Biglari et al. SpringerPlus (2015) 4:542
DOI 10.1186/s40064-015-1309-8

SpringerPlus
a SpringerOpen Journal

RESEARCH

Open Access

Mutations of the phenylalanine hydroxylase gene in Iranian patients with phenylketonuria

Alireza Biglari[1], Fatemeh Saffari[2], Zahra Rashvand[3], Safarali Alizadeh[3], Reza Najafipour[4*] and Mehdi Sahmani[4*]

Abstract

Phenylketonuria (PKU) is an autosomal recessive disease which results from mutations in the phenylalanine hydroxylase (PAH) gene. The aim of this study was the identification of sixteen different mutations in Iranian patients with hyperphenylalaninemia. The mutations were detected during the characterization of PAH genotypes of 39 PKU patients from Qazvin and Zanjan provinces of Iran. PAH mutations have been analyzed by PCR and direct sequencing of PCR products of the promoter region and all 13 exons of PAH gene, including the splicing sites. A mutation detection rate of 74.3 % was realized. Two mutations were found at high frequencies: R176X (10.25 %) and p.P281L (10.25 %). The frequencies of the other mutations were: IVS2+5G>A (2.56 %), IVS2+5G>C (2.56 %), p.L48S (2.56 %), p.R243Q (2.56 %), p.R252Q (5.12 %), p.R261Q (7.69 %), p.R261X (5.12 %), p.E280K (2.56 %), p.I283N (2.56 %), IVS9+5G>A (2.56 %), IVS9+1G>A (1.28 %), IVS11+1G>C (1.28 %), p.C357R (1.28 %), c.632delC (2.56 %). The present results confirm the high heterogeneity of the PAH locus and contribute to information about the distribution and frequency of PKU mutations in the Iranian population.

Keywords: Phenylketonuria, PAH gene, Iranian population, Mutation detection

Background

Deficiency of hepatic phenylalanine hydroxylase (PAH) [EC.1.14.16.1], which converts phenylalanine to tyrosine, is the major frequent cause of hyperphenylalaninemia (Guldberg et al. 1998). This enzyme defect, causes toxic accumulation of phenylalanine in the body fluids and damage to the nervous system that can result in growth failure, microcephaly, mental retardation and neurobehavioral abnormalities (Zhang et al. 2005). Phenylketonuria (PKU) is one of the most common inborn disease of amino acid metabolism, characterized by mutation of the PAH gene (Williams et al. 2008). According the levels of phenylalanine, they are four categories: mild hyperphenylalaninemia (HPA), mild PKU, moderate-PKU, and classic-PKU. Classical PKU is the most severe form of this disorder. A phenylalanine restricted diet, can be useful to prevent the neurotoxic complication of Phe and its metabolites (Olsson et al. 2007). The prevalence of PKU varies worldwide. In Caucasians, the prevalence is about 1/10,000 live births (Olsson et al. 2007), while that in Iranian population was 1/3627 (Koochmeshgi et al. 2002). In fact, the high rate of consanguineous marriages in Iran may be a contributing factor to the high incidence. The human PAH gene is located on chromosome 12q23.2 and is 90 kb in size with 13 exons and 12 introns (Santos et al. 2010). So far, several hundred different mutations in this gene have been identified in PKU patients and listed in the PAH mutation Analysis Consortium database (http://www.Pahdb.mcgill.ca). The most frequently occurring type of these mutations are missense mutations (Scriver 2007). The PAH gene mutations demonstrate considerable ethnic groups and geographic areas variation (Zschocke 2003). Previous studies have shown a correlation between PAH genotype and metabolic phenotype in PKU and have suggested the phenotypic relations of particular mutation combinations (Desviat et al. 1997; Kayaalp et al. 1997; Romano et al. 1996). Mutation

*Correspondence: rnajafipour@gmail.com; m.sahmani@gmail.com
[4] Department of Clinical Biochemistry and Genetics, Faculty of Medicine, Cellular and Molecular Research Center, Qazvin University of Medical Sciences, Qazvin, Iran
Full list of author information is available at the end of the article