Genetics basis of Familial Hypercholesterolaemia in the Iberoamerican FH Network countries

Alves, AC[1]; Alonso, R[2]; Mata, P[3]; Stoll, M[4]; Schreier, L[5]; Cuevas, A[2]; Vázquez Cárdenas, A[6]; Santos R[7]; Bourbon M[1]; on behalf of the Iberoamerican FH network investigators[‡]

[1]Unidade de I&D, Grupo de Investigação Cardiovascular, Departamento de Promoção da Saúde e Prevenção de Doenças Não Transmissíveis, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal; and BioISI – Biosystems & Integrative Sciences Institute, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal.
[2]Department of Clinical Nutrition, Clinica Las Condes, Santiago, Chile.
[3]Fundación Hipercolesterolemia Familiar, Madrid, España.
[4]Cardiovascular Genetic Lab. Cardiovascular Health Commission, Montevideo, Uruguay.
[5]Lab of Lipids and Atherosclerosis, Faculty of Pharmacy and Biochemistry, University of Buenos Aires, Buenos Aires, Argentina.
[6]Facultad de Medicina, Universidad Autónoma de Guadalajara, Mexico
[7]InCor, University of Sao Paulo Medical School Hospital, São Paulo, Brasil
[‡]Iberoamerican FH network investigators – Argentina: Bañares V; Brazil: Jannes C, Pereira A; Mexico: MTM, CA; Portugal: Medeiros AM; P; Uruguay: DellOca N, Reyes X.

Background: More than 3 million patients in Iberoamerican (IBA) countries have Familial hypercholesterolemia (FH), a life threatening disorder that can be prevent by early identification and implementation of adequate counselling/treatment. Spain, Portugal, Argentina, Brazil, Uruguay, Mexico and Chile are the 7 countries, included in the IBA FH network until date; all these countries have started the molecular studies of FH. The IBA FH network has been establish to increase awareness of FH in these countries. The aim of this study is to review the molecular state of the art of FH in Iberoamerica and characterize the genetics of FH in IBA countries.

M**ethods:** A literature review and non-published country specific information has been collected for all countries in IBA FH network.

Results: More than 9000 patients in Iberoamerica have a genetic diagnosis of FH. Countries as Spain, Portugal and Brazil have a considered number of patients with a complete genetic characterization (>500). Spain, Portugal and Uruguay have the highest country specific identification rates, 8%, 3% and 2%, respectively; the remaining countries still have a rate lower that 1%.
LDLR mutations are the most common cause of FH representing > 90% of FH patients. All 7 IBA countries have at least one case of APOB3527, being the prevalence of FH due to functional APOB mutations around 3-3.5% in Brazil and Spain and 5% in Portugal due to the screening of whole APOB gene in this country. Only Portugal and Spain have patients with PCSK9 mutations but this represent less 1% of total cases, although Brazil and Uruguay have implemented the genetic diagnosis for this gene as well. The following alterations in LDLR are the most common in IBA being present in more than one country: c.-135C>G, c.12G>A (p.Trp4*), [c.274C>G(p.Gln92Glu); c.313+1G>C], c.530C>T (p.Ser177Leu), c.662A>G (p.Asp221Gly), c.1285G>A (p.Val429Met), c.1291G>A (p.Ala431Thr),

c.1775G>A (p.Gly592Glu), c.2043C>A (p.Cys681*). A clinical/genetic positive rate between 30%-70% has been observed in the 7 countries.

Conclusions: IBA countries share centuries of common history and most probably share many FH alleles. An integrated analysis of FH in Iberoamerica will contribute to increase knowledge about the genetic causes of FH.