NEWSLETTER

GeneStroke | The Spanish Stroke Genetics Consortium

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Junio 2015

Nº 15

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:

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 publicación

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 replicación

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 análisis 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 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 publicación

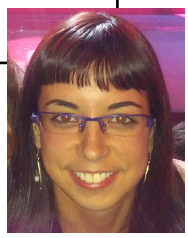
Proyecto: **ChiCHOS** (Case/Control study to analyse tHe genetic risk factOrs of ischemic Stroke)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

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: En fase de análisis

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
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NOVEDADES SOBRE GENÉTICA EN EL ICTUS:

Rare and Coding Region Genetic Variants Associated With Risk of Ischemic Stroke: The NHLBI Exome Sequence Project.

Auer PL, Nalls M et al. National Heart, Lung and Blood Institute Exome Sequencing Project.
JAMA Neurol. 2015 May 11.

Abstract

IMPORTANCE: Stroke is the second leading cause of death and the third leading cause of years of life lost. Genetic factors contribute to strokeprevalence, and candidate gene and genome-wide association studies (GWAS) have identified variants associated with ischemic stroke risk. These variants often have small effects without obvious biological significance. Exome sequencing may discover predicted protein-altering variants with a potentially large effect on ischemic stroke risk.

OBJECTIVE: To investigate the contribution of rare and common genetic variants to ischemic stroke risk by targeting the protein-coding regions of the human genome.

DESIGN, SETTING, AND PARTICIPANTS: The National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (ESP) analyzed approximately 6000 participants from numerous cohorts of European and African ancestry. For discovery, 365 cases of ischemic stroke (small-vessel and large-vessel subtypes) and 809 European ancestry controls were sequenced; for replication, 47 affected sibpairs concordant for strokesubtype and an African American case-control series were sequenced, with 1672 cases and 4509 European ancestry controls genotyped. The ESP's exome sequencing and genotyping started on January 1, 2010, and continued through June 30, 2012. Analyses were conducted on the full data set between July 12, 2012, and July 13, 2013.

MAIN OUTCOMES AND MEASURES: Discovery of new variants or genes contributing to ischemic stroke risk and subtype (primary analysis) and determination of support for protein-coding variants contributing to risk in previously published candidate genes (secondary analysis).

RESULTS: We identified 2 novel genes associated with an increased risk of ischemic stroke: a protein-coding variant in PDE4DIP (rs1778155; odds ratio, 2.15; P = 2.63 × 10-8) with an intracellular signal transduction mechanism and in ACOT4 (rs35724886; odds ratio, 2.04; P = 1.24 × 10-7) with a fatty acid metabolism; confirmation of PDE4DIP was observed in affected sibpair families with large-vessel stroke subtype and in African Americans. Replication of protein-coding variants in candidate genes was observed for 2 previously reported GWAS associations: ZFHX3 (cardioembolic stroke) and ABCA1 (large-vessel stroke).

CONCLUSIONS AND RELEVANCE: Exome sequencing discovered 2 novel genes and mechanisms, PDE4DIP and ACOT4, associated with increased risk for ischemic stroke. In addition, ZFHX3 and ABCA1 were discovered to have protein-coding variants associated with ischemic stroke. These results suggest that genetic variation in novel pathways contributes to ischemic stroke risk and serves as a target for prediction, prevention, and therapy.

Low density lipoprotein receptor related protein 1 and 6 gene variants and ischaemic stroke risk.

Harriott AM, Heckman MG, Rayaprolu S, Soto-Ortolaza AI, Diehl NN, Kanekiyo T, Liu CC, Bu G, Malik R; METASTRO-KE consortium, Cole JW, Meschia JF, Ross OA.
Eur J Neurol. 2015 May 29.

Abstract

BACKGROUND AND PURPOSE: Low density lipoprotein receptor related proteins (LRPs) 1 and 6 have been implicated in cerebral ischaemia. In addition, genetic variation in LRP1 and LRP6 has been linked with various factors that are related to risk of ischaemic stroke. The aim of this study was to examine the association of LRP1 and LRP6 gene variants with risk of ischaemic stroke as part of the Ischemic Stroke Genetics Study (ISGS).

METHODS: A Caucasian series (434 stroke patients, 319 controls) and an African American series (161 stroke patients, 116 controls) were included. Fourteen LRP6 variants and three LRP1 variants were genotyped and assessed for association with ischaemic stroke.

RESULTS: In the Caucasian series, significant associations with ischaemic stroke were observed for LRP6 rs2075241 [odds ratio (OR) 0.42, P = 0.023], rs2302685 (OR 0.44, P = 0.049), rs7975614 (OR 0.07, P = 0.017), rs10492120 (OR 0.62, P = 0.036) and rs10743980 (OR 0.66, P = 0.037). Risk of ischaemic stroke was significantly lower for carriers of any of these five protective LRP6 variants (24.0% of subjects) compared to non-carriers (OR 0.57, P = 0.003). The protective association for LRP6 rs2075241 was observed at a similar magnitude across ischaemic strokesubtypes, whilst the effects of rs23022685, rs10492120 and rs10743980 were most apparent for cardioembolic and large vessel stroke. In the African American series, LRP1 rs11172113 was associated with an increased risk of stroke (OR 1.89, P = 0.006).

CONCLUSIONS: The results of our preliminary study provide evidence that LRP6 and LRP1 variants may be associated with risk of ischaemicstroke. Validation in larger studies is warranted.

COX-2 rs20417 Polymorphism Is Associated with Stroke and White Matter Disease.

Oliveira-Filho J, Ornellas AC, Zhang CR, Oliveira LM, Araújo-Santos T, Borges VM, Ventura LM, Reis FJ, Aras R, Fernandes AM, Rosand J, Greenberg SM, Furie KL, Rost NS. **J Stroke Cerebrovasc Dis.** 2015 May 6.

Abstract

BACKGROUND: To investigate the effect of COX-2 polymorphism and its product, prostaglandin E2 (PGE2), on stroke risk in an endemic area for Chagas disease. In a separate cohort, to investigate the effect of COX-2 polymorphisms on the total burden of cerebral white matter disease.

METHODS: Cases were outpatients with ischemic stroke; controls were stroke-free subjects from 2 outpatient clinics (heart failure and caregivers of a movement disorders clinic). We extracted DNA from total blood to investigate the rs20417 COX-2 polymorphism. Serologic tests (Enzime-linked immunosorbent assay) were performed to confirm Trypanosoma cruzi infection and to quantify PGE2 levels. In the Boston cohort, white matter hyperintensity volume (WMHv) was quantified on the admission brain magnetic resonance images of subjects with ischemic stroke, who also donated DNA for the COX-2 gene region analysis.

RESULTS: We studied 44 patients with stroke and 96 controls (46 with heart failure and 50 caregivers) in the Brazilian cohort; and 788 strokepatients (302 cardioembolic and 486 noncardioembolic) in the Boston cohort. In the Brazilian cohort, rs20417 polymorphism was associated with bothstroke ($P = 5 \times 10^{-6}$) and decreased PGE2 levels ($P = 4 \times 10^{-5}$); similarly, Chagas was associated with stroke ($P = 4 \times 10^{-3}$) and decreased PGE2 levels ($P = 7 \times 10^{-3}$). In the Boston cohort, rs20417 polymorphism was associated with increased WMHv among noncardioembolic (P = .037), but not among cardioembolic stroke patients.

CONCLUSIONS: Variation in COX-2 gene is associated with both symptomatic and silent brain cerebrovascular disease. This candidate gene region should be tested in population-based samples.

Common NOTCH3 Variants and Cerebral Small-Vessel Disease.

Rutten-Jacobs LC, Traylor M, Adib-Samii P, Thijs V, Sudlow C, Rothwell PM, Boncoraglio G, Dichgans M, Bevan S, Meschia J, Levi C, Rost NS, Rosand J, Hassan A, Markus HS.
Stroke. 2015 Jun.

Abstract

BACKGROUND AND PURPOSE: The most common monogenic cause of cerebral small-vessel disease is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, caused by NOTCH3 gene mutations. It has been hypothesized that more common variants in NOTCH3 may also contribute to the risk of sporadic small-vessel disease. Previously, 4 common variants (rs10404382, rs1043994, rs10423702, and rs1043997) were found to be associated with the presence of white matter hyperintensity in hypertensive community-dwelling elderly.

METHODS: We investigated the association of common single nucleotide polymorphisms (SNPs) in NOTCH3 in 1350 patients with MRI-confirmed lacunar stroke and 7397 controls, by meta-analysis of genome-wide association study data sets. In addition, we investigated the association of common SNPs in NOTCH3 with MRI white matter hyperintensity volumes in 3670 white patients with ischemic stroke. In each analysis, we considered all SNPs within the NOTCH3 gene, and within 50-kb upstream and downstream of the coding region. A total of 381 SNPs from the 1000 genome population with a mean allele frequency >0.01 were included in the analysis. A significance level of P<0.0015 was used, adjusted for the effective number of independent SNPs in the region using the Galwey method.

RESULTS: We found no association of any common variants in NOTCH3 (including rs10404382, rs1043994, rs10423702, and rs1043997) with lacunar stroke or white matter hyperintensity volume. We repeated our analysis stratified for hypertension but again found no association.

CONCLUSIONS: Our study does not support a role for common NOTCH3 variation in the risk of sporadic small-vessel disease.

Shared genetic basis for migraine and ischemic stroke: A genome-wide analysis of common variants.

Malik R, Freilinger T, et al. International Headache**Genetics** Consortium, Dichgans M; **METASTROKE Collaboration of the International StrokeGenetics Consortium**.
Neurology. 2015 May 26.

Abstract

OBJECTIVE: To quantify genetic overlap between migraine and ischemic stroke (IS) with respect to common genetic variation.

METHODS: We applied 4 different approaches to large-scale meta-analyses of genome-wide data on migraine (23,285 cases and 95,425 controls) and IS (12,389 cases and 62,004 controls). First, we queried known genome-wide significant loci for both disorders, looking for potential overlap of signals. We then analyzed the overall shared genetic load using polygenic scores and estimated the genetic correlation between disease subtypes using data derived from these models. We further interrogated genomic regions of shared risk using analysis of covariance patterns between the 2 phenotypes using cross-phenotype spatial mapping.

RESULTS: We found substantial genetic overlap between migraine and IS using all 4 approaches. Migraine without aura (MO) showed much stronger overlap with IS and its subtypes than migraine with aura (MA). The strongest overlap existed between MO and large artery stroke (LAS; p = 6.4 × 10(-28) for the LAS polygenic score in MO) and between MO and cardioembolic stroke (CE; p = 2.7 × 10(-20) for the CE score in MO).

CONCLUSIONS: Our findings indicate shared genetic susceptibility to migraine and IS, with a particularly strong overlap between MO and both LAS and CE pointing towards shared mechanisms. Our observations on MA are consistent with a limited role of common genetic variants in this subtype.

CONGRESOS Y REUNIONES DE INTERÉS 2015-2016

Canadian Stroke Congress, September 17-19, 2015. Toronto, Ontario.

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

Society for Neuroscience (SFN) Annual Meeting. 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 17-21, 2015. Valencia.

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

25 European Stroke Conference, April 13-15, 2016. Venice, Italy.

American Academy of Neurology Annual Meeting (AAN), April 15-21, 2016. Vancouver, Canada.

The European Human Genetics Conference, May 21-24, 2016. Barcelona, Spain.

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

10th World Stroke Congress, October 26-29, 2016. Hyderabad, India.

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Sugerencias...
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