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Review

Propionic acidemia in the Arab World

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ABSTRACT

The autosomal recessive disease propionic acidemia (PA) is an inborn error of metabolism with highly variable clinical manifestations, caused by a deficiency of propionyl-CoA carboxylase (PCC) enzyme, due to mutations in either *PCCA* or *PCCB* genes, which encode the alpha and beta subunits of the PCC enzyme, respectively. The classical clinical presentation consists of poor feeding, vomiting, metabolic acidosis, hyperammonemia, lethargy, neurological problems, and developmental delay. PA seems to be a prevalent disease in the Arab World. Arab patients with PA seem to have the same classical clinical picture for PA with distinctive associated complications and other diseases. Most of the mutations found in Arab patients seem to be specific to the Arab population, and not observed in other ethnic groups. In this review, I will discuss in details the clinical and molecular profile of Arab patients with PA.

Contents

1. Introduction

Propionic acidemia (PA; MIM# 232000 and 232050) is an autosomal recessive inherited inborn error of metabolism. It is caused by a deficiency of the mitochondrial enzyme propionyl-CoA carboxylase (PCC) enzyme (Hsia et al., 1971), which converts propionyl coenzyme A (propionyl-CoA) to methylmalonyl-coenzyme A (methylmalonyl-CoA), leading to impaired metabolism of branched-chain amino acids, such as isoleucine and valine, methionine, threonine, cholesterol side chains, odd numbered fatty acids, thymine and uracil. PCC enzyme is a dodecamer comprised of alpha and beta subunits; the alpha subunit is encoded by the *PCCA* gene (chromosome 13q32, MIM#232000; NCBI Reference Sequence: NG_008768.1). The beta subunit is encoded by the *PCCB* gene (chromosome 3q13.3–q22, MIM#232050; NCBI Reference Sequence: NG_008939.1) (Lamhonwah et al., 1986). Mutations in either the *PCCA* or *PCCB* gene cause PCC enzyme deficiency.

To date, the Human Gene Mutation Database (http://www.hgmd.org) has reported 98 mutations in *PCCA* gene and 98 mutations in *PCCB* gene. According to the Exome variant service (EVS), 183 variants have been reported for the *PCCA* gene and 133 in the *PCCB* gene. The majority of these mutations were missense mutation (40%) (http://cbs.lf1.

Abbreviations: PA, propionic acidemia; IEMs, inborn errors of metabolism; PCC, propionyl-CoA carboxylase; PCCA, propionyl-CoA carboxylase, alpha subunit; PCCB, propionyl-CoA carboxylase, beta subunit.

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0378-1119/

cuni.cz/pcc/pccmain.htm; Ugarte et al., 1999) followed by small insertions/deletions and splicing mutations. In the case of the *PCCA* gene, large genomic deletions were more frequent (Desviat et al., 2009).

Patients with PA appear normal at birth; signs of disease might not appear in the first few days of life. Neonates with PA present with poor feeding, vomiting, hypotonia, lethargy, seizures, neurological problems, and developmental delay. Though PA is mostly an infantile disorder, as the patients advanced in age; disease progression is associated with complications affecting the cardiologic, neurologic, immunologic, hematologic, and gastrointestinal systems (Wolf et al., 1981; Henriquez et al., 1994; Lehnert et al., 1994; Ozand et al., 1994; Pena et al., 2012; Grunert et al., 2013; Rafique, 2013), rarely asymptomatic patients with PCC-deficient enzyme have been reported (Wolf et al., 1979). Propionic acidemia has been found to be accompanied by uncommon clinical signs such as intracranial bleeding (Ozand et al., 1994), seizures, and dehydration (Schreiber et al., 2012; Lehnert et al., 1994), and has also been found to be associated with different diseases such as Maple Syrup Urine (Van Calcar et al., 1992), mimicking diabetic ketoacidosis (Dweikat et al., 2011), premature ovarian failure (Lam et al., 2011), Noonan syndrome (Bouet et al., 2012), autism (Al-Owain et al., 2013), optic neuropathy (Arias et al., 2014), and chronic kidney disease (Vernon et al., 2014).

Without a timely intervention to treat PA, the complications would likely lead to coma and death (Lehnert et al., 1994; Pena et al., 2012; Rafique, 2013; Vatanavicharn et al., 2014). The diagnosis of PA usually stems from clinical assessment and biochemical analyses: the most used definitive diagnostic test is gas chromatography/mass spectrometry (GC/MS) analysis of urine organic acids (Wojtowicz et al., 2010; Karam et al., 2013; Al-Owain et al., 2013). Plasma acylcarnitine analysis, which is used as part of newborn screening tests, is among the first diagnostic analysis performed (Rashed et al., 1995). Measuring the PCC enzyme activity and sequencing the *PCCA* and *PCCB* genes for potential pathogenic mutations are confirmatory tests, and used to uncover the molecular causes of the disease (Gravel et al., 1977; Saunders et al., 1979; Perez-Cerda et al., 2002) and to determine potential genotype–phenotype correlation.

2. Genotype–phenotype correlation in non-Arab PA patients belong to diverse ethnic groups

The ability to measure the PCC enzyme activity and molecularly test for mutations for both *PCCA* and *PCCB* genes, made it conducive to draw a potential relationship between the genotype and the clinical features of patients with PA. The effect of mutations on the PCC enzyme activity, *in silico* prediction, family history, age of onset,and clinical features, were compiled to reach a conclusion on the clarity of the relationship between the genotype and phenotype of patients with PA.

2.1. Strong genotype–phenotype correlation

Strong relationship between the genotype and phenotype has been observed in many cases of PA. For example, two Middle Eastern patients, who were homozygous for the *PCCB*: c.1498+2T>C variant (Table 1), and have less than 0.1% of the normal *PCCB* transcript, presented with severe neonatal PA phenotype (Desviat et al., 2006). The *PCCB*: c.1301C>T (p.A434V) variant (Table 1) accounted for 50% of the PCCB mutant alleles in PA patients of Taiwanese origin, who have low enzyme activity and classic form of PA (Chiu et al., 2014). The *PCCA*: c.1118T>A (p.M373K) variant (Table 1) (Perez-Cerda et al., 2000; Clavero et al., 2002) is associated with early onset disease (Perez et al., 2010), and dramatically reduced in *in vitro* enzyme activity. On the other hand, two mutations, *PCCA*: c.223G>C (p.A75P) and *PCCA*: c.412G>A (p.A138T) (Table 1), were found in patients with mild phenotypes, consistent with the residual PCC enzyme activities of 26.7% and 9.4%, respectively (Desviat et al., 2004; Clavero et al., 2002).

The *PCCB*: 1218del14ins12 mutation (p.G407fs) (Table 1) is the most common severe mutation among Caucasians, as it is found in 32% of mutant alleles (Lamhonwah et al., 1990; Tahara et al., 1993; Rodriguez-Pombo et al., 1998; Ugarte et al., 1999). This mutation is found to affect the protein function and is associated with an early onset and severe clinical phenotype (Perez et al., 2010). The PCC enzyme activity was not detectable in any cell lines that harbored this mutation (Perez-Cerda et al., 2000). Another representative example is the *PCCB*: c.1170insT mutation, which is prevalent in Hispanics; it affects the functionality of PCC protein and results in a premature stop codon and leads to the total absence of the beta subunit of the PCC enzyme (Table 1) (Lamhonwah et al., 1986; Rodriguez-Pombo et al., 1998; Ugarte et al., 1999), leading to a severe phenotype with an early onset of the disease (Perez-Cerda et al., 2000). The *PCCB*: c.1283C>T (p.T428I) mutation is common among Japanese and Koreans (Table 1) (Ohura et al., 1993; Ugarte et al., 1999; Kim et al., 2002; Yang et al., 2004) and inactivates PCC enzyme (Kelson et al., 1996), which is consistent with a severe form of PA and neonatal disease presentation (Kim et al., 2002). All of the severe clinical phenotype of these mutations is in agreement with the classical clinical findings of the PA, including, hyperammonemia, metabolic acidosis, and poor feeding and vomiting.

2.2. Inconclusive genotype–phenotype correlation

Although some studies showed a direct correlation between the genotype and the clinical phenotype, it is not always possible to draw conclusions about the phenotype from the genotype. For example, the *PCCB*: c.1228C>T (p.R410W) mutation (Table 1), which is frequently associated with Japanese patients with PA (Ohura et al., 1993; Tahara et al., 1993), exhibited 12% residual enzyme activity (Perez-Cerda

Table 1
genotype–phenotype correlation for PA patients in different ethnic groups.

Origin	Gene	N change	AA change	PCC_A	PP	CP	Reference
Latin	*PCCA*	c.1118T>A	p.M373K	2%	PD	Severe	Clavero et al., 2002; Perez et al., 2010
USA	*PCCA*	c.223G>C	p.A75P	26.7%	PD	Mild	Desviat et al., 2004; Clavero et al., 2002.
Spain	*PCCA*	c.412G>A	p.A138T	9.4%,	PD	Mild	Desviat et al., 2004; Clavero et al., 2002.
USA, Latin	*PCCB*	1218del14ins12	p.G407fs	Null	N/A	Severe	Desviat et al., 2004
Spain	*PCCB*	1170insT	N/A	1.2%	N/A	Severe	Perez-Cerda et al., 2000
Japan, Korea	*PCCB*	c.1283C>T	p.T428I	Null	PD	Severe	Desviat et al., 2004
Japan	*PCCB*	c.1228C>T	p.R410W	12%	PD	Severe	Perez-Cerda et al., 2003; Ohura et al., 1993
Latin	*PCCB*	c.502G>A	p.E168K	1.7%	PD	Mild–severe	Rodriguez-Pombo et al., 1998; Perez-Cerda et al., 2000
Taiwan	*PCCB*	c.1301C>T	p.A434V	3.9%	PD	Severe	Chiu et al., 2014
Iran/Pakistan	*PCCB*	1498+2T>C[a]	p. A468fs	[b]	N/A	Severe	Desviat et al., 2006

Abbreviations: N: nucleotide, PP: polyphen2 prediction, PCC_A: PCC mutant enzyme activity related to normal, PD: probably damaging.
Note: the value of a polyphen2 is very limited, when expression data are available.
[a] This variant led to exon skipping with a significant reduction of the splicing score from 84.7 to 66.9, measured by using the gene bank database (Shapiro and Senapathy, 1987), indicating affected function phenotype.
[b] This variant led to skipping of exon 14 of the *PCCB* gene, leading to a frameshift mutation (p.A468fs). The amount of the normal spliced transcripts in the patients' cells, were less than 0.1% of the normal transcript of the normal control.