# Genome-wide study reveals novel sex-specific loci associated with lacunar stroke

Jara Cárcel-Márquez[1] MSc, Elena Muiño [1] PhD, Cristina Gallego-Fabrega [1,2] PhD, Natalia Cullell [1,3] MSc, Miquel Lledós [1] MSc, Laia Llucià-Carol [1] MSc, Jesús María Martín-Campos[1] PhD, Tomás Sobrino[4] PhD, Francisco Campos[4] PhD, José Castillo[4] PhD, Marimar Freijo[5] PhD, Juan Francisco Arenillas[6] PhD, Victor Obach[7] PhD, José Álvarez-Sabín[8] PhD, Carlos A. Molina[8] PhD, Marc Ribó[8] PhD, Jordi Jiménez-Conde[9] PhD, Jaume Roquer[9] PhD, Lucia Muñoz-Narbona[10] PhD, Elena Lopez-Cancio[11] PhD, Mònica Millán[10] PhD, Rosa Diaz-Navarro[10] PhD, Cristòfol Vives-Bauza[12] PhD, Gemma Serrano-Heras[13] PhD, Tomás Segura[13] PhD, Laura Ibañez[14] PhD, Laura Heitsch[15,16] PhD, Pilar Delgado[17] PhD, Rajat Dhar [16] PhD, Jerzy Krupinski[18] PhD, Luis Prats-Sánchez[2] PhD, Pol Camps-Renom[2] PhD, Rebeca Marín[2] MSc, Marina Guasch[2] MD, Natalia Blay[19] PhD, Lauro Sumoy[20] PhD, Rafael de Cid[19] PhD, Joan Montaner[21] PhD, Carlos Cruchaga[14,22] PhD, Jin-Moo Lee[16] PhD, Joan Martí-Fàbregas[2] PhD, , Israel Fernández-Cadenas [1] PhD.

1- Stroke Pharmacogenomics and Genetics Group, Institut d'Investigació Biomèdica Sant Pau (IIB SANT PAU), Barcelona, 08041, Spain
2- Stroke Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Barcelona, 08041, Spain
3- Stroke Pharmacogenomics and Genetics Laboratory, Fundación Docència I Recerca Mútua Terrassa, Hospital Mútua Terrassa, Terrassa, 08221, Spain
4- Health Research Institute of Santiago de Compostela (IDIS), Clinical Neurosciences Research Laboratory, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, 15706, Spain
5- Biocruces-Bizkaia Health Research Institute. Department of Neurology, Bilbao, 48903, Spain
6- Stroke Unit, Department of Neurology, University Hospital of Valladolid, Valladolid, 47003, Spain
7- Department of Neurology, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, 08036, Spain
8- Stroke Unit, Department of Neurology, Hospital Universitari Vall d'Hebron, Barcelona, 08035, Spain
9- Department of Neurology, IMIM-Hospital del Mar; Neurovascular Research Group, IMIM (Institut Hospital del Mar d'Investigacions Mèdiques); Universitat Autònoma de Barcelona/DCEXS-Universitat Pompeu Fabra, Barcelona, 08003, Spain
10- Department of Neurosciences, Hospital Germans Trias I Pujol, Universitat Autònoma de Barcelona, Barcelona, 08916, Spain
11- Departament of Neurology, University Hospital Central de Asturias (HUCA). Oviedo, 33011, Spain
12- Department of Neurology, Son Espases University Hospital, Illes Balears Health Research Institute (IdISBa), Palma, 07120, Spain
13- Department of Neurology, University Hospital of Albacete, Albacete, 02006, Spain
14- Department of Psychiatry, Washington University School of Medicine, Saint Louis, MO 63110-1010, USA
15- Department of Emergency Medicine, Washington University School of Medicine, Saint Louis, MO 63110-1010, USA
16- Department of Neurology, Washington University School of Medicine, Saint Louis, MO 63110-1010, USA
17- Neurovascular Research Laboratory, Vall d'Hebron Institute of Research, Universitat Autònoma de Barcelona, Barcelona, 08035, Spain
18- Neurology Service, Hospital Universitari Mútua Terrassa, Terrassa, 08221, Spain
19- GenomesForLife-GCAT Lab, Germans Trias i Pujol Research Institute (IGTP), Badalona, 08916, Spain

20- High Content Genomics and Bioinformatics Unit, Germans Trias i Pujol Research Institute (IGTP), Badalona, 08916, Spain
21- Institute de Biomedicine of Seville, IBiS/Hospital Universitario Virgen del Rocío/CSIC/University of Seville & Department of Neurology, Hospital Universitario Virgen Macarena, Seville, 41013, Spain
22- Neurogenomics and Informatics Center at Washington University in St. Louis, Saint Louis, MO 63108, USA.

**Background and aims:**

Little is known about the genetic architecture of lacunar stroke (LS) risk, and the known loci do not explain the overall complexity of the disease. We sought to identify sex specific loci that help explain the mechanistic of LS.

**Methods:**

We included 288 MRI-confirmed LS, and 5,589 non-stroke controls with genetic data available. Single variant analyses were performed using GCTA using the additive model adjusted by age, sex and the first ten genetics principal components. Then we performed the same analysis stratifying by sex to investigate potential loci. Significant threshold was stablished at $p<5x10^{-8}$. Gene-based analysis were performed using MAGMA. Replication was explored in MEGASTROKE and GIGASTROKE cohorts for LS in European population. *In silico* proteomic analysis was performed on whole blood from the INTERVAL cohort (3,301 individuals) for the replicated variants.

**Results:**

We identified one locus in chromosome 5 in both sexes analysis, rs59970332-T ($p=1.99x10^{-8}$;beta(standard error)=0.08(0.01)), prioritised gene *CTNND2*, with the strongest association in male analysis ($p=5.19x10^{-8}$). In females, we identified a private a locus in chromosome 8, rs146966463-C ($p=6.60x10^{-9}$;beta(standard error)=0.08(0.01)), prioritised gene *FGFR1*. Pathways' analyses revealed the involvement of different interleukins, as well as amyloid clearance of the brain as potential players of this genetic susceptibility.

**Conclusions:** We found two novel loci associated with LS risk in the first stratified by sex analysis in this phenotype. We identified *CTNND2* and *FGFR1* as promising genes associated with LS risk. Further analyses are warranted to understand the role of these two genes in the disease.