Recent advances in the epidemiology and genetics of acute intermittent porphyria

Liyan Ma¹, Yu Tian¹, Chenxing Peng¹, Yiran Zhang², Songyun Zhang¹,*

¹ Department of Endocrinology, The second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China; ² School of First Clinical Medical College, Southern Medical University, Guangzhou, Guangdong, China.

SUMMARY Acute intermittent porphyria (AIP) is a dominant inherited disorder with a low penetrance that is caused by mutations in the gene coding for hydroxymethylbilane synthase (HMBS). Information about the epidemiology and molecular genetic features of this rare disorder is crucial to clinical research, and particularly to the evaluation of new treatments. Variations in the prevalence and penetrance of AIP in various studies may due to the different inclusion criteria and methods of assessment. Here, the prevalence and penetrance of AIP are analyzed systematically, and the genetic traits of different populations and findings regarding the genotype-phenotype correlation are summarized. In addition, quite a few studies have indicated that AIP susceptibility was affected by other factors, such as modifying genes. Findings regarding possible modifying genes are documented here, helping to reveal the pathogenesis of and treatments for AIP. The status of research on AIP in China reveals the lack of epidemiological and genetic studies of the Chinese population, a situation that needs to be promptly remedied.

Keywords acute intermittent porphyria, prevalence, penetrance, genetic traits, genotype-phenotype correlation, modifying genes

1. Introduction

Porphyrias are a group of metabolic diseases that result from a specific abnormality in one of the eight enzymes of the heme biosynthetic pathway (1,2). In general, porphyrias are classified either as acute porphyrias or cutaneous porphyrias based on their clinical presentation or as hepatic and erythropoietic porphyrias based on the tissue where heme precursors are overproduced (3).

Acute intermittent porphyria (AIP, OMIM#176000), the most common and severe form of acute hepatic porphyrias (4), is an inherited metabolic disease that exhibits an autosomal dominant pattern of inheritance caused by partial deficiencies in hydroxymethylbilane synthase (HMBS; EC 2.5.1.61), the third enzyme in heme biosynthesis (5). AIP has significant molecular genetic heterogeneity and low penetrance (6). It leads to accumulation of upstream metabolites δ-aminolevulinic acid (ALA) and porphobilinogen (PBG), which induce toxicity to the neurologic system, and then trigger episodic, acute neurovisceral symptoms that can even be life-threatening (7-11). Studies of the prevalence, penetrance, and molecular genetic traits of AIP are crucial to its early diagnosis and rational management. Thanks to the rapid development of next-generation sequencing (NGS) technology, genetic sequencing has been widely used to detect HMBS gene mutations (12,13). Some studies based on genetic testing have revealed that the prevalence of HMBS variants was substantially underestimated, with extremely low penetrance in the general population but higher penetrance in families with AIP (14,15).

Findings regarding modifying genes and the correlation between genotype-phenotype warrant more attention in recent studies on AIP. Although a genotype-phenotype correlation has not been identified, certain mutations may be relevant to penetrance or the severity of clinical manifestations. Some modifying genes that have been identified in recent years are reviewed here, including the PEPT2 gene, PPARA gene, cytochrome P450 gene, and ABCB6 gene.

In China, concern about AIP has increased, but most studies on AIP are various case reports and small series. The prevalence, penetrance, and genetic traits of Chinese patients with AIP are still unclear and need to be fully evaluated.

2. Prevalence and penetrance of AIP

AIP is an autosomal dominant metabolic disorder with
a variable prevalence among different countries (16). Because it is a rare disease with multiple phenotypes, its prevalence is difficult to evaluate (17). Therefore, information about the prevalence of AIP is most often based on estimates. Variations in the prevalence and penetrance of AIP in various studies are probably due to different inclusion criteria and methods of assessment (18). Information is classified in Table 1 as the prevalence of symptomatic AIP, the prevalence of pathogenetic HMBS mutations (including data on the general population and families with AIP), and penetrance (including data on the general population and families with AIP).

Much of the information on AIP comes from a 3-year prospective study of newly diagnosed symptomatic patients with AIP in 11 European countries, and the annual incidence of symptomatic AIP was reported to be 0.13 per million. Its prevalence, which was calculated based on the incidence and mean disease duration, was 5.9 per million in Europe (19). Moreover, the numbers were similar in all countries except Sweden (19). The rate of recurrence, which was 3-5%, was also been estimated in that study. In addition, the sliding prevalence of symptomatic AIP indicates the importance of improved management and educational strategies (19-22). Similarly, a 60-year retrospective study in Finland revealed a decrease in patients with active AIP (23,24).

In light of the number of patients with AIP referred to a French facility, the prevalence of overt AIP was estimated to be 7.6 per million, which was in line with the aforementioned figure of 5.9 per million (25).

Due to founder effects, the prevalence of AIP was markedly higher in some regions, such as 17.7 per million in southeastern Spain (26) and 23 per million in Sweden (19). In northern Sweden, it was even 192 per million (27). Information from Argentina and Western Australia may less credible because no gene sequencing was performed (28,29).

Although symptomatic patients with AIP are quite rare, some findings based on population have indicated that the prevalence of pathogenetic HMBS mutations was higher than previously estimated. A study based on Caucasians indicated that the prevalence of pathogenetic HMBS mutations was 1/1,782 (14). This result was consistent with the findings of two studies in France, which estimated the prevalence of mutations in the HMBS gene to be 1/1,675 to 1/1,299 (15,25).

Thus, this information indicates a marked discrepancy in the estimated prevalence of HMBS mutations and the occurrence of acute attacks in patients with AIP, which means that its penetrance is very low. As of the current point in time, penetrance is estimated to be approximately 20-50% in families with AIP but only ~1% in the general population, with the exception of 23% in the Swedish and 42% in the Northern Swedish (14,19,25,27,31,32). This finding strongly suggests that other factors act as a catalyst for AIP attacks, such as modifying genes and environmental factors.

| Table 1. The estimated prevalence and penetrance of AIP |
|-------------------------------------------------------|
| **Country (region) or Population** | **Prevalence of symptomatic AIP**<br>(case per million inhabitants) | **Prevalence of pathogenetic HMBS mutations**<br>(in the general population in families with AIP(%)) | **Penetrance (%)**<br>(in the general population in families with AIP) | **Ref.** |
|-----------------------------------|-------------------------------------------------|---------------------------------|---------------------------------|--------|
| Caucasian                         | 1/1,782                                         | < 1                            | 14                              |
| Europe                            | 5.9                                             |                                 | 19                              |
| France                            | 7.6                                             | 1/1,299                         | 0.5-1                           | 25                              |
|                                   |                                                 | 1/1,675                         | 22.9                            | 15                              |
| Sweden                            | 5.5                                             |                                 | 19                              |
|                                   | 23                                              |                                 | 19                              |
| Northern Sweden                   | 192                                             | 1/10,000                        | 23                              | 30                              |
|                                   |                                                 | 1/1,000                         |                                 | 30                              |
|                                   |                                                 | 1/2,000                         | 42                              | 27                              |
| Switzerland                       | 10-15                                           | 50                              | 52                              | 31                              |
|                                   | 9.9                                             |                                 |                                 | 19                              |
| Southeastern Spain                | 17.7                                            |                                 | 23                              | 26                              |
| Spain                             | 6.3                                             |                                 | 52                              | 19                              |
| Finland                           | 47                                              |                                 | 35                              | 32                              |
| Norway                            | 6.3                                             |                                 |                                 | 19                              |
| Northern Italy                    | 5.0                                             |                                 |                                 | 19                              |
| Poland                            | 7.2                                             |                                 |                                 | 19                              |
| UK                                | 7.2                                             |                                 |                                 | 19                              |
| Netherlands                       | 8.1                                             |                                 |                                 | 19                              |
| Russia                            |                                                 |                                 |                                 | 19                              |
| Argentina*                        | 8                                               |                                 | 40                              | 28                              |
| Western Australia*                | 24                                              |                                 | 29                              | 29                              |

*No gene sequencing was performed in the study
3. Genetics of AIP

3.1. Molecular bases

Genetically, AIP is an autosomal dominant disorder resulting from mutations in the HMBS gene (33), which is located at the chromosomal region 11q24.1-24.2 (GRCh38.p11:119,084,003-119,094,417). There are two isoforms of HMBS, the housekeeping and the erythroid isoforms (34). The transcript including exons 1 and 3-15 is directed by housekeeping promoter located in the 5' flanking region upstream of exon 1, and the transcript containing exons 2-15 is produced by an erythroid-specific promoter located in a region 3 kb downstream of intron 1 (35-37). Most patients with AIP carry mutations in exons 3-15, which affect not only the housekeeping but also the erythroid isoforms of HMBS, which are the classic form of AIP. When mutations occur within or close to the coding region of exon 1, the activity of HMBS in erythroid cells is normal (38-40). Regulatory gene defects in the 5' -promoter regions of the HMBS gene have been found in patients with AIP (41). To date, no variants have been found in the erythroid-specific promoter or in exon 2 (42).

3.2. Molecular genetic features

Thus far, over 500 different mutations in the HMBS gene have been identified (Human Gene Mutation Database HGMD, http://www.hgmd.cf.ac.uk/ac/index.php). There are 31 CpG dinucleotides, at which most of the de novo events in human genes appear, in the 1,086 base-pair coding sequence of HMBS (14,43). Because of oxidative deamination of methylated cytosines, the CpG dinucleotides are believed to be hypermutable (44). Most of the mutations resulting in AIP are private or present only in a few unrelated families, a fact that highlights the molecular genetic heterogeneity of AIP (45-53,73). Nevertheless, a few mutations are relatively common either due to CpG dinucleotide mutational hotspots in the gene (43), such as the mutations encoding p.R173W and p.R167Q, or due to a founder effect, such as HMBS P.G111R in Argentina and p.W198X in Sweden (54,55). (Table 2 shows the founder effect mutations causing AIP among different populations).

Since AIP is an autosomal dominant disease, no sex differences in gene carriers are expected (60,61), but all studies have found that acute attacks affect females much more frequently than males (19,54,59,60,62-64). A recent study in Finland found a high penetrance of 41% for AIP acute attacks and 50% for all acute manifestations associated with AIP in female patients (32). Similar findings have been gleaned from families with the founder mutation p.W198X in northern Sweden (27,65). These studies emphasize that female hormones trigger AIP attacks (23,66,67).

3.3. Genotype-phenotype correlation

To date, no clear genotype-phenotype correlation for AIP has been determined (24,63,68). However, some studies have indicated that some mutations may be related to a higher penetrance and/or more severe clinical manifestations, such as p.W198X, c.1073delA, and p.R26C (32,69), while some variants may be associated with a lower penetrance and/or milder manifestations, including p.R167W, p.R225G, and c.G33T(24,32,69). Interestingly, conflicting findings were obtained from studies on P.R173W; a study in Finland reported a lower penetrance but studies in Northern Sweden and Spain reported a higher penetrance (16,32,69). Although a study in Finland found similar genotypes, penetrance differed greatly among families (32). This shows that the phenotype of AIP is not determined by the HMBS genotype alone but that other factors such as modifying genes and the environment also play a vital role in the pathogenesis of AIP attacks (6,24,25,32,70,71). Moreover, protein function analysis and bioinformatic tools have been used to identify a genotype-phenotype correlation. Some mutations in the HMBS gene including p.R116W, p.R173W, p.R149X, p.Q217H, p.G218R, p.A219P, and p.A330P have been predicted to lead to severe clinical manifestations (72). The correlation between genotype and phenotype is still a topic of interest in research on AIP.

3.4. Modifying genes

The low penetrance of AIP and the significant difference between the penetrance found in families with AIP and that found in the general population indicate that AIP susceptibility is affected by the inheritance of HMBS gene mutation as well as other genetic or environmental factors. A hypothesis has been put forth that AIP

| Population | Mutation (cDNA) | Mutation (Amino Acid) | Exon | Ref. |
|------------|----------------|-----------------------|------|-----|
| Dutch      | c.346C > T     | P.R116W               | 8    | 51  |
| Canadian (Nova Scotia) | c.517C > T     | P.R173W               | 10   | 56  |
| Swedish    | c.593G > A     | P.W198X               | 10   | 55  |
| Swiss (German-speaking) | c.848G > A     | P.W283X               | 14   | 31  |
| Argentinian| c.331G > A     | P.G111R               | 7    | 54  |
| Spanish (Murcia, southeastern region of Spain) | c.669...698del | p.R173W               | 12   | 57  |
| Russian    | c.53delT       | p.Met18ArgfsX3        | 3    | 58  |
inheritance does not follow the classical autosomal dominant pattern but an oligogenic or polygenic inheritance pattern with environmental modifiers (25,58,74,75).

Many attempts using various approaches have been made to search for those modifying genes in order to both further understand the pathogenesis of AIP and to identify reliable therapeutic targets.

3.4.1. PEPT2 gene

Genetic variation in human peptide transporter 2 (PEPT2, also known as SLC15A2) has been identified as an aspect in modulating the severity of renal and neurologic impairment (6,76-78). ALA is reabsorbed in the proximal tubules by PEPT2 variants. Variants of PEPT2 have different affinities for ALA: PEPT2*1 has a higher affinity for ALA while PEPT2*2 has a lower affinity (79,80). Thus, more significant neurotoxicity may occur in PEPT2*2 carriers because they have lower ALA brain efflux (81-83). That said, PEPT2 *1 with a higher affinity for ALA is associated with an increased risk of renal disease (6,76).

3.4.2. Cytochrome P450 gene

The enzyme 5-aminolevulinic acid synthase (ALAS) 1 catalyzes the rate-limiting step in the production of heme and is regulated by heme through a negative feedback loop (84). Many of the substances that induce cytochromes (CYPs) in the endoplasmic reticulum of the liver can also result in increased hepatic ALAS1 activity (85,86).

Studies have indicated that the hepatic cytochrome P450 gene may play a role in AIP attacks (87). A study found that CYP2C40, CYP2C68, and CYP2C69 were upregulated in mice with induced AIP but downregulated in wild-type mice. These genes are respectively equivalent to CYP2C8, CYP2C9, and CYP2C19, which are the primary human CYP450 enzymes involved in drug metabolism. CYP21A1, the homolog of human CYP21A2 or CYP17A1 (-37), is a crucial enzyme in corticosteroid and sex hormone synthesis; CYP21A1 is downregulated in mice with induced AIP but upregulated in wild-type mice (88,89). A study based on the population in the Spanish region of Murcia revealed parallel findings: the alleles CYP2D6*4 and *5 may prevent acute attacks in patients with AIP while CYP2D6 may constitute a penetrance-modifying gene (26).

In short, the cytochrome P450 gene may be related to the pathogenesis of AIP, but further studies are needed to confirm this hypothesis.

3.4.3. PPARα gene

Peroxisome proliferator-activated receptor alpha (PPARα) is a transcription factor belonging to the nuclear receptor superfamily, and ALAS1 has been identified as a target (90). In general, nuclear receptors regulate transcription through interactions with coactivator or corepressor molecules (91-95). Binding of agonists to PPARα leads to an enhanced binding of co-activator proteins, such as the proliferator-activated receptor γ coactivator 1α (PGC-1α) (96,97). PGC-1α, which acts as a bridge from the activated PPARs to the basal transcriptional machinery (90), activates the ALAS1 promoter by coactivating the nuclear respiratory factor-1 (NRF-1) and the forkhead box O1 (FOXO1), both of which directly bind to the ALAS1 promoter (98).

Recently, a study based on protein functional analysis indicated that the PPARα gene has obvious functional overlap with ALAS1 (72). That study also indicated that transcription of CYP2C8 and CYP3A4 is directly regulated by the PPARα gene (99), which is similar to previous findings that genes in CYP classes 1-3 are specifically regulated by PPARα in humans (100-103). Thus, mutations in PPARα may affect the heme biosynthesis pathway by regulating the cytochrome P450 system and eventually lead to AIP attacks (104).

3.4.4. Some genes regulating the nervous system

Currently, a few defects in genes regulating the nervous system (UNC13A, ALG8, FBXO38, AGRN, DOK7, and SCN4A) have been detected in a study in Russia (58). The latter three genes are related to congenital myasthenic syndrome (CMS), whose symptoms bear a remarkable resemblance to neurologic features of AIP attacks. Thus, the combination of a mutation in the HMBS gene with defects in genes regulating the nervous system may play a key role in triggering acute AIP attacks and prompting the development of specific symptomatic traits (58). However, this assumption needs to be verified in future studies.

3.4.5. ABCB6 gene

Elevated porphyrins are a hallmark of various types of porphyria. ABCB6, a type of porphyrin transporter, has been investigated as a modulator of porphyria severity through deep sequencing and biochemical analysis. A study found that patients with severe porphyria have variant alleles in the ABCB6 gene (105). Plasma membrane ABCB6 exports multiple disease-related porphyrins. Functional studies have revealed that most of these ABCB6 variants are poorly expressed and also dysfunctional. Therefore, ABCB6 is presumably a genetic modifier of porphyria that alleviates its severity by expelling porphyrins.

Nevertheless, most reports of modifying genes are only preliminary findings, and further clinical studies are needed to verify their reliability.
Intractable & Rare Diseases Research Advance Publication

4. Status of research on AIP in China

For a long time, China’s healthcare system has paid less attention to rare diseases, including AIP (106,107). An early study in the Mainland found a high rate of AIP misdiagnosis (33). Over a decade ago, a study involving 24 unrelated Chinese patients with AIP in Taiwan found no genotype/phenotype correlations, but the spectrum of HMBS gene mutations detected in these patients with AIP coincided with those observed in patients of other ethnic origins (61).

In recent years, this rare disorder has garnered attention from Chinese physicians, and small series of case reports on AIP, and especially reports of novel mutations, have increased in China, indicating that AIP may not be as “rare” as was previously assumed (108-114). In addition, some studies have analyzed clinical features of Chinese patients with AIP, such as posterior reversible encephalopathy syndrome (110,115-118). Peking Union Medical College Hospital first described how acute attacks affected the quality of life and psychological state of patients with AIP in Northern China (119).

Unfortunately, there are as of yet no studies on the prevalence, penetrance, and genetic traits of Chinese patients with AIP. Findings from Western counties are most likely inapplicable to the Chinese population due to the obvious differences in ethnic characteristics. Therefore, data on Chinese patients need to be evaluated in order to promptly identifying patients with HMBS mutations that have not yet suffered attacks, to properly manage patients, and to improve prognosis.

5. Conclusion

AIP is an inherited metabolic disease that exhibits an autosomal dominant pattern of inheritance caused by partial deficiencies in HMBS. In Europe, the estimated prevalence of AIP was 5.9 cases per million population, while the prevalence of HMBS variants was 1/1,299–1/1,782, with penetrance estimated at 20-50% in families with AIP but only ~1% in the general population. AIP has marked molecular genetic heterogeneity. No clear correlation between genotype and phenotype has been confirmed for AIP, although studies have reported that some mutations may be relevant to its penetrance or the severity of clinical manifestations. Consequently, the prevailing view is that other factors, such as modifying genes, may play an essential role in AIP attacks. Studies have identified some likely modifying genes, but most of those studies are just initial studies based on trials or predictions. Further clinical studies are needed to verify their reliability. Recently, studies on AIP have increased in China, but the prevalence, penetrance, and genetic traits of AIP in Chinese patients are unclear. Studies are urgently needed to reveal those aspects.

References

1. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet. 2010; 375:924-937.
2. Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias, in: The Online Metabolic and Molecular Bases of Inherited Disease (Scriver C, Beaudet A, Sly W, Valle D, eds.). McGraw Hill, New York, 2001; pp. 2961-3062.
3. Besur S, Hou W, Schmeltzer P, Bonkovsky HL. Clinically important features of porphyrin and heme metabolism and the porphyrias. Metabolites. 2014; 4:977-1006.
4. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: Review and recent progress. Hepatol Commun. 2019; 3:193-206.
5. Bung N, Roy A, Chen B, Das D, Pradhan M, Yasuda M, New MI, Desnick RJ, Bulusu G. Human hydroxymethylbilane synthase: Molecular dynamics of the pyrrole chain elongation identifies step-specific residues that cause AIP. Proc Natl Acad Sci U.S.A. 2018; 115:E4071-E4080.
6. Yasuda M, Chen B, Desnick RJ. Recent advances on porphyria genetics: Inheritance, penetrance & molecular heterogeneity, including new modifying/causative genes. Mol Genet Metab. 2019; 128:320-331.
7. Floderus Y, Sardh E, Möller C, Andersson C, Rejkjaer L, Andersson DE, Harper P. Variations in porphobiligen and 5-aminolevulinic acid concentrations in plasma and urine from symptomatic carriers of the acute intermittent porphyria gene with increased porphyrin precursor excretion. Clin Chem. 2006; 52: 701-707.
8. Besur S, Schmeltzer P, Bonkovsky HL. Acute porphyrias. J Emerg Med. 2015; 49:305-312.
9. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. N Engl J Med. 2017; 377:2101.
10. Duque-Serrano L, Patarroyo-Rodriguez L, Gotlib D, Molano-Eslava JC. Psychiatric aspects of acute porphyria: a comprehensive review. Curr Psychiatry Rep. 2018; 20:5.
11. Naik H, Stoecker M, Sanderson SC, Balwani M, Desnick RJ. Experiences and concerns of patients with recurrent attacks of acute hepatic porphyria: a qualitative study. Mol Genet Metab. 2016; 119:278-283.
12. Gill R, Kolstoe SE, Mohammed F, Al D-Bass A, Mosley JE, Sarwar M, Cooper JB, Wood SP. Structure of human porphobilinogen deaminase at 2.8 A: the molecular basis of acute intermittent porphyria. Biochem J. 2009; 420:17-25.
13. Shen, Y. Next-generation sequencing based molecular testing is an equalizer for diagnostic service of rare genetic disorders in China. Pediatr Invest. 2018; 2:96-97.
14. Chen B, Solis-Villa C, Hakenberg J, Qiao W, Srinivasan RR, Yasuda M, Balwani M, Doheny D, Peter I, Chen R, Desnick RJ. Acute intermittent porphyria: predicted pathogenicity of HMBS variants indicates extremely low penetrance of the autosomal dominant disease. Hum Mutat. 2016; 37:1215-1222.
15. Nordmann Y, Puy H, Da Silva V, Simonin S, Robreau AM, Bonaiti C, Phung LN, Deybach JC. Acute intermittent porphyria: prevalence of mutations in the porphobilinogen deaminase gene in blood donors in France. J Intern Med. 1997; 242:213-217.
16. To-Figueras J, Badenas C, Carrera C, Muñoz C, Milá M, Lecha M, Herrero C. Genetic and biochemical
characterization of 16 acute intermittent porphyria cases with a high prevalence of the R173W mutation. J Inherit Metab Dis. 2006; 29:580-585.

17. Spiritos Z, Salvador S, Mosquera D, Wilder J. Acute intermittent porphyria: Current perspectives and case presentation. Ther Clin Risk Manag. 2019; 15:1443-1451.

18. Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. Br J Haematol. 2017; 176:527-538.

19. Elder G, Harper P, Badminton M, Sandberg S, Deybach JC. The incidence of inherited porphyrias in Europe. J Inherit Metab Dis. 2013; 36:849-857.

20. Kauppinen R. Porphyrias. Lancet. 2005; 365:241-252.

21. Stein PE, Badminton MN, Barth JH, Rees DC, Sarkany R, Stewart MF, Cox TM. Acute intermittent porphyria: fatal complications of treatment. Clin Med (Lond). 2012; 12:293-294.

22. Ramanujam VS, Anderson KE. Porphyria diagnostics-Part 1: a brief overview of the porphyrias. Curr Protoc Hum Genet. 2015; 86.17.20.1-17.20.26.

23. Kauppinen R, Mustajoki P. Prognosis of acute porphyria: Occurrence of acute attacks, precipitating factors, and associated diseases. Medicine (Baltimore). 1992; 71:11-13.

24. von und zu Fraunberg M, Pischik E, Udd L, Kauppinen R. Clinical and biochemical characteristics and genotype-phenotype correlation in 143 Finnish and Russian patients with acute intermittent porphyria. Medicine (Baltimore). 2005; 84:35-47.

25. Lenglet H, Schmitt C, Grange T, et al. From a dominant to an oligogenic model of inheritance with environmental modifiers in acute intermittent porphyria. Hum Mol Genet. 2018; 27:1164-1173.

26. Barreda-Sánchez M, Buendia-Martinez J, Glover-Martinez G, Carazo-Díaz C, Ballesta-Martínez MJ, López-González V, Sánchez-Soler MJ, Rodríguez-Peña L, Serrano-Antón AT, Gil-Ferrer R, Martinez-Romero MDC, Carbonell-Meseguer P, Guillén-Navarro E. High penetrance of acute intermittent porphyria in a Spanish founder population mutation and CYP2D6 genotype as a susceptibility factor. Orphanet J Rare Dis. 2019; 14:59.

27. Bylesjö I, Wikberg A, Andersson C. Clinical aspects of acute intermittent porphyria in northern Sweden: a population-based study. Scand J Clin Lab Invest. 2009; 69:612-618.

28. De Siervi A, Rosetti MV, Parera VE, Mendez M, Varela LS, del C Batlle AM. Acute intermittent porphyria: biochemical and clinical analysis in the Argentinean population. Clin Chim Acta. 1999; 288:63-71.

29. Saint EG, Curnow DH. Porphyria in Western Australia. Lancet. 1962; 1:133-136.

30. Floderus Y, Shoelining-Jordan PM, Harper P. Acute intermittent porphyria in Sweden. Molecular, functional and clinical consequences of some new mutations found in the porphobilinogen deaminase gene. Clin Genet. 2002; 62:288-297.

31. Schneider-Yin X, Bogard C, Rüfenacht UB, Puy H, Nordmann Y, Minder EL, Deybach J. Identification of a prevalent nonsense mutation (W283X) and two novel mutations in the porphobilinogen deaminase gene of Swiss patients with acute intermittent porphyria. Hum Hered. 2000; 50:247-250.

32. Baumann K, Kauppinen R. Penetration and predictive value of genetic screening in acute porphyria. Mol Genet Metab. 2020; 130:87-99.

33. Ren Y, Xu LX, Liu YF, Xiang CY, Gao F, Wang Y, Bai T, Yin JH, Zhao YL, Yang J. A novel 55-basepair deletion of hydroxymethylbilane synthase gene found in a Chinese patient with acute intermittent porphyria and her family: A case report. Medicine (Baltimore). 2018; 97:e12295.

34. Namba H, Narahara K, Tsuji K, Yokoyama Y, Seino Y. Assignment of human porphobilinogen deaminase to 11q24.1----q24.2 by in situ hybridization and gene dosage studies. CytoGenet Cell Genet.1991; 57:105-108.

35. Yoo HW, Warner CA, Chen CH, Desnick RJ. Hydroxymethylbilane synthase: complete genomic sequence and amplifiable polymorphisms in the human gene. Genomics. 1993; 15:21-19.

36. Chretien S, Dubart A, Beaupain D, Raich N, Grandchamp B, Rosa J, Goossens M, Romeo PH. Alternative transcription and splicing of the human porphobilinogen deaminase gene result either in tissue-specific or in housekeeping expression. Proc Natl Acad Sci U.S.A. 1988; 85:6-10.

37. Grandchamp B, De Verneuil H, Beaumont C, Chretien S, Walter O, Nordmann Y. Tissue-specific expression of porphobilinogen deaminase. Two isoenzymes from a single gene. Eur J Biochem. 1987; 162:105-110.

38. Chen CH, Astrin KH, Lee G, Anderson KE, Desnick RJ. Acute intermittent porphyria: Identification and expression of exonic mutations in the hydroxymethylbilane synthase gene. An initiation codon missense mutation in the housekeeping transcript causes "variant acute intermittent porphyria" with normal expression of the erythroid-specific enzyme. J Clin Invest. 1994; 94:1927-1937.

39. Grandchamp B, Picat C, Kauppinen R, Mignotte V, Peltonen L, Mustajoki P, Roméo PH, Goossens M, Nordmann Y. Molecular analysis of acute intermittent porphyria in a Finnish family with normal erythrocyte porphobilinogen deaminase. Eur J Clin Invest. 1989; 19:415-418.

40. Granata F, Mendez M, Brancalonei V, Castelbon FJ, Graziaidei G, Ventura P, Di Pierro E. Molecular characterization, by digital PCR analysis of four HMBS gene mutations affecting the ubiquitous isoform of Porphobilinogen Deaminase (PBGD) in patients with Acute Intermittent Porphyria (AIP). Mol Genet Metab. 2018; 125:295-301.

41. Brancalonei V, Granata F, Colancecco A, Tavazzi D, Cappellini MD, Di Pierno E. Seven novel genetic mutations within the 5'UTR and the housekeeping promoter of HMBS gene responsible for the non-erythroid form of acute intermittent porphyria. Blood Cells Mol Dis. 2012; 49:147-151.

42. Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017; 136:665-677.

43. Cooper DN, Youssoufian H. The Cpg dinucleotide and human genetic disease. Hum Genet. 1988; 78:151-155.

44. Youssoufian H, Antonarakis SE, Bell W, Griffin AM, Kazazian HH. Nonsense and missense mutations in hemophilia A: estimate of the relative mutation rate at CpG dinucleotides. Am J Hum Genet.1991; 49:1279-1287.

45. Ulbrichova D, Schneider-Yin X, Mamet R, Saudek V, Martasek P, Graziadei G, Ventura P, Di Pierro E. Molecular characterization of Acute Intermittent Porphyria (AIP). Mol Genet Metab. 2012; 49:147-151.
families with acute intermittent porphyria. Blood Cells Mol Dis. 2009; 42:167-173.

46. Solis C, Lopez-Echanchi I, Sefarty-Graneda D, Astrin KH, Desnick RJ. Identification and expression of mutations in the hydroxymethylbilane synthase gene causing acute intermittent porphyria (AIP). Mol Med. 1999; 5:664-671.

47. Puy H, Deybach JC, Lamaril J, Robreau AM, Da Silva V, Guoya L, Grandchamp B, Nordmann Y. Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. Am J Hum Genet. 1997; 60:1373-1383.

48. Grandchamp B. Acute intermittent porphyria. Semin Liver Dis. 1998; 18:17-24.

49. Martinez di Montemuros F, Di Pierro E, Fargion S, Biolcati G, Griso D, Macri A, Fiorelli G, Cappellini MD. Molecular analysis of the hydroxymethylbilane synthase (HMBS) gene in Italian patients with acute intermittent porphyria: report of four novel mutations. Hum Mutat. 2000; 15:480.

50. Kauppinen R, Mustajoki S, Pihlaja H, Peltonen L, Mustajoki P. Acute intermittent porphyria in Finland: 19 mutations in the porphobilinogen deaminase gene. Hum Mol Genet. 1995; 4:215-222.

51. Gu XF, de Rooij F, Lee JS, Te Velde K, Deybach JC, Nordmann Y, Grandchamp B. High prevalence of a point mutation in the porphobilinogen deaminase gene in Dutch patients with acute intermittent porphyria. Hum Genet. 1993; 91:128-130.

52. Whatley SD, Woolf JR, Elder GH. Comparison of complementary and genomic DNA sequencing for the detection of mutations in the HMBS gene in British patients with acute intermittent porphyria: Identification of 25 novel mutations. Hum Genet. 1999; 104:505-510.

53. Petersen NE, Nissen H, Horder M, Senz J, Jamani A, Schreiber WE. Mutation screening by denaturing gradient gel electrophoresis in North American patients with acute intermittent porphyria. Clin Chem. 1998; 44:1766-1768.

54. De Siervi A, Rossetti M V, Parera V E, Astrin KH, Aizencang GI, Glass IA, Battile AM, Desnick RJ. Identification and characterization of hydroxymethylbilane synthase mutations causing acute intermittent porphyria: evidence for an ancestral founder of the common G111R mutation. Am J Med Genet. 1999; 86:366-375.

55. Lee JS, Anvret M. Identification of the most common mutation within the porphobilinogen deaminase gene in Swedish patients with acute intermittent porphyria. Proc Natl Acad Sci U.S.A. 1991; 88:10912-10915.

56. Greene-Davis ST, Neumann PE, Mann OE, Moss MA, Schreiber WE, Welch JP, Langley GR, Sangalang VE, Dempsey GI, Nassar BA. Detection of a R173W mutation in the porphobilinogen deaminase gene in the Nova Scotian "foreign Protestant" population with acute intermittent porphyria: a founder effect. Clin Biochem. 1997; 30:607-612.

57. Guillén-Navarro E, Carbonell P, Glover G, Sánchez-Solís M, Fernández-Barreiro A. Novel HMBS founder mutation and significant intronic polymorphism in Spanish patients with acute intermittent porphyria. Ann Hum Genet. 2004; 68:509-514.

58. Goncharova M, Pshenichnikova O, Luchinina Y, Pustovoit Y, Karpova I, Surin V. Molecular genetic study of acute intermittent porphyria in Russia: HMBS gene mutation spectrum and problem of penetrance. Clin Genet. 2019; 96:91-97.

59. Gregor A, Schneider-Yin X, Szlendak U, Wettstein A, Lipniacka A, Rüfenacht UB, Minder EL. Molecular study of the hydroxymethylbilane synthase gene (HMBS) among Polish patients with acute intermittent porphyria. Hum Mutat. 2002; 19:310.

60. Schuurmans MM, Schneider-Yin X, Rüfenacht UB, Schnyder C, Minder CE, Puy H, Deybach JC, Minder EL. Influence of age and gender on the clinical expression of acute intermittent porphyria based on molecular study of porphobilinogen deaminase gene among Swiss patients. Mol Med. 2001; 7:535-542.

61. Kauppinen R, von und zu Fraunberg M. Molecular and biochemical studies of acute intermittent porphyria in 196 patients and their families. Clin Chem. 2002; 48:1891-1900.

62. Yang CC, Kuo HC, You HL, Wang J, Huang CC, Liu CY, Lan MY, Stephenson DA, Lee MJ. HMBS mutations in Chinese patients with acute intermittent porphyria. Hum Genet. 2008; 72:683-686.

63. Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell DM, Bloomer JR, Phillips JD, Naik H, Peter I, Baillargeon G, Bossi K, Gandolfi L, Light C, Bishop D, Desnick RJ. Acute porphyrias in the USA: features of 108 subjects from Porphyrias Consortium. Am J Med. 2014; 127:1233-1241.

64. Szlendak U, Bykovska K, Lipniacka A. Clinical, biochemical and molecular characteristics of the main types of porphyria. Adv Clin Exp Med. 2016; 25:361-368.

65. Andersson C, Innala E, Bäckström T. Acute intermittent porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. J Intern Med. 2003; 254:176-183.

66. Bonkovsky HL, Dixon N, Rudnick S. Pathogenesis and clinical features of the acute hepatic porphyrias (AHPs). Mol Genet Metab. 2019; 128:213-218.

67. Anderson KE, Bradlow HL, Sassa S, Kappas A. Studies in porphyria. VIII. Relationship of the 5 alpha-reductive metabolism of steroid hormones to clinical expression of the genetic defect in acute intermittent porphyria. Am J Med. 1979; 66:644-650.

68. Arora S, Young S, Kodali S, Singal AK. Hepatic porphyria: a narrative review. Indian J Gastroenterol. 2016; 35:405-418.

69. Andersson C, Floderus Y, Wikberg A, Lither F. The W198X and R173W mutations in the porphobilinogen deaminase gene in acute intermittent porphyria have higher clinical penetrance than R167W. A population-based study. Scand J Clin Lab Invest. 2000; 60:643-648.

70. Stölzel U, Doss MO, Schuppan D. Clinical guide and update on porphyrias. Gastroenterology. 2019; 157:365-381.

71. Hift RJ, Meissner PN. An analysis of 112 acute porphyric patients: Systematically analyzing the pathogenic variations for the genetic defect in acute intermittent porphyria. J Inherit Metab Dis. 1997; 20:381.

72. Fu Y, Jia J, Yue L, Yang R, Guo Y, Ni X, Shi T. The clinical features and problem of penetrance. Clin Genet. 2019; 1018.

73. Chen B, Solis-Villa C, Erwin AL, Balwani M, Nazarenko I, Phillips JD, Desnick RJ, Yasuda M. Identification and characterization of 40 novel hydroxymethylbilane synthase mutations that cause acute intermittent porphyria. J Inherit Metab Dis. 2019; 42:186-194.

www.irdrjournal.com
74. Thunell S. (Far) Outside the box: genomic approach to acute porphyria. Physiol Res. 2006; null:S43-66.

75. Badminton MN, Elder GH. Molecular mechanisms of dominant expression in porphyria. J Inherit Metab Dis. 2005; 28:277-286.

76. Tchernitchko D, Tavernier Q, Lamoril J, Schmitt C, Talbi N, Lyouni S, Robreau AM, Karim Z, Gouya L, Thervet E, Karras A, Puy H, Pallet N. A variant of peptide transporter 2 predicts the severity of porphyria-associated kidney disease. J Am Soc Nephrol. 2017; 28:1924-1932.

77. Hu Y, Shen H, Keep RF, Smith DE. Peptide transporter 2 (hPEPT2) expression in brain protects against 5-aminolevulinic acid neurotoxicity. J Neurochem. 2007; 103:2058-2065.

78. Novotny A, Xiang J, Stummer W, Teuscher NS, Smith DE, Keep RF. Mechanisms of 5-aminolevulinic acid uptake at the choroid plexus. J Neurochem. 2000; 75:321-328.

79. Düring F, Walter J, Will J, Föcking M, Boll M, Amasheh S, Clauss W, Daniel H. Delta-aminolevulinic acid transport by intestinal and renal peptide transporters and its physiological and clinical implications. J Clin Invest. 1998; 101:2761-2767.

80. Pinsouneault J, Nielsen CU, Sádeé W. Genetic variants of the human Hþ/dipeptide transporter PEPT2: analysis of haplotype functions. J Pharmacol Exp Ther. 2004; 311:1088-1096.

81. Jaramillo-Calle DA, Solano JM, Rabinstein AA, Bonkovsky HL. Porphyria-induced posterior reversible encephalopathy syndrome and central nervous system dysfunction. Mol Genet Metab. 2019; 128:124-253.

82. Ennis SR, Novotny A, Xiang J, Shakui P, Masada T, Stummer W, Smith DE, Keep RF. Transport of 5-aminolevulinic acid between blood and brain. Brain Res. 2003; 959:226-234.

83. Sobin C, Flores-Montoya MG, Gutierrez M, Parisi N, Jaramillo-Calle DA, Solano JM, Rabinstein AA, Bonkovsky HL. Characterization of the hepatic transcriptome following phenobarbital induction in mice with AIP. Mol Genet Metab. 2019; 128:190-197.

84. Phillips JD. Heme biosynthesis and the porphyrias. Mol Genet Metab. 2019; 128:164-177.

85. Manceau H, Gouya L, Puy H. Acute hepatic and alternative-splice variants. Pharmacogenetics. 2004; 14:1-18.

86. Manceau H, Gouya L, Puy H, Lefebvre T, Smith DE, Keep RF. Mechanisms of 5-aminolevulinic acid uptake at the choroid plexus. J Neurochem. 2000; 75:321-328.

87. Düring F, Walter J, Will J, Föcking M, Boll M, Amasheh S, Clauss W, Daniel H. Delta-aminolevulinic acid transport by intestinal and renal peptide transporters and its physiological and clinical implications. J Clin Invest. 1998; 101:2761-2767.

88. Pinsouneault J, Nielsen CU, Sádeé W. Genetic variants of the human Hþ/dipeptide transporter PEPT2: analysis of haplotype functions. J Pharmacol Exp Ther. 2004; 311:1088-1096.

89. Degenhardt T, Väisänen R, Rakhshandehroo M, Kersten S, Carlberg C. Peroxisome proliferator-activated receptor alpha controls hepatic heme biosynthesis through ALAS1. J Mol Biol. 2009; 388:225-238.

90. Cavaillé V, Daouvois S, Danielian PS, Parker MG. Interaction of proteins with transcriptionally active estrogen receptors. Proc Natl Acad Sci U.S.A. 1994; 91:10009-10013.

91. Chen JD, Umesono K, Evans RM. SMRT isoforms mediate repression and anti-repression of nuclear receptor heterodimers. Proc Natl Acad Sci U.S.A. 1996; 93:7567-7571.

92. Halachmi S, Marden E, Martin G, MacKay H, Bonkovsky HL. Porphyria-induced posterior reversible encephalopathy syndrome and central nervous system dysfunction. Mol Genet Metab. 2019; 128:242-253.

93. Vega R B, Huss J M, Kelly D P. The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. Mol Cell Biol. 2000; 20:1868-1876.

94. Tudor C, Feige JN, Pingali H, Lohrav YB, Wahl W, Desvergne B, Engelborghs Y, Gelman L. Association with coregulators is the major determinant governing peroxisome proliferator-activated receptor mobility in living cells. J Biol Chem. 2007; 282:4417-4426.

95. Handschin C, Lin J, Rhee J, Peyer AK, Chin S, Wu PH, Meyer UA, Spiegelman BM. Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. Cell. 2005; 122:505-515.

96. Thomas M, Burk O, Klumpp B, Kandel BA, Damm G, Weiss TS, Klein K, Schwab M, Zanger UM. Direct transcriptional regulation of human hepatic cytochrome P450 3A4 (CYP3A4) by peroxisome proliferator-activated receptor alpha (PPARα). Mol Pharmacol. 2013; 83:709-718.

97. Halachmi S, Marden E, Martin G, MacKay H, Bonkovsky HL. Porphyria-induced posterior reversible encephalopathy syndrome and central nervous system dysfunction. Mol Genet Metab. 2019; 128:190-197.

98. Handschin C, Lin J, Rhee J, Peyer AK, Chin S, Wu PH, Meyer UA, Spiegelman BM. Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. Cell. 2005; 122:505-515.

99. Tudor C, Feige JN, Pingali H, Lohrav YB, Wahl W, Desvergne B, Engelborghs Y, Gelman L. Association with coregulators is the major determinant governing peroxisome proliferator-activated receptor mobility in living cells. J Biol Chem. 2007; 282:4417-4426.

100. Handschin C, Lin J, Rhee J, Peyer AK, Chin S, Wu PH, Meyer UA, Spiegelman BM. Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. Cell. 2005; 122:505-515.
105. Fukuda Y, Cheong PL, Lynch J, et al. The severity of hereditary porphyria is modulated by the porphyrin exporter and Lan antigen ABCB6. Nat Commun. 2016; 7:12353.

106. Li C, Zhang J, Li S, Han T, Kuang W, Zhou Y, Deng J, Tan X. Gene mutations and clinical phenotypes in Chinese children with Blau syndrome. Sci China Life Sci. 2017; 60:758-762.

107. Ni X, Shi T. The challenge and promise of rare disease diagnosis in China. Sci China Life Sci. 2017; 60:681-685.

108. Yang Y, Chen X, Wu H, Peng H, Sun W, He B, Yuan Z. A novel heterozygous mutation in the HMBS gene in a patient with acute intermittent porphyria and posterior reversible encephalopathy syndrome. Mol Med Rep. 2020; 22:516-524.

109. Yang J, Han F, Chen Q, Zhu T, Zhao Y, Yu X, Zhu H, Cao J, Li X. Reversible splenial lesion syndrome (RESLES) due to acute intermittent porphyria with a novel mutation in the hydroxymethylbilane synthase gene. Orphanet J Rare Dis, 2020; 15:98.

110. Zheng X, Liu X, Wang Y, Zhao R, Qu L, Pei H, Tuo M, Zhang Y, Song Y, Ji X, Li H, Tang L, Yin X. Acute intermittent porphyria presenting with seizures and posterior reversible encephalopathy syndrome: two case reports and a literature review. Medicine (Baltimore). 2018; 97:e11665.

111. Zheng Y, Xu J, Liang S, Lin D, Banerjee S. HMBS whole exome sequencing identified a novel heterozygous mutation in gene in a Chinese patient with acute intermittent porphyria with rare type of mild anemia. Front Genet. 2018; 9:129.

112. Jiao H, Xianfeng Z, Hui H, MaLizhen, Yuhong Z, Chu Z. A novel mutation, IVS2-2AgG, associated with acute intermittent porphyria in a Chinese family. J Pak Med Assoc. 2015; 65:898-900.

113. Yang J, Wang H, Yin K, Hua B, Zhu T, Zhao Y, Guo S, Yu X, Wu W, Zhou Z. A novel mutation in the porphobilinogen deaminase gene in an extended Chinese family with acute intermittent porphyria. Gene. 2015; 565:288-290.

114. Li Y, Qu H, Wang H, Deng H, Liu Z. Novel A219P mutation of hydroxymethylbilane synthase identified in a Chinese woman with acute intermittent porphyria and syndrome of inappropriate antidiuretic hormone. Ann Hum Genet. 2015; 79:310-312.

115. Zhao B, Wei Q, Wang Y, Chen Y, Shang H. Posterior reversible encephalopathy syndrome in acute intermittent porphyria. Pediatr Neurol. 2014; 51:457-460.

116. Wang Y, Chen XY, Li Y, Dong XH, Xu F. Clinical characteristics of 50 patients with acute intermittent porphyria. Zhonghua Nei Ke Za Zhi. 2019; 58:520-524. (in Chinese).

117. Yang J, Chen Q, Yang H, Hua B, Zhu T, Zhao Y, Zhu H, Yu X, Zhang L, Zhou Z. Clinical and laboratory features of acute porphyria: A study of 36 subjects in a Chinese tertiary referral center. Biomed Res Int. 2016; 2016:3927635.

118. Ni J, Zhou LX, Hao HL, Liu Q, Yao M, Li ML, Peng B, Cui LY. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: a retrospective series of 24 patients. J Neuroimaging. 2011; 21:219-224.

119. Yang J, Zhu T, Zhao Y, Yu X, Zhu H, Jiang Y, Li X. Acute intermittent porphyria in the North of China: The acute attack effect on quality of life and psychological condition. Biomed Res Int. 2018; 2018:3216802.

Received July 20, 2020; Revised August 7, 2020; Accepted August 11, 2020.

*Address correspondence to:
Songyun Zhang, Endocrinology, The Second Hospital of Hebei medical University, Shijiazhuang 050000, Hebei, China.
E-mail: zsy2020@hebmu.edu.cn

Released online in J-STAGE as advance publication August 14, 2020.