Stroke Pharmacogenomics and Genetics

Group leader

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DESCRIPTION

The Stroke Pharmacogenomics and Genetics group is a multidisciplinary group composed of 11 members including biologists, biotechnologists and neurologists. The objectives of the group are to find treatments for stroke and other neurological diseases that can be used in clinical practice. To find these treatments we are using genome-wide techniques such as GWAS, EWAS, TWAS, PWAS, or microbiome analysis. This includes genetics, epigenetics, transcriptomics, proteomics, and microbiomics with large cohorts of patients.

MAIN LINES OF RESEARCH

L1 Genetic risk factors in stroke.

- In this line, we study the genetic risk factors associated with ischemic stroke. Currently, the Generation project (PI15 / 01978, PI: Israel Fernández) is being carried out, which intends to carry out the first study using Genome Wide Association Studies (GWAs) in the Spanish population with the aim of generating a clinical-genetic prediction algorithm to be applied in clinical practice. In this study we conducted a discovery phase where we analyzed more than 6,000 patients and controls using GWAs arrays (Infinium Human-Exon BeadChip (Illumina) that can detect 500,000 genetic variants across the genome.
- We have found loci associated with cardioembolic stroke and we generated a clinical-genetic score to predict the risk of cardioembolic stroke (Carcel et al, 2022).
- Finally in this line, we have actively collaborated in the study Megastroke and Gigastroke an interna-

tional project and consortium that has analyzed more than 1.000,000 cases of stroke and controls through GWAs. The results of this study have been published in the journal Nature Genetics and Nature being our group the only Spanish group that is part of the executive / scientific committee of these two studies (Malik et al Nat Gen 2018; Mishra et al Nature 2022).

- Jara Cárcel Postdoctoral researcher from our group is the coordinator of this line of research.

L2 Pharmacogenetics of neurovascular diseases.

- In this line, the genetic factors associated with the response to drugs used in ischemic stroke are studied both in the acute phase (rt-PA) and for secondary prevention (antiplatelet agents and anticoagulants). In the field of pharmacogenetics associated with the response to rt-PA our group is one of the most important research groups in the field with the largest number of published articles. Last year we obtained a grant from the Medicina Personalizada program to study the pharmacogenetics of rt-PA and its implementation in the clinical-practise.
- In this line, we have obtained international funding for two projects: SEDMAN Project and APHAS Project. The two projects are focused on the search for genetic factors associated with the response to anticoagulant drugs. Israel Fernández is PI of these two projects.
- In this line, we have carried out the first study with GWAs in patients with ischemic stroke treated with t-PA. We have performed an analysis on more than 1.000 patients. Several of these results will be published in the journal Neurology and Brain (Carrera et al, Neurology 2019; Carrera et al. Brain 2021).

L3 Genetic and epigenetic risk factors associated with the neurological deterioration and the disability after stroke.

- In this line we study whether the genetic and epigenetic factors can influence the stroke outcome. We analyze the neurological deterioration during the acute phase of stroke (24h) and the long-term disability (three months).
- A GWAS analysis performed by our group (n = 3500 patients with ischemic stroke) revealed a locus associated with disability post-stroke. This loci is found in the INADL / PATJ gene. It has been the first gene confirmed to be associated with long term outcome in stroke. These results have been published in Circulation Research this year. Israel Fernández is the corresponding author of this paper (Mola-Caminal et al Circulation Research 2019).
- Currently, we are conducting studies in cell cultures and animal models to study the reasons for this association and the potential use of the protein codified in the gene as a new drug target.
- Natalia Cullell post-doctoral researcher from our group is the coordinator of this line of research.

L4 Genetic, epigenetic, and proteomic factors associated with the endophenotypes of the acute phase of stroke. Integromics.

- The aim of this research line is to find genetic, epigenetic, and protein factors associated with different endophenotypes of the acute phase of stroke, such as post-stroke infections, edema formation, leukocyte levels during the acute phase of stroke. The hypothesis is that neurological evolution and post-stroke disability is influenced by multiple factors.
- We have now carried out a genetic analysis in 1,183 patients with neutrophil and post-stroke outcome data. We collaborate in the GENESIS study, led by Dr. Jin-Moo Lee an international study with different networks (United States, Spain, South America, and Central Europe). Currently, we are leading the Spanish network. This study analyzed 6.000 strokes with endophenotype data of the acute phase of stroke using GWAs and found loci associated with neurological deterioration (Ibañez et al Brain 2022).

L5 Microbiome and Stroke.

- The estimated total cell count of a typical human body is 6.8×1013. However, 66% of these cells are bacteria that live within us. At the same time, the genome size of the human gut microbiota is 150 larger than the human genome. The dysbiosis of the gut microbiome (changes in the composition of the types of microorganisms) has been identified as a potential risk factor for susceptibility to numerous diseases, including stroke, influencing systemic inflammation by altering intestinal permeability.

- In this line, we aim to investigate whether the gut microbiome could also be influencing the neurological evolution after a stroke, modulating the antigen-specific immune responses of the central nervous system. If this is confirmed, changes in the intestinal flora could be promoted, either through the use of probiotics in the diet or through fecal transplantation from healthy donors, in order to discover new therapies that could improve the evolution of patients after having suffered a stroke. Miquel Lledós coordinates this line of research.

L6 Lipids and Stroke.

- According to numerous observational studies and randomized controlled trials, low-density lipoprotein cholesterol (LDL-C) is a risk factor for cardiovascular disease, including myocardial infarction, peripheral vascular disease, and stroke. Other studies, however, have described an inverse association between the plasma level of LDL-C and the risk of hemorrhagic stroke. The mechanism by which dyslipidemias are associated with coronary heart disease has been widely studied. However, the mechanism underlying the association between cholesterol and stroke is not well established and could present significant differences due to the peculiar structure of the cerebral arteries and the peculiarities of cerebral metabolism.
- Our goal is to apply genomic analysis techniques to detect genes and lipid metabolism pathways involved in the risk and prognosis of different types of stroke, identify potential therapeutic targets and thus improve stroke prevention and treatment.
- The senior researcher Jesús Martín coordinates this line of research.

L7 CADASIL and other orphan diseases associated with stroke.

- The objective of this research line is to study monogenic diseases associated with stroke. We have focused specifically on CADASIL and other monogenic causes of small vessel stroke. Currently we are performing transcriptomics and proteomics studies in CADASIL. In addition, we have the first clinical consult focus on CADASIL disease and other monogenic diseases associated with stroke and small vessel disease in the country.
- We have a fluid relationship with the Spanish association of CADASIL patients. We collaborate with the CADASIL SPAIN Patient Association (https://cadasil.org/) organizing and participating in informative days about the disease.
- In this line we have created a website www.cadasil.es where we respond the clinical doubts from CADASIL patients or relatives. In this line we have carried out a crowdfunding project with the PRECIPITA project of the Spanish Science and Technology Foundation (FECYT) with the aim of raising funds for CADASIL studies: https://www.precipita.es/precipitado/cadasil-una-enfermedad-genetica-sin-tratamiento.html.
- We recently have obtained an international grant to study CADASIL from the Million Dollar Bike Program being our group the coordinator of this study. The postdoctoral researcher Elena Muiño participates in this line.

L8 Genetic susceptibility to COVID-19. COVID-19 and stroke.

- In this line we analyze the genetic factors associated with the risk and severity of COVID-19 using broad-spectrum genetic tools. Also, we analyze the genetic factors associated with post-COVID-19 stroke. We have analyzed a cohort of more than 600 patients with GWAS data. We are part of the INMUNGEN-CoV2 study financed by the CSIC and of which Anna Planas (CSIC-IDIBAPS) is the principal investigator. In this line we also collaborate with Drs Jordi Pérez Cruz (CSIC-Valencia) and Marta López de Diego (CSIC-Madrid). We have also received funding from the Marató of TV3 for the omic study of the severity of COVID-19 and its relationship with the persistent symptoms of this pathology.
- Laia Llucià and Sayoa Alzate work in this line of research.

ACTIVE GRANTS

- Fernández Cadenas, Israel. iBioStroke: Identificación y validación clínica de biomarcadores para la evolución clínica post-ictus. AC19/00106. Instituto de Salud Carlos III (ISCIII). Duration: 2020-2023. 93.170,00 €.

- Fernández Cadenas, Israel. COPYCTUS: Estudio de la variación en el número de copias y análisis genómico 3D para encontrar dianas terapéuticas en relación al deterioro neurológico post-ictus. PI21/01088. Instituto de Salud Carlos III (ISCIII). Duration: 2022-2024. 96.800,00 €.
- Fernández Cadenas, Israel. CNV and Stroke (CaNVAS). NIH MARYLANDO (CaNVAS) 1R01NS114045-01. National Institute of Neurological Disorders . Duration: 2020-2023. 100.084,00 €.
- Fernández Cadenas, Israel. Single-nuclei RNA-seq for CADASIL understanding and therapeutic target discovery. MDBR-22-127-CADASIL. . Duration: 2022-2023. 53.205,00 €.
- Fernández Cadenas, Israel. Biomarcadors proteòmics cardiometabòlics i immunitaris de la Covid-19 per a l'avaluació clínica de la infecció, la gravetat de la malaltia i les complicacions post-pandèmiques de salut. MARATO 202107-31. Fundació La Marató de TV3. Duration: 2022-2024. 129.750,00 €.
- Fernández Cadenas, Israel. Elucidating the Key Mediators and Mechanisms of Cerebral Edema and Hemorrhagic Transformation after Hemispheric Stroke using Quantitative Imaging and Genetics. NIH RO1 edema. (Raj Dhar and Spanish network) NIH - WUSTL . Duration: 2022-2027. 344.242,00 €.

GRANTS AWARDED

- Fernández Cadenas, Israel. CADASIL-Historia Natural (CADANHIS). AC23_2/00041. Instituto de Salud Carlos III (ISCIII). Duration: 2024-2026. 179.375,00 €.
- Fernández Cadenas, Israel. Stopped-Stroke. Reversible epigenetic therapies to SToP biological age and reduce STroke risk. MARATO 202310-30. Fundació La Marató de TV3. Duration: 2024-2027. 133.972,50 €.
- Carcel Marquez, Jara. Gen-X project: Genetic and epigenetic study of ischemic stroke and its sex differences. MARATO 202306-30. Fundació La Marató de TV3. Duration: 2024-2027. 199.801,25 €.

DOCTORAL THESES DEFENDED

- Cárcel Márquez, Jara. Study of genetic risk factors associated with ischemic stroke. 24/01/2023. Universitat Autònoma de Barcelona. Supervisors: Fernández Cadenas, Israel; Martí i Fàbregas, Joan. http://hdl.handle.net/10803/688764
- Cullell Fornés, Natalia. Estudio Epigenómico de los factores de riesgo y pronostico del ictus isquémico. 21/06/2023. Universitat Autònoma de Barcelona. Supervisors: Fernández Cadenas, Israel; Krupinski, Jerzy; Chamorro, Ángel.

SCIENTIFIC PRODUCTION

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