NEWSLETTER

GeneStroke | The Spanish Stroke Genetics Consortium

Marzo 2015

Nº 14

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

Contenido:

TITULARES

NOVEDAD! Próximamente...

I CURSO DE ACTUALIZACIÓN DE GENÉTICA EN ENFERMEDADES COMPLEJAS

VI REUNIÓN ANUAL DEL CONSORCIO ESPAÑOL DE GENÉTICA DEL ICTUS

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Últimas publicaciones con participación de *GeneStroke:*

Common variation in COL4A1/COL4A2 is associated with sporadic cerebral small vessel disease.

K Rannikmäe, …, J **Jimenez-Conde**, **J Montaner**, …, Jonathan Rosand, Cathie LM Sudlow on behalf of the Metastroke Consortium, the CHARGE WMH Group, the ISGC ICH GWAS Study Collaboration, the WMH in ischemic stroke GWAS Study Collaboration and the International Stroke Genetics Consortium. **Neurology. 2015 Mar 3.**

Agreement between TOAST and CCS ischemic stroke classification: The NINDS SiGN Study.

McArdle PF, …, **Jiménez-Conde J**, **Roquer J**, …, Worrall BB, On behalf of the NINDS SiGN Study. **Neurology. 2014 Oct 28.**

Pathogenic Ischemic Stroke Phenotypes in the NINDS-Stroke Genetics Network. Ay H, **Giralt E,** Grewal RP, Gwinn K, Jern C, **Jiménez-Conde J**, …, Worrall BB, Meschia JF. **Stroke. 2014 Dec.**

Recommendations from the International Stroke Genetics Consortium, Part 2: Biological Sample Collection and Storage.

Thomas Battey, …, **Jordi Jiménez-Conde, Israel Fernandez-Cadenas**, Guillaume Paré, Cathie Sudlow and Jonathan Rosand on behalf of the International Stroke Genetics Consortium. **Stroke. 2015 Jan.**

Recommendations From the International Stroke Genetics Consortium, Part 1. Standardized Phenotypic Data Collection.

Jennifer Majersik, …, Israel **Fernandez-Cadenas**, **Joan Montaner**, **Jaume Roquer**, **Jordi Jiménez-Conde**, Jonathan Rosand, and Jane Maguire on behalf of the International Stroke Genetics Consortium. **Stroke. 2015 Jan.**

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

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 metaanálisis

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 metaanálisis

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 publicación

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: En fase de 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

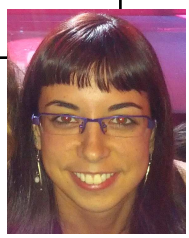
Proyecto: **ChiCHOS** (Case/Control study to analyse tHe genetic risk factOrs of ischemic Stroke)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

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 replicación

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: Pendiente de resultados genotipación

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:

Genetic overlap between diagnostic subtypes of ischemic stroke. Holliday EG, Traylor M, Malik R, Bevan S, Falcone G, Hopewell JC, Cheng YC, Cotlarciuc I, Bis JC, Boerwinkle E, Boncoraglio GB, Clarke R, Cole JW, Fornage M, Furie KL, Ikram MA, Jannes J, Kittner SJ, Lincz LF, Maguire JM, Meschia JF, Mosley TH, Nalls MA, Oldmeadow C, Parati EA, Psaty BM, Rothwell PM, Seshadri S, Scott RJ, Sharma P, Sudlow C, Wiggins KL, Worrall BB, Rosand J, Mitchell BD, Dichgans M, Markus HS, Levi C, Attia J, Wray NR; Australian Stroke Genetics Collaborative, the Wellcome Trust Case Control Consortium 2, and **the International Stroke Genetics Consortium**.
Stroke. 2015 Mar.

Abstract

BACKGROUND AND PURPOSE: Despite moderate heritability, the phenotypic heterogeneity of ischemic stroke has hampered gene discovery, motivating analyses of diagnostic subtypes with reduced sample sizes. We assessed evidence for a shared genetic basis among the 3 major subtypes: large artery atherosclerosis (LAA), cardioembolism, and small vessel disease (SVD), to inform potential cross-subtype analyses.

METHODS: Analyses used genome-wide summary data for 12 389 ischemic stroke cases (including 2167 LAA, 2405 cardioembolism, and 1854 SVD) and 62 004 controls from the Metastroke consortium. For 4561 cases and 7094 controls, individual-level genotype data were also available.Genetic correlations between subtypes were estimated using linear mixed models and polygenic profile scores. Meta-analysis of a combined LAA-SVD phenotype (4021 cases and 51 976 controls) was performed to identify shared risk alleles.

RESULTS: High genetic correlation was identified between LAA and SVD using linear mixed models (rg=0.96, SE=0.47, P=9×10(-4)) and profile scores (rg=0.72; 95% confidence interval, 0.52-0.93). Between LAA and cardioembolism and SVD and cardioembolism, correlation was moderate using linear mixed models but not significantly different from zero for profile scoring. Joint meta-analysis of LAA and SVD identified strong association (P=1×10(-7)) for single nucleotide polymorphisms near the opioid receptor μ1 (OPRM1) gene.

CONCLUSIONS: Our results suggest that LAA and SVD, which have been hitherto treated as genetically distinct, may share a substantial genetic component. Combined analyses of LAA and SVD may increase power to identify small-effect alleles influencing shared pathophysiological processes.

Common variation in COL4A1/COL4A2 is associated with sporadic cerebral small vessel disease.

Rannikmäe K, Davies G, Thomson PA, Bevan S, Devan WJ, Falcone GJ, Traylor M, Anderson CD, Battey TW, Radmanesh F, Deka R, Woo JG, Martin LJ, Jimenez-Conde J, Selim M, Brown DL, Silliman SL, Kidwell CS, Montaner J, Langefeld CD, Slowik A, Hansen BM, Lindgren AG, Meschia JF, Fornage M, Bis JC, Debette S, Ikram MA, Longstreth WT, Schmidt R, Zhang CR, Yang Q, Sharma P, Kittner SJ, Mitchell BD, Holliday EG, Levi CR, Attia J, Rothwell PM, Poole DL, Boncoraglio GB, Psaty BM, Malik R, Rost N, Worrall BB, Dichgans M, Van Agtmael T, Woo D, Markus HS, Seshadri S, Rosand J, Sudlow CL; METASTROKE Consortium, the CHARGE WMH Group, the ISGC ICH GWAS Study Collaboration, the WMH in Ischemic Stroke GWAS Study Collaboration, and the International Stroke Genetics Consortium.

Neurology. 2015 Mar.

Abstract

OBJECTIVES: We hypothesized that common variants in the collagen genes COL4A1/COL4A2 are associated with sporadic forms of cerebral small vessel disease.

METHODS: We conducted meta-analyses of existing genotype data among individuals of European ancestry to determine associations of 1,070 common single nucleotide polymorphisms (SNPs) in the COL4A1/COL4A2 genomic region with the following: intracerebral hemorrhage and its subtypes (deep, lobar) (1,545 cases, 1,485 controls); ischemic stroke and its subtypes (cardioembolic, large vessel disease, lacunar) (12,389 cases, 62,004 controls); and white matter hyperintensities (2,733 individuals with ischemic stroke and 9,361 from population-based cohorts with brain MRI data). We calculated a statistical significance threshold that accounted for multiple testing and linkage disequilibrium between SNPs ($p < 0.000084$).

RESULTS: Three intronic SNPs in COL4A2 were significantly associated with deep intracerebral hemorrhage (lead SNP odds ratio [OR] 1.29, 95% confidence interval [CI] 1.14-1.46, $p = 0.00003$; $r(2) > 0.9$ between SNPs). Although SNPs associated with deep intracerebral hemorrhage did not reach our significance threshold for association with lacunar ischemic stroke (lead SNP OR 1.10, 95% CI 1.03-1.18, $p = 0.0073$), and with white matter hyperintensity volume in symptomatic ischemic stroke patients (lead SNP OR 1.07, 95% CI 1.01-1.13, $p = 0.016$), the direction of association was the same. There was no convincing evidence of association with white matter hyperintensities in population-based studies or with non-small vessel disease cerebrovascular phenotypes.

CONCLUSIONS: Our results indicate an association between common variation in the COL4A2 gene and symptomatic small vessel disease, particularly deep intracerebral hemorrhage. These findings merit replication studies, including in ethnic groups of non-European ancestry.

Shared genetic aetiology of coronary artery disease and atherosclerotic stroke-2015.

Kessler T, Erdmann J, Dichgans M, Schunkert H.

Curr Atheroscler Rep. 2015 Apr.

Abstract

In the last years, genome-wide association studies have allowed to identify multiple genetic variants associated with atherosclerosis. In this review, we highlight the identification of genomic variants associated with coronary artery disease and myocardial infarction as well as large-vessel stroke. We will focus on genetic variants that displayed overlap for these atherosclerotic diseases. Current research is focusing on the identification of the functional mechanisms underlying these associations. As frequent variants are often only associated with small increases in risk, the search for the identification of rare variants with large increases in risk is ongoing. Whole-exome sequencing recently revealed rare variants dramatically increasing cardiovascular risk. Taken together, the developments of the past few years light the vision of improved prevention and therapy of coronary artery disease and stroke.

Multi-Ethnic Genome-Wide Association Study of Cerebral White Matter Hyperintensities on MRI.

Verhaaren BF, Debette S, et al. **Circ Cardiovasc Genet**. 2015 Feb.

Abstract

BACKGROUND: The burden of cerebral white matter hyperintensities (WMH) is associated with an increased risk of stroke, dementia, and death. WMH are highly heritable, but their genetic underpinnings are incompletely characterized. To identify novel genetic variants influencing WMH burden, we conducted a meta-analysis of multi-ethnic genome-wide association studies.

METHODS AND RESULTS: We included 21,079 middle-aged to elderly individuals from 29 population-based cohorts, who were free of dementia and stroke and were of European (N=17,936), African (N=1,943), Hispanic (N=795), and Asian (N=405) descent. WMH burden was quantified on MRI either by a validated automated segmentation method or a validated visual grading scale. Genotype data in each study were imputed to the 1000 Genomes reference. Within each ethnic group, we investigated the relationship between each SNP and WMH burden using a linear regression model adjusted for age, sex, intracranial volume, and principal components of ancestry. A meta-analysis was conducted for each ethnicity separately and for the combined sample. In the European descent samples, we confirmed a previously known locus on chr17q25 ($p=2.7\times10^{-19}$) and identified novel loci on chr10q24 ($p=1.6\times10^{-9}$) and chr2p21 ($p=4.4\times10^{-8}$). In the multi-ethnic meta-analysis, we identified two additional loci, on chr1q22 ($p=2.0\times10^{-8}$) and chr2p16 ($p=1.5\times10^{-8}$). The novel loci contained genes that have been implicated in Alzheimer's disease (chr2p21, chr10q24), intracerebral hemorrhage (chr1q22), neuro-inflammatory diseases (chr2p21), and glioma (chr10q24, chr2p16).

CONCLUSIONS: We identified four novel genetic loci that implicate inflammatory and glial proliferative pathways in the development of white matter hyperintensities in addition to previously-proposed ischemic mechanisms.

Genetic architecture of white matter hyperintensities differs in hypertensive and nonhypertensive ischemic stroke.

Adib-Samii P, Devan W, et al. **Stroke**. 2015 Feb.

Abstract

BACKGROUND AND PURPOSE: Epidemiological studies suggest that white matter hyperintensities (WMH) are extremely heritable, but the underlying genetic variants are largely unknown. Pathophysiological heterogeneity is known to reduce the power of genome-wide association studies (GWAS). Hypertensive and nonhypertensive individuals with WMH might have different underlying pathologies.

METHODS: WMHV was measured on MRI in the stroke-free cerebral hemisphere of 2336 ischemic stroke cases with GWAS data. After adjustment for age and intracranial volume, we determined which cardiovascular risk factors were independent predictors of WMHV. Using the genome-wide complex trait analysis tool to estimate HSNP for WMHV overall and within subgroups stratified by risk factors found to be significant in multivariate analyses.

RESULTS: A significant proportion of the variance of WMHV was attributable to common SNPs after adjustment for significant risk factors (HSNP=0.23; P=0.0026). HSNP estimates were higher among hypertensive individuals (HSNP=0.45; P=7.99×10(-5)); this increase was greater than expected by chance (P=0.012). In contrast, estimates were lower, and nonsignificant, in nonhypertensive individuals (HSNP=0.13; P=0.13).

CONCLUSIONS: A quarter of variance is attributable to common SNPs, but this estimate was greater in hypertensive individuals. These findings suggest that the genetic architecture of WMH in ischemic stroke differs between hypertensives and nonhypertensives. Future WMHV GWAS studies may gain power by accounting for this interaction.

CONGRESOS Y REUNIONES DE INTERÉS 2014-2015

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.

Canadian Stroke Congress, October 3-6, 2015. Toronto, Ontario.

American Society of Human Genetics (ASHG), October 6-10, 2015. Baltimore, USA.

Society for Neuroscience (SFN) Annual Meeting: Neuroscience 2014, October 17-21, 2015. Chicago, Illinois.

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

LXVII Reunión Anual de la Sociedad Española de Neurología, Noviembre 2015. Valencia.

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

10th World Stroke Congress, 2016. Place to be confirmed.

International Stroke Conference, February 17-19, 2016. Los Angeles, California.

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Sugerencias...
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Estamos en la web!
www.GeneStroke.com

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What is genetics... ?