Title: Phenylalanine Hydroxylase Deficiency *GeneReview* – Historical Perspective
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Date: October 2016
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Historical Perspective

Hyperphenylalaninemia (HPA) has been called the epitome of human biochemical genetics. In 1934, Asjbørn Følling recognized that a certain type of intellectual disability was caused by elevated levels of phenylalanine in body fluids. He identified the disease as an autosomal recessive condition. In the 1940s, Lionel Penrose, who had recognized 'phenylketonuria' (PKU) to be the first form of intellectual disability with a chemical explanation, introduced the idea that PKU was not randomly distributed in human populations and could be treatable. In the mid-1950s, it was demonstrated that individuals with PKU had a deficiency of hepatic cytosolic phenylalanine hydroxylase (PAH) enzyme activity.

Next it was shown that affected individuals responded to dietary restriction of the essential nutrient phenylalanine. In the 1960s, the Guthrie microbial inhibition assay was introduced for mass screening of newborns, providing early diagnosis and access to successful treatment. Newborn screening for elevated Phe has been routine throughout North America and the UK since the mid-1960s and in most other developed countries since the early 1970s [Scriver 1998, Levy 1999]. The test became routine because of the excellent prognosis for children with PAH deficiency who are treated early and the high risk for severe and irreversible brain damage for children who are not treated. In most countries a parental right of refusal for this test exists; however, this right is exercised only in rare circumstances.

In the 1970s, it was discovered that not all elevated Phe levels were caused by PKU. Some forms were caused by disorders of synthesis and recycling of the cofactor (tetrahydrobiopterin, or BH_4) involved in the Phe hydroxylation reaction. During the 1980s, the human *PAH* gene was mapped and cloned, and the first pathogenic variants identified. In the 1990s, in vitro expression analysis was being used to study the effects of different *PAH* alleles on enzyme function and the crystal structure of *PAH* was elucidated.

Affected individuals can lead normal lives. Continuous efforts are made to improve the taste and convenience of the current synthetic dietary supplements [Rohr et al 2001]. Research to improve the current treatment with restrictive phenylalanine diets, supplemented by medical formula, is ongoing.

References

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