) cardiac T2* MRI ≤20 ms; [c]5 patients without known transfusion status or history of iron overload were not included; M/M, missense/missense; M/NM, missense/non-missense; MRI, magnetic resonance imaging; NA, non-applicable; NM/NM, non-missense/non-missense

STRENGTHS AND LIMITATIONS

Strengths

- The Peak Registry is a global study, with patients based at numerous sites around the world, which reduces biases toward genotypes that are more common in certain geographic areas or populations
- The breadth of complications captured in the real-world setting for this analysis spans a wide range of clinical phenotypes experienced by patients with each *PKLR* genotype
- Centralized classification of genotypes in the Peak Registry allows for consistent interpretation of data in line with previous research and publications in patients with PK deficiency[2]

Limitations

- The absence of certain complications, such as biliary events and bone complications, in the NM/NM group may reflect the low number of NM/NM patients with available data in the analysis (n=5), making the true prevalence of these complications difficult to assess
- Although electronic case report forms require input of lifetime medical history, for many adult patients, recall errors or incomplete medical histories may result in their medical records inadequately reflecting conditions that they may have had as children or young adults; thus, the frequencies reported here could be understated
- Prevalence rates for comorbidities and complications in this analysis represent only diagnosed prevalence, so may exclude complications that have not yet been diagnosed or have been misdiagnosed, therefore potentially underestimating their true prevalence

CONCLUSIONS

- **This analysis reveals that adult patients across *PKLR* genotypes experienced a wide range of serious comorbidities/complications across multiple systems**
- **In addition to the breadth of comorbidities presented, these data highlight the existence of multiple complications in individual patients with PK deficiency and the need for appropriate monitoring and management of these patients, regardless of genotype**

The longitudinal (up to 9 years[a]) design of the Peak Registry will allow for continued monitoring and follow-up of comorbidities and complications in patients with PK deficiency

[a]Patients who crossed over from the NHS to the Peak Registry may have follow-up of up to 11 years

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References: 1. Grace RF et al. *Blood* 2018;131(20):2183–92. **2.** Bianchi P et al. *Am J Hematol* 2020;95(5):472–82. **3.** van Beers EJ et al. *Haematologica* 2019;104(2):e51–3. **4.** Grace RF et al. *Blood* 2019;134(Suppl 1):2223. **5.** Boscoe AN et al. *Eur J Haematol* 2021;106(4):484–92.

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