NEWSLETTER

GeneStroke | The Spanish Stroke Genetics Consortium

Diciembre 2014

Nº 13

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

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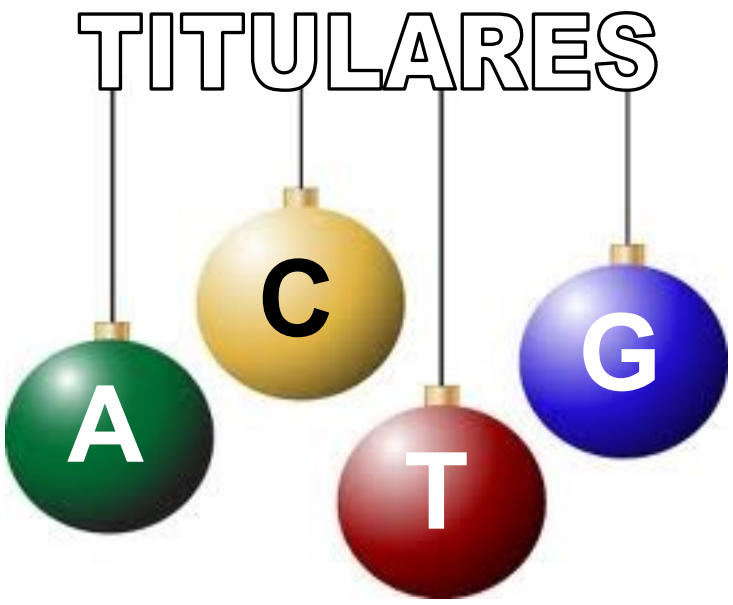


Últimas publicaciones con participación de *GeneStroke:*

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

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 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

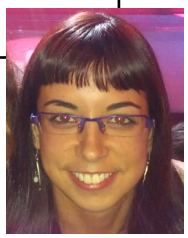
Proyecto: **ChiCHOS** (Case/Control study to analyse tHe genetic risk factOrs of ischemic Stroke)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

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 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: 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
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NOVEDADES SOBRE GENÉTICA EN EL ICTUS:

NURR1 Involvement in Recombinant Tissue-Type Plasminogen Activator Treatment Complications After Ischemic Stroke.

Merino-Zamorano C, Hernández-Guillamon M, Jullienne A, Béhot AL, Bardou I, Parés M, Fernández-Cadenas I, Giralt D, Carrera C, Ribó M, Vivien D, Ali C, Rosell A, Montaner J.
Stroke. 2014 Dec 11.

Abstract

BACKGROUND AND PURPOSE: Despite the effectiveness of recombinant tissue-type plasminogen activator (r-tPA) during the acute phase of ischemic stroke, the therapy remains limited by a narrow time window and the occurrence of occasional vascular side effects, particularly symptomatic hemorrhages. Our aim was to investigate the mechanisms underlying the endothelial damage resulting from r-tPA treatment in ischemic-like conditions.

METHODS: Microarray analyses were performed on cerebral endothelial cells submitted to r-tPA treatment during oxygen and glucose deprivation to identify novel biomarker candidates. Validation was then performed in vivo in a mouse model of thromboembolic stroke and culminated in an analysis in a clinical cohort of patients with ischemic stroke treated with thrombolysis.

RESULTS: The transcription factor NURR1 (NR4A2) was identified as a downstream target induced by r-tPA during oxygen and glucose deprivation. Silencing NURR1 expression reversed the endothelial-toxicity induced by the combined stimuli, a protective effect attributable to reduced levels of proinflammatory mediators, such as nuclear factor-kappa-beta 2 (NF-κ-B2), interleukin 1 alpha (IL1α), intercellular adhesion molecule 1 (ICAM1), SMAD family member 3 (SMAD3), colony stimulating factor 2 (granulocyte-macrophage; CSF2). The detrimental effect of delayed thrombolysis, in conditions in which NURR1 gene expression was enhanced, was confirmed in the preclinical stroke model. Finally, we determined that patients with stroke who had a symptomatic hemorrhagic transformation after r-tPA treatment exhibited higher baseline serum NURR1 levels than did patients with an asymptomatic or absence of cerebral bleedings.

CONCLUSIONS: Our results suggest that NURR1 upregulation by r-tPA during ischemic stroke is associated with endothelial dysfunction and inflammation and the enhancement of hemorrhagic complications associated to thrombolysis.

Pathogenic Ischemic Stroke Phenotypes in the NINDS-Stroke Genetics Network. Ay H, Arsava EM, Andsberg G, Benner T, Brown RD Jr, Chapman SN, Cole JW, Delavaran H, Dichgans M, Engström G, Giralt-Steinhauer E, Grewal RP, Gwinn K, Jern C, Jimenez-Conde J, Jood K, Katsnelson M, Kissela B, Kittner SJ, Kleindorfer DO, Labovitz DL, Lanfranconi S, Lee JM, Lehm M, Lemmens R, Levi C, Li L, Lindgren A, Markus HS, McArdle PF, Melander O, Norrving B, Peddareddygari LR, Pedersén A, Pera J, Rannikmäe K, Rexrode KM, Rhodes D, Rich SS, Roquer J, Rosand J, […], et al. **Stroke**. 2014 Dec.

Abstract

BACKGROUND AND PURPOSE: NINDS (National Institute of Neurological Disorders and Stroke)-SiGN (Stroke Genetics Network) is an international consortium of ischemic stroke studies that aims to generate high-quality phenotype data to identify the genetic basis of pathogenic stroke subtypes. This analysis characterizes the etiopathogenetic basis of ischemic stroke and reliability of stroke classification in the consortium.

METHODS: Fifty-two trained and certified adjudicators determined both phenotypic (abnormal test findings categorized in major pathogenic groups without weighting toward the most likely cause) and causative ischemic stroke subtypes in 16 954 subjects with imaging-confirmed ischemic strokefrom 12 US studies and 11 studies from 8 European countries using the web-based Causative Classification of Stroke System. Classification reliability was assessed with blinded readjudication of 1509 randomly selected cases.

RESULTS: The distribution of pathogenic categories varied by study, age, sex, and race (P<0.001 for each). Overall, only 40% to 54% of cases with a given major ischemic stroke pathogenesis (phenotypic subtype) were classified into the same final causative category with high confidence. There was good agreement for both causative (κ 0.72; 95% confidence interval, 0.69-0.75) and phenotypic classifications (κ 0.73; 95% confidence interval, 0.70-0.75).

CONCLUSIONS: This study demonstrates that pathogenic subtypes can be determined with good reliability in studies that include investigators with different expertise and background, institutions with different stroke evaluation protocols and geographic location, and patient populations with different epidemiological characteristics. The discordance between phenotypic and causative stroke subtypes highlights the fact that the presence of an abnormality in a patient with stroke does not necessarily mean that it is the cause of stroke.

A genetic risk score for hypertension associates with the risk of ischemic stroke in a Swedish case-control study. Fava C, Sjögren M, Olsson S, Lövkvist H, Jood K, Engström G, Hedblad B, Norrving B, Jern C, Lindgren A, Melander O. **Eur J Hum Genet.** 2014 Oct 8.

Abstract

Genetic risk scores (GRS), summing up the total effect of several single-nucleotide polymorphisms (SNPs) in genes associated with either coronary risk or cardiovascular risk factors, have been tested for association with ischemic stroke with conflicting results. Recently an association was found between a GRS based on 29 SNPs discovered by genome-wide association studies and hypertension. The aim of our study was to investigate the possible association of the same GRS with ischemic stroke on top of other 'traditional risk factors', also testing its potential improvement in indices of discrimination and reclassification, in a Swedish case-control study. Twenty-nine SNPs were genotyped in 3677 stroke cases and 2415 controls included in the Lund Stroke Register (LSR), the Malmö Diet and Cancer (MDC) study and the Sahlgrenska Academy Study on Ischemic Stroke(SAHLSIS). The analysis was conducted in the combined sample, and separately for the three studies. After adjustment for hypertension, diabetes mellitus and smoking habits, the GRS was associated with ischemic stroke in the combined sample (OR (95% CI) 1.086 (1.029-1.147) per SD increase in the GRS P=0.003) with similar trends in all three samples: LSR (1.050 (0.967-1.140); P=0.25), MDC (1.168 (1.060-1.288); P=0.002) and SAHLSIS (1.124 (0.997-1.267); P=0.055). Measures of risk discrimination and reclassification improved marginally using the GRS. A blood pressure GRS is independently associated with ischemic stroke risk in three Swedish case-control studies, however, the effect size is low and adds marginally to prediction of stroke on top of traditional risk factors including hypertension.

Genetic variation at the BDNF locus: evidence for association with long-term outcome after ischemic stroke. Stanne TM, Tjärnlund-Wolf A, Olsson S, Jood K, Blomstrand C, Jern C. **PLoS One**. 2014 Dec.

Abstract

BACKGROUND AND PURPOSE: Rates and extent of recovery after stroke vary considerably between individuals and genetic factors are thought to contribute to post-stroke outcome. Brain-derived neurotrophic factor (BDNF) plays important roles in brain plasticity and repair and has been shown to be involved in stroke severity, recovery, and outcome in animal models. Few clinical studies on BDNF genotypes in relation to ischemic stroke have been performed. The aims of the present study are therefore to investigate whether genetic variation at the BDNF locus is associated with initial stroke severity, recovery and/or short-term and long-term functional outcome after ischemic stroke.

METHODS: Four BDNF tagSNPs were analyzed in the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS; 600 patients and 600 controls, all aged 18-70 years). Stroke severity was assessed using the NIH Stroke Scale (NIHSS). Stroke recovery was defined as the change in NIHSS over a 3-month period. Short- and long-term functional outcome post-stroke was assessed using the modified Rankin Scale at 3 months and at 2 and 7 years after stroke, respectively.

RESULTS: No SNP was associated with stroke severity or recovery at 3 months and no SNP had an impact on short-term outcome. However, rs11030119 was independently associated with poor functional outcome 7-years after stroke (OR 0.66, 95% CI 0.46-0.92; P = 0.006).

CONCLUSIONS: BDNF gene variants were not major contributors to ischemic stroke severity, recovery, or short-term functional outcome. However, this study suggests that variants in the BDNF gene may contribute to poor long-term functional outcome after ischemic stroke.

review **Mechanisms and treatment of ischaemic stroke-insights from genetic associations.** Markus HS, Bevan S. **Nat Rev Neurol**. 2014 Dec.

Abstract

The precise pathophysiology of ischaemic stroke is unclear, and a greater understanding of the different mechanisms that underlie large-artery, cardioembolic and lacunar ischaemic stroke subtypes would enable the development of more-effective, subtype-specific therapies. Genome-wide association studies (GWASs) are identifying novel genetic variants that associate with the risk of stroke. These associations provide insight into the pathophysiological mechanisms, and present opportunities for novel therapeutic approaches. In this Review, we summarize the genetic variants that have been linked to ischaemic stroke in GWASs to date and discuss the implications of these associations for both our understanding and treatment of ischaemic stroke. The majority of genetic variants identified are associated with specific subtypes of ischaemic stroke, implying that these subtypes have distinct genetic architectures and pathophysiological mechanisms. The findings from the GWASs highlight the need to consider whether therapies should be subtype-specific. Further GWASs that include large cohorts are likely to provide further insights, and emerging technologies will complement and build on the GWAS findings.

Recommendations From the International Stroke Genetics Consortium:

Part 1: Standardized Phenotypic Data Collection. Majersik JJ, […], Fernandez-Cadenas I, Roquer J, Jiménez-Conde J, Rosand J, Maguire J; on behalf of the **International Stroke Genetics Consortium. Stroke.** 2014 Dec 9.

Part 2: Biological Sample Collection and Storage. Battey TW, […], Jimenez-Conde J, Fernandez-Cadenas I, Rosand J; on behalf of the **International Stroke Genetics Consortium**. **Stroke** 2014 Dec 9.

Keywords:
Cooperative behavior, genetics, population, outcome, risk factors, stroke, biobank, collaboration, consortium.

16th Workshop of the International Stroke Genetics Consortium

6-7 November 2014, Paris, France

Foto de la sede de la reunión del ISGC en París, donde se actualizaron y se presentaron nuevos proyectos del Consorcio.

¡Nueva Foto de algunos de los miembros del equipo GeneStroke!

CONGRESOS Y REUNIONES DE INTERÉS 2014-2015

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.

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.

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

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