Pathogenic variants of DNAJC12 and evaluation of the encoded cochaperone as a genetic modifier of hyperphenylalaninemia

By: Gallego, D (Gallego, Diana)[1]; Leal, F (Leal, Fatima)[1]; Gamez, A (Gamez, Alejandra)[1]; Castro, M (Castro, Margarita)[1]; Navarrete, R (Navarrete, Rosa)[1]; Sanchez-Lijarcio, O (Sanchez-Lijarcio, Obdulia)[1]; Vitoria, I (Vitoria, Isidro)[2]; Bueno-Delgado, M (Bueno-Delgado, Maria)[3]; Belanger-Quintana, A (Belanger-Quintana, Amaya)[4]; Morais, A (Morais, Ana)[5] ...More

HUMAN MUTATION
DOI: 10.1002/humu.24026
Early Access: APR 2020
Document Type: Article; Early Access
View Journal Impact

Abstract

Biallelic variants of the gene DNAJC12, which encodes a cochaperone, were recently described in patients with hyperphenylalaninemia (HPA). This paper reports the retrospective genetic analysis of a cohort of unsolved cases of HPA. Biallelic variants of DNAJC12 were identified in 20 patients (generally neurologically asymptomatic) previously diagnosed with phenylalanine hydroxylase (PAH) deficiency (phenylketonuria [PKU]). Further, mutations of DNAJC12 were identified in four carriers of a pathogenic variant of PAH. The genetic spectrum of DNAJC12 in the present patients included four new variants, two intronic changes c.298-2A>C and c.502+1G>C, presumably affecting the splicing process, and two exonic changes c.309G>T (p.Trp103Cys) and c.524G>A (p.Trp175Ter), classified as variants of unknown clinical significance (VUS). The variant p.Trp175Ter was detected in 83% of the mutant alleles, with 14 cases homozygous, and was present in 0.3% of a Spanish control population. Functional analysis indicated a significant reduction in PAH and its activity, reduced tyrosine hydroxylase stability, but no effect on tryptophan hydroxylase 2 stability, classifying the two VUS as pathogenic variants. Additionally, the effect of the overexpression of DNAJC12 on some destabilizing PAH mutations was examined and a mutation-specific effect on stabilization was detected suggesting that the proteostasis network could be a genetic modifier of PAH deficiency and a potential target for developing mutation-specific treatments for PKU.

Keywords

Author Keywords: DNAJC12; hyperphenylalaninemia; molecular chaperones; phenylketonuria; proteostasis network
KeyWords Plus: PHENYLKETONURIA; TETRAHYDROBIOPTERIN; DEFICIENCY; MUTATIONS; DIAGNOSIS; STABILITY; FAMILY

Author Information

Reprint Address: Perez, B (reprint author)

Univ Autonoma Madrid, Ctr Diagnost Enfermedades Mol, Ctr Biol Mol, CIBERER,IdiPAZ, Campus Cantoblanco, Madrid 28049, Spain.

Addresses:

[1] Univ Autonoma Madrid, Ctr Diagnost Enfermedades Mol, Madrid, Spain

[2] Hosp Univ La Fe, Unidad Nut & Metabolopatias, Valencia, Spain

[3] Hosp Virgen del Rocio, Dept Pediat, Seville, Spain

[4] Hosp Univ Ramon y Cajal, Unidad Enfermedades Metabol Congenitas, Madrid, Spain

[5] Hosp Univ La Paz, Unidad Nutric Infantil & Enfermedades Metabol, Madrid, Spain

[6] Hosp Infantil Univ Nino Jesus, Unidad Gastroenterol & Nutr, Madrid, Spain

[7] Hosp Univ Miguel Servet, Unidad Enfermedades Metabol, Zaragoza, Spain

[8] Inst Recerca, Unidad Enfermedades Metabol Congenitas, Barcelona, Spain

[9] Hosp Univ St Joan de Deu, Barcelona, Spain

[10] Hosp Univ Rio Hortega, Valladolid, Spain

[11] INTA, Santiago, Chile

[12] Hosp Virgen Arrixaca, Unidad Gastroenterol Hepatol & Nutr Pediat, Murcia, Spain

[13] Hosp Reg Univ Malaga, Unidad Metabolopatias, Inst Invest Biomed Malaga IBIMA, Malaga, Spain

[14] Univ Bergen, Dept Biomed, Bergen, Norway

E-mail Addresses:bperez@cbm.csic.es

Funding

Funding Agency	Grant Number
Consejeria de Educacion e Investigacion	B2017/BMD-3721
Fundacion Isabel Gemio-La Caixa	LCF/PR/PR16/11110018
Ministerio de Ciencia Tecnologia y Telecomunicaciones	PI16/00573

View funding text

Publisher

WILEY, 111 RIVER ST, HOBOKEN 07030-5774, NJ USA

Journal Information

- **Impact Factor:** Journal Citation Reports

Categories / Classification

Research Areas: Genetics & Heredity
Web of Science Categories: Genetics & Heredity

Document Information

Language: English
Accession Number: WOS:000529608500001
PubMed ID: 32333439
ISSN: 1059-7794
eISSN: 1098-1004