Epidemiological, clinical and biochemical characterization of the p.(Ala359Asp) SMPD1 variant causing Niemann-Pick disease type B

Por: Acuna, M (Acuna, Mariana)[1,2]; Martinez, P (Martinez, Pablo)[1,2]; Moraga, C (Moraga, Carol)[2,3]; He, XX (He, Xingxuan)[4]; Moraga, M (Moraga, Mauricio)[5]; Hunter, B (Hunter, Bessie)[6]; Nuernberg, P (Nuernberg, Peter)[7]; Gutierrez, RA(Gutierrez, Rodrigo A.)[2,3]; Gonzalez, M (Gonzalez, Mauricio)[2,8]; Schuchman, EH (Schuchman, Edward H.)[4] ...Más

EUROPEAN JOURNAL OF HUMAN GENETICS
Volumen: 24
Número: 2
Páginas: 208-213
DOI: 10.1038/ejhg.2015.89
Fecha de publicación: FEB 2016
Ver información de revista

Resumen

Niemann-Pick disease type B (NPDB) is a rare, inherited lysosomal storage disorder that occurs due to variants in the sphingomyelin phosphodiesterase 1 (SMPD1) gene and the resultant deficiency of acid sphingomyelinase (ASM) activity. While numerous variants causing NPDB have been described, only a small number have been studied in any detail. Herein, we describe the frequency of the p.(Ala359Asp) variant in the healthy Chilean population, and determine the haplotype background of homozygous patients to establish if this variant originated from a common founder. Genomic DNA samples from 1691 healthy individuals were analyzed for the p.(Ala359Asp) variant. The frequency of p.(Ala359Asp) was found to be 1/105.7, predicting a disease incidence of 1/44 960 in Chile, higher than the incidence estimated by the number of confirmed NPDB cases. We also describe the clinical characteristics of 13 patients homozygous for p.(Ala359Asp) and all of them had moderate to severe NPDB disease. In addition, a conserved haplotype and shared 280 Kb region around the SMPD1 gene was observed in the patients analyzed, indicating that the variant originated from a common ancestor. The haplotype frequency and mitochondrial DNA analysis suggest an Amerindian origin for the variant. To assess the effect of the p.(Ala359Asp) variant, we transfected cells with the ASM-p.(Ala359Asp) cDNA and the activity was only 4.2% compared with the wild-type cDNA, definitively demonstrating the causative effect of the variant on ASM function. Information on common variants such as p.(Ala359Asp) is essential to guide the successful implementation for future therapies and benefit to patients.

Palabras clave

KeyWords Plus:ACID SPHINGOMYELINASE DEFICIENCY; MUTATIONS CAUSING TYPES; INTERMEDIATE PHENOTYPE;SOUTHERN CONE; PREVALENCE; SEQUENCE; HISTORY

Información del autor

Dirección para petición de copias: Zanlungo, S (autor para petición de copias)

Pontificia Univ Catolica Chile, Fac Med, Dept Gastroenterol, Marcoleta 367,Casilla 114-D, Santiago, Chile.

Dirección para petición de copias: Mabe, P (autor para petición de copias)

Hosp Dr Exequiel Gonzalez Cortes, Unidad Neurol, Ramon Barros Luco 3301, Santiago, Chile.

Direcciones:

[1] Pontificia Univ Catolica Chile, Fac Med, Dept Gastroenterol, Marcoleta 367,Casilla 114-D, Santiago, Chile

[2] FONDAP Ctr Genome Regulat CGR, Santiago, Chile

[3] Pontificia Univ Catolica Chile, Fac Ciencias Biol, Dept Genet Mol & Microbiol, Santiago, Chile

[4] Icahn Sch Med Mt Sinai, Dept Genet & Genom Sci, New York, NY 10029 USA

[5] Univ Chile, Fac Med, Inst Ciencias Biomed, Programa Genet Humana, Santiago, Chile

[6] Hosp Ninos Luis Calvo Mackenna, Santiago, Chile

[7] Univ Cologne, CCG, D-50931 Cologne, Germany

[8] Univ Chile, INTA, Santiago, Chile

[9] Pontificia Univ Catolica Chile, Dept Nutr, Santiago, Chile

[10] Hosp Dr Exequiel Gonzalez Cortes, Unidad Neurol, Ramon Barros Luco 3301, Santiago, Chile

Direcciones de correo electrónico:pymabe@yahoo.de; silvana.zanlungo@gmail.com

Financiación

Entidad financiadora	Número de concesión
Fondo Nacional de Desarrollo Cientifico y Tecnologico (FONDECYT)	1110310 1150186 1130303
Fondo Nacional de Desarrollo de Areas Prioritarias, FONDAP Center for Genome Regulation (CGR)	15090007
Genzyme grant 'Assessment of the p.(Ala359Asp) acid sphingomyelinase gene variant frequency in the Chilean population'	
Comision Nacional de Ciencia y Tecnologia (CONICYT)	21120490
National Institutes of Health	HD28607

Ver texto de financiación

Editorial

NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND

Categorías / Clasificación

Áreas de investigación: Biochemistry & Molecular Biology; Genetics & Heredity
Categorías de Web of Science: Biochemistry & Molecular Biology; Genetics & Heredity

Información del documento

Tipo de documento: Article
Idioma: English
Número de acceso: WOS:000370469400009
ID de PubMed: 25920558
ISSN: 1018-4813
eISSN: 1476-5438

Información de la revista

- **Impact Factor:** Journal Citation Reports®

Otra información

Número IDS: DE2PO
Referencias citadas en la Colección principal de Web of Science: 27
Veces citado en la Colección principal de Web of Science: 1