GODS PROJECT: GENETIC CONTRIBUTION TO FUNCTIONAL OUTCOME AND DISABILITY AFTER STROKE

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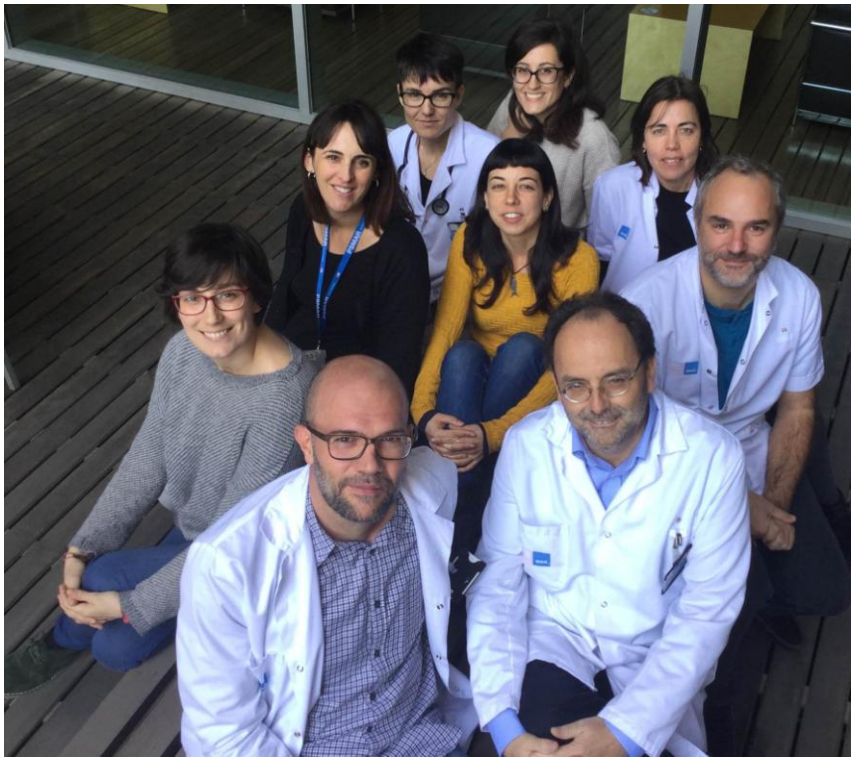


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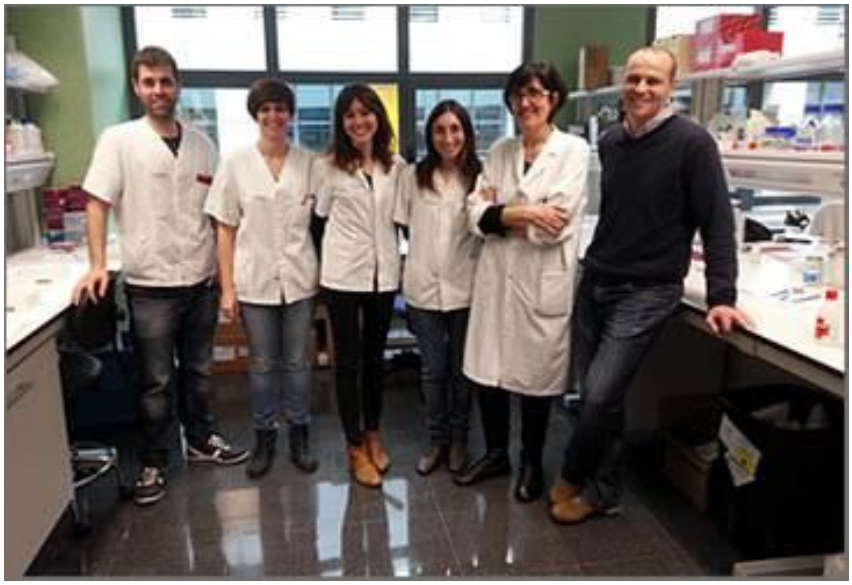

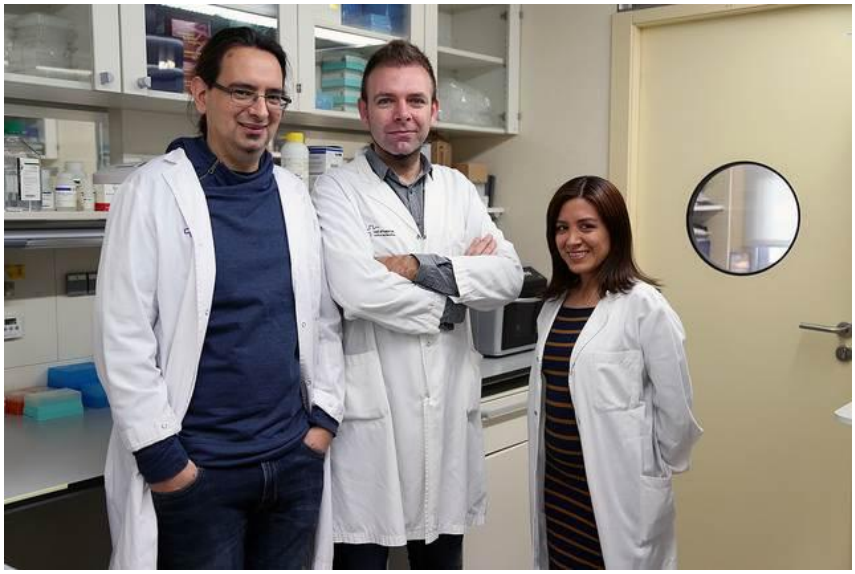

1. Project summary

BACKGROUND:
Cerebrovascular diseases are the main cause of dependence in our society. Interindividual variation in degree of disability after stroke is thought to be influenced by genetic factors. The aim of the study is to discover genetic variants to predict and improve the recovery processes.

OBJECTIVES
Primary Objectives:
1. Identify genetic variants and regions associated with degree of disability after ischemic stroke.
2. Validate and consistently replicate these associated variants.

Secondary Objectives:
3. Create a clinical-genetic risk score and test it for capability of prediction of clinical outcome.
4. Establish the basis for future studies in the field:
a. Via the associated genes and regions, discover new pathways and mechanisms involved in functional recovery.
b. Identifying new potential therapeutic/pharmacological targets.

DESIGN AND METHODOLOGY
Phase 1: Selection of candidate regions/variants:

1. GWAS-meta-analysis of 4 GWAs of ischemic stroke (n=1252). We ran the analyses to test the association with functional outcome 3 months after stroke, using the modified Rankin Scale (mRS), adjusted by initial severity (NIHSS), age and sex. We selected those variants most strongly associated (p<E-5) for replication phase.
2. Exome sequencing. We compared cases of stroke with poor (mRS=4-5) and favourable (mRS<2) outcomes at 3 months, matched by stroke subtype, adjusted by NIHSS, age, sex and vascular risk factors (VRF). We selected those genes associated with a p-value <0.01 for *Genomic Convergence* analyses.

Phase 2: Validation/Replication:

Those selected variants from GWAS-meta-analysis, and variants in the most significant genes p<0.01 in *Exome seq analyses* (prioritizing regions showing results consistent with the GWA) were included in *Replication phase*. Replication will be done in about 5000 individuals of different international cohorts from the *International Stroke Genetics Consortium (ISGC)*. Genetic variants will be tested for association with 3 months functional status (mRS), adjusting for age, sex, initial NIHSS and VRF. Based on these results, we will develop a clinical-genetic score.

Phase 3: Functional experiments: To explore the functional basis of the associations observed in Phase 2 and the pathways in which they are involved.

Our results will improve understanding of neuronal plasticity processes, potentially leading to the identification of new therapeutic targets. Moreover, the clinical-genetic score may reduce the disability rates by personalizing the rehabilitation strategies.

2. Results

- After the meta-analysis of the 4 GWAS (MetaGWAs), we found 400 common variants that show a trend to the association (p <E-5) with prognosis at 3 months post stroke (assessed with the modified Rankin scale). From them, there are 2 genes (INADL and GOLGA6B) with 4 SNPs that reach a significance of p <5E-8 and an enrichment of surrounding variants near the significance that have high chances to be confirmed as real associations. Gene-based analyses points to the same results. Replication in GISCOME study of the Stroke International Genetic Consortium is pending.

- Exome analysis showed 76 genes with differences in the accumulation of rare variants among individuals with good prognosis against those with poor prognosis, with a p-value <0.01. No gene reached a sufficient level of significance after correcting for multiple analyses, but one of the suggested genes in MetaGWAs is among those that are nominally significant. This increases the strength and consistency of results.

- *Convergence Genomic* process to select the candidate areas has not generated new results beyond the candidates obtained by meta-analysis of GWAS and gene-based analysis.

At the current stage of the project we could conclude:

- We identified several genetic variants, especially in 2 genes, which could be related to a better recovery after stroke. If confirmed and replicated, these findings would be the first identified genetic variants that influence the disability degree after suffering a stroke.

- The study of the genetic component of complex traits, such as the prognosis of stroke, requires a very precise and accurate phenotyping to avoid interferences with other involved factors.

- The approach from different techniques (GWAS and exome sequencing) can be complementary and synergistic, giving more consistency to the findings. In the present study, however, the process of *Genomic Convergence* did not provided new variants or regions that had not been seen with the techniques individually.

3. Relevance and possible implications

Disability after stroke is a great burden for individuals and for public health (€17,000 per year per individual). The role of genetic factors in the degree of disability seems to be significant, but there are few data and studies about the issue. The potential utility of discovering the genetic component behind the interindividual variability in the recovery capacity after stroke could have a great impact in different aspects:

From a scientific point of view, this topic has relevant interest because the majority of the underlying mechanisms involved in cerebral response against injuries still remain unknown. This project may contribute to advance our understanding through unveiling genetic variants associated with clinical recovery and potentially leading to the molecular basis of neuronal plasticity processes, tissue regeneration, angiogenesis or synaptogenesis.

But the identification of new mechanisms and pathways involved in recovery after stroke not only has interest in increasing our knowledge; it may also imply finding new therapeutic targets susceptible to being modulated by current or new drugs. Moreover, the development of a clinical-genetic risk score that predicts evolution and risk of disability after stroke may also help in identifying, from the very first moment, the most appropriate rehabilitation strategy. As we explained in the background section, if we were able just to reduce only 2% of disability using our clinical-genetic model, this would mean a reduction of between €2,880,000 and €17,850,000 per year in our country.

Therefore, and apart from the immediate applicability of a clinical-genetic score, our project is a necessary step to help establish the basis for future further research in the field. The future development of active molecules or drugs that may contribute in neuronal recovery processes may be a next step, representing, for sure, a great impact in our society and a substantial advance in improving the quality of life of stroke patients.

4. Generated bibliography

COMMUNICATIONS:

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- Communication Title: "GWALA!! GODS!! What is this Leukoaraiosis? Multiple Approaches in Research for a Complex Phenomenon"

Speaker: **Jordi Jiménez-Conde**

Title of activity: Sessions Científiques Programa de Neurociències

Date: 11 d'Abril 2014

Location: Parc de Recerca Biomèdica de Barcelona

- Communication Title: "Implicació de la Genètica al Diagnòstic de la Patologia Vascular Cerebral"

Speaker: **Jordi Jiménez-Conde**

Title of activity: III Jornada d'Actualització en el Tractament i Diagnòstic de les Malalties Neurològiques més Prevalents.

Date: 16 d'Octubre 2014

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PUBLICATIONS DERIVED DIRECTLY FROM THE OBJECTIVES OF THE PROJECT:
In writing process.

PUBLICATIONS WITH PARTIAL OR INDIRECT CONTRIBUTION OF FUNDED PROJECT:

- Sara L. Pulit*, Patrick F. McArdle*, Quenna Wong*, Rainer Malik*, (… Elisa Cuadrado-Godia, **Xavier Estivill Pallejà, Israel Fernandez Cadenas**, **Eva Giralt-Steinhauer, Jordi Jiménez-Conde****, **Marina Mola-Caminal**, Ángel Ois, Ana Rodriguez-Campello, **Raquel Rabionet, Jaume Roquer, Carolina Soriano,** …) Australian Stroke Genetics Consortium, Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study, Cohorts of Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, Consortium of Minority Population genome-wide Association Studies of Stroke (COMPASS), METASTROKE consortium, Wellcome Trust Case-Control Consortium, Bradford B. Worrall*, Paul I.W. de Bakker*, Steven J. Kittner*, Braxton D. Mitchell*, Jonathan Rosand*. *Contributed equally. ** Steering committee. Loci associated with ischaemic stroke and its subtypes (SiGN): a genome-wide association study. NINDS Stroke Genetics Network (SiGN) and International Stroke Genetics Consortium (ISGC). Lancet Neurol. 2015 Dec 18. pii: S1474-4422(15)00338-5. **IF: 21.823**