NEWSLETTER

Junio 2014

Nº 11

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:*

new **Global DNA methylation of ischemic stroke subtypes.** [pág.3]
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.

new **Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage.** [pág.5]
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.

new **Drug resistance and secondary treatment of ischaemic stroke: The genetic component of the response to acetylsalicylic acid and clopidogrel.** [pág.3]
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

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

Actualmente tenemos estos proyectos en curso:

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 análisis y 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

Proyecto: **SEDMAN** (Estudio de Seguridad/Eficacia de Dabigatran en fase precoz de ictus, estudio de nuevos MArcadores de Neuroimagen y biomarcadores)
IP: Jurek Krupinski (Mútua de Terrassa)
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:

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.

Abstract

Ischemic stroke (IS), a heterogeneous multifactorial disorder, is among the leading causes of mortality and long-term disability in the western world. Epidemiological data provides evidence for a genetic component to the disease, but its epigenetic involvement is still largely unknown. Epigenetic mechanisms, such as DNA methylation, change over time and may be associated with aging processes and with modulation of the risk of various pathologies, such as cardiovascular disease and stroke. We analyzed 2 independent cohorts of IS patients. Global DNA methylation was measured by luminometric methylation assay (LUMA) of DNA blood samples. Univariate and multivariate regression analyses were used to assess the methylation differences between the 3 most common IS subtypes, large-artery atherosclerosis (LAA), small-artery disease (SAD), and cardio-aortic embolism (CE). A total of 485 IS patients from 2 independent hospital cohorts (n = 281 and n = 204) were included, distributed across 3 IS subtypes: LAA (78/281, 59/204), SAD (97/281, 53/204), and CE (106/281, 89/204). In univariate analyses, no statistical differences in LUMA levels were observed between the 3 etiologies in either cohort. Multivariate analysis, adjusted by age, sex, hyperlipidemia, and smoking habit, confirmed the lack of differences in methylation levels between the analyzed IS subtypes in both cohorts. Despite differences in pathogenesis, our results showed no global methylation differences between LAA, SAD, and CE subtypes of IS. Further work is required to establish whether the epigenetic mechanism of methylation might play a role in this complex disease.

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.
Genestroke, Consorcio Español para el Estudio Genético del Ictus.
Neurologia. 2014 Mar 21.

Abstract

INTRODUCTION: Cerebrovascular diseases are among the leading causes of death and disability in developed countries. Acetylsalicylic acid (ASA) and clopidogrel are the most widely-used antiplatelet drugs for secondary prevention of recurrent thromboembolic events. However, there have been cases in which antiplatelet drugs did not inhibit platelet activity; this phenomenon is called resistance, and it may be modulated at the genetic level.

DEVELOPMENT: Following a literature search, we reviewed the current state of antiplatelet therapy and covered the different types of resistance to antiplatelet therapy, how it is measured, current problems and limitations, and any genetic factors that have been associated with resistance. We mainly used the Genome Wide Association Studies in the field of ASA and clopidogrel resistance.

CONCLUSIONS: We observed an association between different genetic factors and antiplatelet drug resistance as measured by platelet activity. However, there is no evident association between these genetic factors and risk of new thromboembolic events.

Effect of Genetic Variants Associated With Plasma Homocysteine Levels on Stroke Risk.

Cotlarciuc I, Malik R, Holliday EG, Ahmadi KR, Paré G, Psaty BM, Fornage M, Hasan N, Rinne PE, Ikram MA, Markus HS, Rosand J, Mitchell BD, Kittner SJ, Meschia JF, van Meurs JB, Uitterlinden AG, Worrall BB, Dichgans M, Sharma P; on behalf of **METASTROKE** and the International **Stroke Genetics Consortium**.
Stroke. 2014 May 20.

Abstract

BACKGROUND AND PURPOSE: Elevated total plasma homocysteine (tHcy) levels are known to be associated with increased risk of ischemicstroke (IS). Given that both tHcy and IS are heritable traits, we investigated a potential genetic relationship between homocysteine levels and strokerisk by assessing 18 polymorphisms previously associated with tHcy levels for their association with IS and its subtypes.

METHODS: Previous meta-analysis results from an international stroke collaborative network, METASTROKE, were used to assess association of the 18 tHcy-associated single-nucleotide polymorphisms (SNPs) in 12 389 IS cases and 62 004 controls. We also investigated the associations in regions located within 50 kb from the 18 tHcy -related SNPs and the association of a genetic risk score, including the 18 SNPs.

RESULTS: One SNP located in the RASIP1 gene and a cluster of 3 SNPs located at and near SLC17A3 were significantly associated with IS ($P<0.0003$) after correcting for multiple testing. For stroke subtypes, the sentinel SNP located upstream of MUT was significantly associated with small-vessel disease ($P=0.0022$), whereas 1 SNP located in MTHFR was significantly associated with large-vessel disease ($P=0.00019$). A genetic risk score, including the 18 SNPs, did not show significant association with IS or its subtypes.

CONCLUSIONS: This study found several potential associations with IS and its subtypes: an association of an MUT variant with small-vessel disease, an MTHFR variant with large-vessel disease, and associations of RASIP1 and SLC17A3 variants with overall IS.

Rare coding variation in paraoxonase-1 is associated with ischemic stroke in the NHLBI Exome Sequencing Project.

Kim DS, Crosslin DR, Auer PL, Suzuki SM, Marsillach J, Burt AA, Gordon AS, Meschia JF, Nalls MA, Worrall BB, Longstreth WT Jr, Gottesman RF, Furlong CE, Peters U, Rich SS, Nickerson DA, Jarvik GP; on behalf of the NHLBI Exome Sequencing Project. **J Lipid Res**. 2014 Apr 7.

Abstract

HDL-associated paraoxonase-1 (PON1) is an enzyme whose activity is associated with cerebrovascular disease. Common PON1 genetic variants have not been consistently associated with cerebrovascular disease. Rare coding variation that likely alters PON1 enzyme function may be more strongly associated with stroke. The National Heart, Lung, and Blood Institute Exome Sequencing Project sequenced the coding regions (exomes) of the genome for heart, lung, and blood-related phenotypes (including ischemic stroke). In this sample of 4,204 unrelated participants, 496 had verified, noncardioembolic ischemic stroke. After filtering, 28 nonsynonymous PON1 variants were identified. Analysis with the sequence kernel association test, adjusted for covariates, identified significant associations between PON1 variants and ischemic stroke ($P = 3.01 \times 10^{-3}$). Stratified analyses demonstrated a stronger association of PON1 variants with ischemic stroke in African ancestry (AA) participants ($P = 5.03 \times 10^{-3}$). Ethnic differences in the association between PON1 variants with stroke could be due to the effects of $PON1_{Val109Ile}$ (overall $P = 7.88 \times 10^{-3}$; AA $P = 6.52 \times 10^{-4}$), found at higher frequency in AA participants (1.16% vs. 0.02%) and whose protein is less stable than the common allele. In summary, rare genetic variation in PON1 was associated with ischemic stroke, with stronger associations identified in those of AA. Increased focus on PON1 enzyme function and its role in cerebrovascular disease is warranted.

Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage.

Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, Anderson CD, Brouwers HB, Valant V, Battey TW, Radmanesh F, Raffeld MR, Baedorf-Kassis S, Deka R, Woo JG, Martin LJ, Haverbusch M, Moomaw CJ, Sun G, Broderick JP, Flaherty ML, Martini SR, Kleindorfer DO, Kissela B, Comeau ME, Jagiella JM, Schmidt H, Freudenberger P, Pichler A, Enzinger C, Hansen BM, Norrving B, **Jimenez-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, Stögerer EM, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, **Montaner J, Fernandez-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.

Abstract

Intracerebral hemorrhage (ICH) is the stroke subtype with the worst prognosis and has no established acute treatment. ICH is classified as lobar or nonlobar based on the location of ruptured blood vessels within the brain. These different locations also signal different underlying vascular pathologies. Heritability estimates indicate a substantial genetic contribution to risk of ICH in both locations. We report a genome-wide association study of this condition that meta-analyzed data from six studies that enrolled individuals of European ancestry. Case subjects were ascertained by neurologists blinded to genotype data and classified as lobar or nonlobar based on brain computed tomography. ICH-free control subjects were sampled from ambulatory clinics or random digit dialing. Replication of signals identified in the discovery cohort with $p < 1 \times 10(-6)$ was pursued in an independent multiethnic sample utilizing both direct and genome-wide genotyping. The discovery phase included a case cohort of 1,545 individuals (664 lobar and 881 nonlobar cases) and a control cohort of 1,481 individuals and identified two susceptibility loci: for lobar ICH, chromosomal region 12q21.1 (rs11179580, odds ratio [OR] = 1.56, $p = 7.0 \times 10(-8)$); and for nonlobar ICH, chromosomal region 1q22 (rs2984613, OR = 1.44, $p = 1.6 \times 10(-8)$). The replication included a case cohort of 1,681 individuals (484 lobar and 1,194 nonlobar cases) and a control cohort of 2,261 individuals and corroborated the association for 1q22 ($p = 6.5 \times 10(-4)$; meta-analysis $p = 2.2 \times 10(-10)$) but not for 12q21.1 ($p = 0.55$; meta-analysis $p = 2.6 \times 10(-5)$). These results demonstrate biological heterogeneity across ICH subtypes and highlight the importance of ascertaining ICH cases accordingly.

review

Current concepts and clinical applications of stroke genetics.

Falcone GJ, Malik R, Dichgans M, Rosand J. **Lancet Neurol.** 2014 Apr 13.

Abstract

Driven by innovative technologies, novel analytical methods, and collaborations unimaginable not long ago, our understanding of the role of genetic variation in stroke has advanced substantially in recent years. However, a vast amount of data have accumulated quickly, and increasingly complex methodologies used in studies make keeping up to date on relevant findings difficult. In addition to well known, highly penetrant rare mutations that cause mendelian disorders related to stroke, several common genetic variants have been associated with common stroke subtypes, some of which also affect disease severity and clinical outcome. Furthermore, common genetic variations in biological pathways that have an important role in the pathophysiology of cerebrovascular diseases-such as blood pressure and oxidative phosphorylation-have been implicated in stroke. Clinical and translational applications of these and future discoveries in stroke genetics include identification of novel targets for treatment and development of personalised approaches to stroke prevention and management.

CONGRESOS Y REUNIONES DE INTERÉS 2013-2014

9th FENS Forum of Neuroscience, July 5-9, 2014. Milan, Italy.

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.

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

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