NEWSLETTER

Septiembre 2014

Nº 12

GeneStroke | The Spanish Stroke Genetics Consortium

Estimados compañeros

Os enviamos la Newsletter del consorcio GeneStroke, donde esperamos encontraréis información de vuestro interés sobre las novedades del consorcio y de la genética en el ictus.

Equipo GeneStroke
www.GeneStroke.com

TITULARES

Contenido:

Últimas publicaciones con participación de *GeneStroke:*

Global DNA methylation of ischemic stroke subtypes.
Soriano-Tárraga C, Jiménez-Conde J, Giralt-Steinhauer E, Mola M, Ois A, Rodríguez-Campello A, Cuadrado-Godia E, Fernández-Cadenas I, Carrera C, Montaner J, Elosua R**, Roquer J. GeneStroke,** "The Spanish Stroke Genetics Consortium". PLoS One. 2014 Apr 30.

Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage.
Woo D, Falcone GJ, Devan WJ, [...], **Jiménez-Conde J, Giralt-Steinhauer E**, Elosua R, **Cuadrado-Godia E, Soriano C, Roquer J,** Kraft P, Ayres AM, Schwab K, McCauley JL, Pera J, Urbanik A, Rost NS, Goldstein JN, Viswanathan A, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, **Montaner J, Fernández-Cadenas I**, **Delgado P**, Malik R, Dichgans M, Greenberg SM, Rothwell PM, Lindgren A, Slowik A, Schmidt R, Langefeld CD, Rosand J. **International Stroke Genetics Consortium**. **Am J Hum Genet.** 2014 Apr 3.

Drug resistance and secondary treatment of ischaemic stroke: The genetic component of the response to acetylsalicylic acid and clopidogrel.
Gallego-Fabrega C, Krupinski J, Fernandez-Cadenas I; en nombre de **Genestroke Consortium, Consorcio Español para el Estudio Genético del Ictus. Neurologia.** 2014 Mar 21.

Stroke Genetics Network (SiGN) Study: Design and Rationale for a Genome-Wide Association Study of Ischemic Stroke Subtypes.
Meschia JF, Arnett DK, Ay H, Brown RD Jr, Benavente OR, Cole JW, de Bakker PI, Dichgans M, Doheny KF, Fornage M, **Conde JJ**, Rosand J, Woo D et al; on behalf of the **NINDS SiGN Study.** Stroke 2013 Sep 12.

PROYECTOS GENESTROKE EN ACTIVO

Actualmente tenemos estos proyectos en curso:

¿Quieres realizar un estudio y necesitas colaboraciones? ¡¡¡ Envía tu propuesta !!! ¡PARTICIPAD!

Proyecto: **GWALA!!** (Bases genéticas de la leucoaraiosis. Estudio de Genome Wide Association en población española)
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: En fase de análisis volumétricos

Proyecto: **GWAs GenotPA** (Estudio de Genome-Wide Association en pacientes tratados con tPA)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

Proyecto: **GODS project** (Genetic contribution to functional Outcome and Disability after Stroke)
Coord y IP grupo: Jordi Jiménez Conde (Hospital del Mar); *IP grupo*: Israel Fernández Cadenas (Vall d'Hebron); *IP grupo*: Xavier Estivill (Centro de Regulación Genómica); *IP grupo*: Jerzy Krupinski (Mutua Terrassa); *IP grupo*: Cristòfol Vives (Hospital Son Espases)
Estado: En fase de replicación

Proyecto: **Cardioembolic Exome** (Secuenciación de exoma completo de pacientes con ictus cardioembólicos)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

Proyecto: **GRECAS Project (**Genotyping Risk and Efficacy of Clopidogrel or Aspirin following Stroke)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: Replicación completada. En fase de más análisis

Proyecto: **EWAS-Stroke** (Estudio de Epigenome-Wide Association en los subtipos etiológicos de ictus isquémico)
IP: Carolina Soriano (Hospital del Mar)
Estado: En fase de análisis

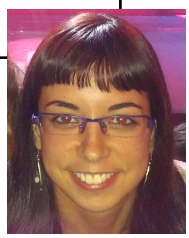
Proyecto: **ChiCHOS** (Case/Control study to analyse tHe genetic risk factOrs of ischemic Stroke)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

Proyecto: **Pharmastroke** (Epigenética en pacientes tratados con antiagregantes)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

Proyecto: **MENEAS** (MEthylation of DNA depending on Nutrition and Exercise habits. Developing a marker of "biological Age" and risk of Stroke)
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: Financiado. Pendiente de genotipado

new *Proyecto:* **The WINGS Project** (The Wide INtegrative Genomics in Stroke. Utilidad del análisis integrado de diferentes abordajes genómicos masivos en el estudio del ictus y su pronóstico clínico)
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: Pendiente de financiación

Para solicitar más información sobre los proyectos podéis contactar conmigo



Marina Mola
(mmola@imim.es)

NOVEDADES SOBRE GENÉTICA EN EL ICTUS:

Meta-analysis in more than 17,900 cases of ischemic stroke reveals a novel association at 12q24.12.

Kilarski LL, Achterberg S, Devan WJ, Traylor M, Malik R, Lindgren A, Pare G, Sharma P, Slowik A, Thijs V, Walters M, Worrall BB, Sale MM, Algra A, Kappelle LJ, Wijmenga C, Norrving B, Sandling JK, Rönnblom L, Goris A, Franke A, Sudlow C, Rothwell PM, Levi C, Holliday EG, Fornage M, Psaty B, Gretarsdottir S, Thorsteinsdottir U, Seshadri S, Mitchell BD, Kittner S, Clarke R, Hopewell JC, Bis JC, Boncoraglio GB, Meschia J, Ikram MA, Hansen BM, Montaner J, Thorleifsson G, Stefanson K,**Rosand** J, de Bakker PI, Farrall M, Dichgans M, Markus HS, Bevan S; GARNET Collaborative Research Group, Wellcome Trust Case Control Consortium 2, Australian Stroke Genetic Collaborative, **the METASTROKE Consortium**, and the **International Stroke Genetics Consortium.**
Neurology. 2014 Aug 19.

Abstract

OBJECTIVES: To perform a genome-wide association study (GWAS) using the Immunochip array in 3,420 cases of ischemic stroke and 6,821 controls, followed by a meta-analysis with data from more than 14,000 additional ischemic stroke cases.

METHODS: Using the Immunochip, we genotyped 3,420 ischemic stroke cases and 6,821 controls. After imputation we meta-analyzed the results with imputed GWAS data from 3,548 cases and 5,972 controls recruited from the ischemic stroke WTCCC2 study, and with summary statistics from a further 8,480 cases and 56,032 controls in the METASTROKE consortium. A final in silico "look-up" of 2 single nucleotide polymorphisms in 2,522 cases and 1,899 controls was performed. Associations were also examined in 1,088 cases with intracerebral hemorrhage and 1,102 controls.

RESULTS: In an overall analysis of 17,970 cases of ischemic stroke and 70,764 controls, we identified a novel association on chromosome 12q24 (rs10744777, odds ratio [OR] 1.10 [1.07-1.13], p = 7.12 × 10(-11)) with ischemic stroke. The association was with all ischemic stroke rather than an individual stroke subtype, with similar effect sizes seen in different stroke subtypes. There was no association with intracerebral hemorrhage (OR 1.03 [0.90-1.17], p = 0.695).

CONCLUSION: Our results show, for the first time, a genetic risk locus associated with ischemic stroke as a whole, rather than in a subtype-specific manner. This finding was not associated with intracerebral hemorrhage.

Twelve-Single Nucleotide Polymorphism Genetic Risk Score Identifies Individuals at Increased Risk for Future Atrial Fibrillation and Stroke.

Tada H, Shiffman D, Smith JG, Sjögren M, Lubitz SA, Ellinor PT, Louie JZ, Catanese JJ, Engström G, Devlin JJ, Kathiresan S, Melander O. **Stroke**. 2014 Aug 14.

Abstract

BACKGROUND AND PURPOSE: Atrial fibrillation (AF) is prevalent and there is a clinical need for biomarkers to identify individuals at higher risk for AF. Fixed throughout a life course and assayable early in life, genetic biomarkers may meet this need. Here, we investigate whether multiple single nucleotide polymorphisms together as an AF genetic risk score (AF-GRS) can improve prediction of one's risk for AF.

METHODS: In 27 471 participants of the Malmö Diet and Cancer Study, a prospective, community-based cohort, we used Cox models that adjusted for established AF risk factors to assess the association of AF-GRS with incident AF and ischemic stroke. Median follow-up was 14.4 years for incident AF and 14.5 years for ischemic stroke. The AF-GRS comprised 12 single nucleotide polymorphisms that had been previously shown to be associated with AF at genome-wide significance.

RESULTS: During follow-up, 2160 participants experienced a first AF event and 1495 had a first ischemic stroke event. Participants in the top AF-GRS quintile were at increased risk for incident AF (hazard ratio, 2.00; 95% confidence interval, 1.73-2.31; $P=2.7\times10^{-21}$) and ischemic stroke (hazard ratio, 1.23; 95% confidence interval, 1.04-1.46; P=0.02) when compared with the bottom quintile. Addition of the AF-GRS to established AF risk factors modestly improved both discrimination and reclassification (P<0.0001 for both).

CONCLUSIONS: An AF-GRS can identify 20% of individuals who are at ≈2-fold increased risk for incident AF and at 23% increased risk for ischemicstroke. Targeting diagnostic or therapeutic interventions to this subset may prove clinically useful.

A Novel MMP12 Locus Is Associated with Large Artery Atherosclerotic Stroke Using a Genome-Wide Age-at-Onset Informed Approach.

Traylor M, Mäkelä KM, et al. METASTROKE, International Stroke Genetics Consortium, Wellcome Trust Case Consortium 2 (WTCCC2). **PLoS Genet**. 2014 Jul 31.

Abstract

Genome-wide association studies (GWAS) have begun to identify the common genetic component to ischaemic stroke (IS). However, IS has considerable phenotypic heterogeneity. Where clinical covariates explain a large fraction of disease risk, covariate informed designs can increase power to detect associations. As prevalence rates in IS are markedly affected by age, and younger onset cases may have higher genetic predisposition, we investigated whether an age-at-onset informed approach could detect novel associations with IS and its subtypes; cardioembolic (CE), large artery atherosclerosis (LAA) and small vessel disease (SVD) in 6,778 cases of European ancestry and 12,095 ancestry-matched controls. Regression analysis to identify SNP associations was performed on posterior liabilities after conditioning on age-at-onset and affection status. We sought further evidence of an association with LAA in 1,881 cases and 50,817 controls, and examined mRNA expression levels of the nearby genes in atherosclerotic carotid artery plaques. Secondly, we performed permutation analyses to evaluate the extent to which age-at-onset informed analysis improves significance for novel loci. We identified a novel association with an MMP12 locus in LAA (rs660599; p = 2.5×10-7), with independent replication in a second population (p = 0.0048, OR(95% CI) = 1.18(1.05-1.32); meta-analysis p = 2.6×10-8). The nearby gene, MMP12, was significantly overexpressed in carotid plaques compared to atherosclerosis-free control arteries (p = 1.2×10-15; fold change = 335.6). Permutation analyses demonstrated improved significance for associations when accounting for age-at-onset in all four stroke phenotypes (p<0.001). Our results show that a covariate-informed design, by adjusting for age-at-onset of stroke, can detect variants not identified by conventional GWAS.

APOE ε variants increase risk of warfarin-related intracerebral hemorrhage.

Falcone GJ, Radmanesh F, et al. On Behalf of the **International Stroke Genetics Consortium**. **Neurology**. 2014 Aug 22.

Abstract

OBJECTIVE: We aimed to assess the effect of APOE ε variants on warfarin-related intracerebral hemorrhage (wICH), evaluated their predictive power, and tested for interaction with warfarin in causing wICH.

METHODS: This was a prospective, 2-stage (discovery and replication), case-control study. wICH was classified as lobar or nonlobar based on the location of the hematoma. Controls were sampled from ambulatory clinics (discovery) and random digit dialing (replication). APOE ε variants were directly genotyped. A case-control design and logistic regression analysis were utilized to test for association between APOE ε and wICH. A case-only design and logistic regression analysis were utilized to test for interaction between APOE ε and warfarin. Receiver operating characteristic curves were implemented to evaluate predictive power.

RESULTS: The discovery stage included 319 wICHs (44% lobar) and 355 controls. APOE ε2 was associated with lobar (odds ratio [OR] 2.46; $p < 0.001$) and nonlobar wICH (OR 1.67; $p = 0.04$), whereas ε4 was associated with lobar (OR 2.09; $p < 0.001$) but not nonlobar wICH ($p = 0.35$). The replication stage (63 wICHs and 1,030 controls) confirmed the association with ε2 ($p = 0.03$) and ε4 ($p = 0.003$) for lobar but not for nonlobar wICH ($p > 0.20$). Genotyping information on APOE ε variants significantly improved case/control discrimination of lobar wICH (C statistic 0.80). No statistical interaction between warfarin and APOE was found ($p > 0.20$).

CONCLUSIONS: APOE ε variants constitute strong risk factors for lobar wICH. APOE exerts its effect independently of warfarin, although power limitations render this absence of interaction preliminary. Evaluation of the predictive ability of APOE in cohort studies is warranted.

Associations of NINJ2 sequence variants with incident ischemic stroke in the Cohorts for Heart and Aging in Genomic Epidemiology (CHARGE) consortium.

Bis JC, DeStefano A, et al. **PLoS One**. 2014 Jun 24.

Abstract

BACKGROUND: Stroke, the leading neurologic cause of death and disability, has a substantial genetic component. We previously conducted a genome-wide association study (GWAS) in four prospective studies from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium and demonstrated that sequence variants near the NINJ2 gene are associated with incident ischemic stroke. Here, we sought to fine-map functional variants in the region and evaluate the contribution of rare variants to ischemic stroke risk.

METHODS AND RESULTS: We sequenced 196 kb around NINJ2 on chromosome 12p13 among 3,986 European ancestry participants, including 475 ischemic stroke cases, from the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, and Framingham Heart Study. Meta-analyses of single-variant tests for 425 common variants (minor allele frequency [MAF] ≥ 1%) confirmed the original GWAS results and identified an independent intronic variant, rs34166160 (MAF = 0.012), most significantly associated with incident ischemic stroke (HR = 1.80, p = 0.0003). Aggregating 278 putatively-functional variants with MAF≤ 1% using count statistics, we observed a nominally statistically significant association, with the burden of rare NINJ2 variants contributing to decreased ischemic stroke incidence (HR = 0.81; p = 0.026).

CONCLUSION: Common and rare variants in the NINJ2 region were nominally associated with incident ischemic stroke among a subset of CHARGE participants. Allelic heterogeneity at this locus, caused by multiple rare, low frequency, and common variants with disparate effects on risk, may explain the difficulties in replicating the original GWAS results. Additional studies that take into account the complex allelic architecture at this locus are needed to confirm these findings.

CONGRESOS Y REUNIONES DE INTERÉS 2013-2014

Canadian Stroke Congress, October 4-7, 2014. Vancouver, Canada.

American Society of Human Genetics (ASHG), October 18-22, 2014. San Diego, USA.

9th World Stroke Congress, October 22-25, 2014. Istanbul, Turkey.

Society for Neuroscience (SFN) Annual Meeting: Neuroscience 2014, November 15-19, 2014. Washington DC, USA.

SEN 14- LXVI Reunión Anual de la Sociedad Española de Neurología, Noviembre 2014. Valencia.

XXII World Congress of Neurology, October 31- November 5, 2015. Santiago, Chile.

International Stroke Conference, February 11-13, 2015. Nashville, Tennessee.

American Academy of Neurology Annual Meeting (AAN), April 18-25, 2015. Washington, USA.

24 European Stroke Conference, May 12-15, 2015. Vienna, Austria.

The European Human Genetics Conference, June 6-9, 2015. Glasgow, Scotland, UK.

10th FENS Forum of Neuroscience, July 2-6, 2016. Copenhagen, Denmark.

GE, GE, GE...

Sugerencias...
mmola@imim.es

Estamos en la web!
www.GeneStroke.com

GeneStroke