Disclosure Slide

Financial Disclosure for:
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Cases of acute hepatic porphyria in the UK Biobank: insights from exome sequencing

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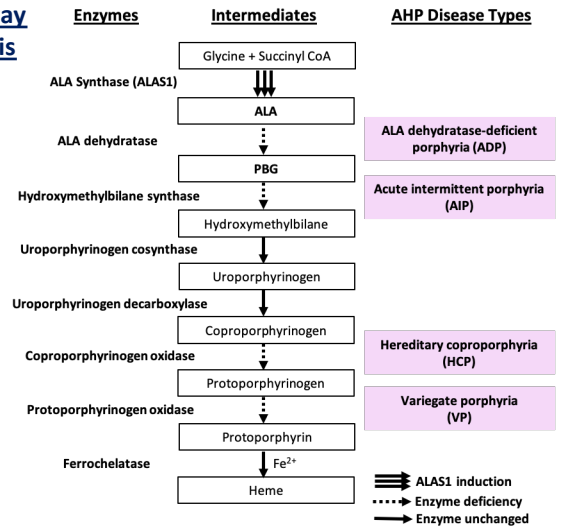
Introduction

- Acute hepatic porphyria (AHP) is a family of rare diseases in heme biosynthesis: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and ALAD-deficiency porphyria (ADP). They are caused by loss-of-function variants in *HMBS* (dominant), *PPOX* (dominant), *CPOX* (dominant and recessive), and *ALAD* (recessive), respectively. [1,2]
- Accumulation of ALA/PBG is believed to cause disease manifestations.[2,3]
- AHP is frequently misdiagnosed as it manifests through a wide range of nonspecific symptoms including those affecting the nervous, gastrointestinal, cutaneous, and cardiovascular systems.[4-9]
- Biochemical and genetic tests are available to help diagnose AHP and guide subsequent treatment decisions.

Metabolic Pathway of Heme Synthesis



Methods

- The UK Biobank (UKBB) was utilized to explore rare variants in AHP-causing genes in individuals diagnosed with porphyria. The UKBB includes 502,616 volunteers aged 40-69 at recruitment, with accompanying questionnaire, inpatient hospitalization, and array genotyping data; subsets also have primary care data and whole-exome sequences.
- Inpatient hospitalization diagnosis of "other porphyria" (ICD10 E80.2), which includes AHP and pseudoporphyria, was found in 25/502,493 individuals. General practitioner (GP) data on 230,105 individuals contained 3 AIP diagnoses, 1 VP, 2 HCP, and 8 "other porphyria" or "porphyria NOS."

Patient History and Exome Analysis

Individual	Diagnosis	Suspected Causal Exome Variants
1	C3715 Coproporphyria	CPOX p.Tyr312Cys [D]
2	Cyu8H Other porphyria	
3	E802 Other porphyria (I)	
4	E800 Hereditary Erythropoietic Porphyria (I), E802 Other porphyria (I)	PPOX p.Leu295Pro [D]
5	E802 Other porphyria (I)	
6	E802 Other porphyria (I)	
7	E802 Other porphyria (I)	PPOX p.Gln435Ter [D]
8	E802 Other porphyria (I), C371z Porphyria NOS (GP)	PPOX p.Val84Gly [D], HMBS p.Glu86Val [D]
9	E802 Other porphyria (I)	PPOX p.Val84Gly [D]
10	E802 Other porphyria (I), C3713 Variegate porphyria (GP)	PPOX p.Leu15Phe [D]
11	C3715 Coproporphyria (GP)	
12	E802 Other porphyria (I), C3712 Acute intermittent porphyria (GP)	
13	C3712 Acute intermittent porphyria (GP)	
14	E802 Other porphyria (I)	HMBS p.Arg167Gln [P, D]
15	E802 Other porphyria (I)	
16	C371z Porphyria NOS (GP)	
17	E802 Other porphyria (I)	
18	E802 Other porphyria (I), C3710 Congenital porphyria (GP), Cyu8H Other porphyria (GP)	
19	E802 Other porphyria (I)	
20	E802 Other porphyria (I)	PPOX p.Ile180GlnfsTer11 [L]
21	E802 Other porphyria (I)	
22	E802 Other porphyria (I)	PPOX p.Arg59Trp [P, D]
23	E802 Other porphyria (I)	
24	C3714 Porphyria cutanea tarda (GP), C3714 Porphyria NOS (GP)	HMBS c.345-1G>A [L, D]
25	E802 Other porphyria (I), XM0qH Porphyria (GP)	
26	E802 Other porphyria (I), C371z Porphyria NOS (GP)	HMBS p.Arg167Trp [P, D]
27	E802 Other porphyria (I)	PPOX p.Leu15Phe [D]
28	E802 Other porphyria (I)	
29	C3712 Acute intermittent porphyria (GP)	PPOX p.Arg59Trp [P, D]

(I) = Inpatient Diagnosis
(GP) = GP Diagnosis
[P] = ClinVar pathogenic or likely pathogenic
[L] = predicted protein-truncating by LOFTEE
[D] = missense coding MAF < 1% and CADD > 25

Yellow = Complex clinical cases that are likely AHP in light of exome data but have evidence of misdiagnosis
Blue = Other high-confidence AHP cases: either a definitive GP diagnosis or an inpatient E80.2 code plus exome variant

Methods (continued)

- Exome sequencing data was available for 454,787 individuals in the UKBB, and we used these data to investigate AHP-causing genes in 29 exome-sequenced individuals who had either an AHP or nonspecific porphyria diagnosis.
- We then searched for previously unreported putative variants, focusing on predicted protein-truncating variants or rare damaging missense variants.

Results

- We found potentially causal AHP variants in 13 of the 29 individuals with exome data.
- Four individuals had variants annotated by ClinVar as "pathogenic" or "likely pathogenic":
  - A carrier of *HMBS* p.Arg167Trp (expected to be AIP) diagnosed with porphyria NOS
  - A carrier of *HMBS* p.Arg167Gln (expected to be AIP) diagnosed with porphyria NOS
  - Two carriers of *PPOX* p.Arg59Trp (expected to be VP), one of whom had been diagnosed with AIP, suggesting a potential misdiagnosis, and the other having a porphyria NOS diagnosis.
- Eight individuals had porphyria diagnoses and a single damaging variant previously unreported in an AHP gene:
  - *CPOX* p.Tyr312Cys (diagnosed as HCP), *PPOX* p.Ile180GlnfsTer11 (diagnosed as porphyria NOS), *PPOX* p.Leu295Pro (diagnosed as hereditary erythropoietic porphyria, a potential misdiagnosis, and porphyria NOS), *PPOX* p.Gln435Ter (diagnosed as porphyria NOS), *PPOX* p.Val84Gly (diagnosed as porphyria NOS), *HMBS* c.345-1G>A (diagnosed as porphyria cutanea tarda, a potential misdiagnosis), and two individuals with *PPOX* p.Leu15Phe (diagnosed as porphyria NOS and VP).
- An individual with a history of severe AHP symptoms and psychiatric illness had a diagnosis of "porphyria NOS" but carried predicted damaging variants in both *HMBS* p.Glu86Val and *PPOX* p.Val84Gly (the second individual with this mutation), suggesting combined AIP and VP.

Conclusion

- These results reveal eight previously unreported putative AHP variants from nine cases where the available inpatient and GP records only contain broad porphyria diagnoses, but exome sequencing leads us to strongly suspect AHP.
- We describe four instances where exome data suggest a diagnosis of AHP, but medical records indicate complex clinical cases or potential misdiagnoses.

Abbreviations: Porphyria NOS, Porphyria not otherwise specified. **Acknowledgements:** Analyses were performed using the REVEAL/SciDB translational analytics platform from Paradigm4; We thank the staff and participants of the UK Biobank study. This research has been conducted using the UK Biobank resource under Application Number 26041.

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