NEWSLETTER

GeneStroke | The Spanish Stroke Genetics Consortium

Diciembre 2015

№ 17

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 **EPIGENOME-WIDE ASSOCIATION STUDY IDENTIFIES TXNIP GENE ASSOCIATED WITH TYPE 2 DIABETES MELLITUS AND SUSTAINED HYPERGLYCEMIA.**

Soriano-Tárraga C, Jiménez-Conde J, Giralt-Steinhauer E, Mola-Caminal M, Vivanco-Hidalgo RM, Ois A, Rodríguez-Campello A, Cuadrado-Godia E, Sayols-Baixeras S, Elosua R, **Roquer J; GENESTROKE Consortium. Hum Mol Genet, 2015 Dec.**

New **DNA methylation levels are highly correlated between pooled samples and averaged values when analysed using the Infinium HumanMethylation450 BeadChip array.**

Gallego-Fabrega C, Carrera C, Muiño E, Montaner J, Krupinski J, Fernandez-Cadenas I; Spanish Stroke Genetics Consortium. Clin Epigenetics, 2015 Jul.

An Inflammatory Polymorphisms Risk Scoring System for the Differentiation of Ischemic Stroke Subtypes.

Muiño E, Krupinski J, Carrera C, Gallego-Fabrega C, Montaner J, Fernández-Cadenas I. Mediators Inflamm, 2015 Aug.

Common variation in COL4A1/COL 4A2 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.**

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.**

PROYECTOS GENESTROKE EN ACTIVO

Actualmente tenemos estos proyectos en curso:

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

New ***Proyecto:*** **Impacto de la polución ambiental aérea (carbón negro y material particulado) en el ictus isquémico.**
IP: Jaume Roquer (Hospital del Mar)
Estado: Financiado. Pendiente iniciar

New ***Proyecto:*** **EWAL (Estudio de Epigenome Wide Association en Leucoaraiosis. Contribución de la epigenética en el envejecimiento cerebral.**
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: Financiado. Pendiente iniciar

New ***Proyecto:*** **GENERACIÓN (Estudio GENÉtico de mutaciones RAras en el ictus isquémico y creación de un score clínico-genético de predicCIÓN de riesgo)**
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: Financiado. Pendiente iniciar

Proyecto: **miRO (miRNA associated to functional Outcome in Stroke)**
IP: Cristòfol Vives (Hospital Son Espases)
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: 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: **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 (Mútua Terrassa); *IP grupo*: Cristòfol Vives (Hospital Son Espases)
Estado: En fase de replicación

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 publicación

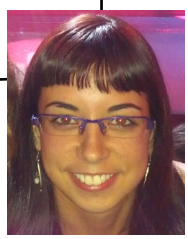
Proyecto: **MENEAS (MEthylation of DNA depending on Nutrition and Exercise habits. Developing a marker of "biological Age" and risk of Stroke)**
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: En fase de publicación

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: **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: **EWAS-Stroke (Estudio de Epigenome-Wide Association en los subtipos etiológicos de ictus isquémico)**
IP: Jaume Roquer (Hospital del Mar)
Estado: En fase de publicación

Para solicitar más información sobre los proyectos podéis contactar conmi-



Marina Mola
(mmola@imim.es)

NOVEDADES SOBRE GENÉTICA EN EL ICTUS:

GeneStroke

DNA methylation levels are highly correlated between pooled samples and averaged values when analysed using the Infinium HumanMethylation450 BeadChip array.

Gallego-Fabrega C, Carrera C, Muiño E, Montaner J, Krupinski J, Fernandez-Cadenas I.
Spanish Stroke Genetics Consortium. **Clin Epigenetics. 2015 Jul.**

Abstract

BACKGROUND: DNA methylation is a heritable and stable epigenetic mark implicated in complex human traits. Epigenome-wide association studies (EWAS) using array-based technology are becoming widely used to identify differentially methylated sites associated with complex diseases. EWAS studies require large sample sizes to detect small effects, which increases project costs. In the present study we propose to pool DNA samples in methylation array studies as an affordable and accurate alternative to individual samples studies, in order to reduce economic costs or when low amounts of DNA are available. For this study, 20 individual DNA samples and 4 pooled DNA samples were analysed using the Illumina Infinium HumanMethylation450 BeadChip array to evaluate the efficiency of the pooling approach in EWAS studies. Statistical power calculations were also performed to discover the minimum sample size needed for the pooling strategy in EWAS.

RESULTS: A total of 485,577 CpG sites across the whole genome were assessed. Comparison of methylation levels of all CpG sites between individual samples and their related pooled samples revealed highly significant correlations (rho > 0.99, p-val < 10(-16)). These results remained similar when assessing the 101 most differentially methylated CpG sites (rho > 0.98, p-val < 10(-16)). Also, it was calculated that n = 43 is the minimum sample size required to achieve a 95 % statistical power and a 10(-06) significance level in EWAS, when using a DNA pool strategy.

CONCLUSIONS: DNA pooling strategies seems to accurately provide estimations of averaged DNA methylation state using array based EWAS studies. This type of approach can be applied to the assessment of disease phenotypes, reducing the amount of DNA required and the cost of large-scale epigenetic analyses.

EPIGENOME-WIDE ASSOCIATION STUDY IDENTIFIES TXNIP GENE ASSOCIATED WITH TYPE 2 DIABETES MELLITUS AND SUSTAINED HYPERGLYCEMIA.

Soriano-Tárraga C, Jiménez-Conde J, Giralt-Steinhauer E, Mola-Caminal M, Vivanco-Hidalgo RM, Ois A, Rodríguez-Campello A, Cuadrado-Godia E, Sayols-Baixeras S, Elosua R, **Roquer J**; **GENESTROKE Consortium. Hum Mol Genet. 2015 Dec**.

Abstract

Type 2 diabetes mellitus (DM) is an established risk factor for a wide range of vascular diseases, including ischemic stroke (IS). Glycated hemoglobin A1c (HbA1c), a marker for average blood glucose levels over the previous 12 weeks, is used as a measure of glycemic control and also as a diagnostic criterion for diabetes (HbA1c levels≥6.5%). Epigenetic mechanisms, such as DNA methylation, may be associated with aging processes and with modulation of the risk of various pathologies, such as DM. Specifically, DNA methylation could be one of the mechanisms mediating the relation between DM and environmental exposures. Our goal was to identify new CpG methylation sites associated with DM.We performed a genome-wide methylation study in whole-blood DNA from a IS patient cohorts. Illumina HumanMethylation450 BeadChip array was used to measure DNA methylation in CpG sites. All statistical analyses were adjusted for sex, age, hyperlipidemia, body mass index (BMI), smoking habit and cell count. Findings were replicated in two independent cohorts, an IS cohort and a population-based cohort, using the same array.In the discovery phase (N=355), we identified a CpG site, cg19693031 (located in the TXNIP gene) that was associated with DM ($p=1.17\times10^{-12}$); this CpG was replicated in two independent cohorts (N=167 and N=645). Methylation of TXNIP was inversely and intensely associated with HbA1c levels ($p=7.3\times10^{-16}$), specifically related to diabetic patients with poor control of glucose levels.We identified an association between the TXNIP gene and DM through epigenetic mechanisms, related to sustained hyperglycemia levels (HbA1c≥7%).

Demethylation of Circulating Estrogen Receptor Alpha Gene in Cerebral Ischemic Stroke.

Lin HF, Hsi E, Liao YC, Chhor B, Hung J, Juo SH, Lin RT. **PLoS One. 2015 Sep.**

Abstract

BACKGROUND: Estrogen is involved in neuron plasticity and can promote neuronal survival in stroke. Its actions are mostly exerted via estrogen receptor alpha (ERα). Previous animal studies have shown that ERα is upregulated by DNA demethylation following ischemic injury. This study investigated the methylation levels in the ERα promoter in the peripheral blood of ischemic stroke patients.

METHODS: The study included 201 ischemic stroke patients, and 217 age- and sex-comparable healthy controls. The quantitative methylation level in the 14 CpG sites of the ERα promoter was measured by pyrosequencing in each participant. Multivariate regression model was used to adjust for stroke traditional risk factors. Stroke subtypes and sex-specific analysis were also conducted.

RESULTS: The results demonstrated that the stroke cases had a lower ERα methylation level than controls in all 14 CpG sites, and site13 and site14 had significant adjusted p-values of 0.035 and 0.026, respectively. Stroke subtypes analysis showed that large-artery atherosclerosis and cardio-embolic subtypes had significantly lower methylation levels than the healthy controls at CpG site5, site9, site12, site13 and site14 with adjusted p = 0.039, 0.009, 0.025, 0.046 and 0.027 respectively. However, the methylation level for the patients with small vessel subtype was not significant. We combined the methylation data from the above five sites for further sex-specific analysis. The results showed that the significant association only existed in women (adjusted p = 0.011), but not in men (adjusted p = 0.300).

CONCLUSIONS: Female stroke cases have lower ERα methylation levels than those in the controls, especially in large-artery and cardio-embolic stroke subtypes. The study implies that women suffering from ischemic stroke of specific subtype may undergo different protective mechanisms to reduce the brain injury.

Differences in Common Genetic Predisposition to Ischemic Stroke by Age and Sex.

Traylor M, Rutten-Jacobs LC, Holliday EG, Malik R, Sudlow C, Rothwell PM, Maguire JM, Koblar SA, Bevan S, Boncoraglio G, Dichgans M, Levi C, Lewis CM, Markus HS. **Stroke 2015 Nov.**

Abstract

BACKGROUND AND PURPOSE: Evidence from epidemiological studies points to differences in factors predisposing to stroke by age and sex. Whether these arise because of different genetic influences remained untested. Here, we use data from 4 genome-wide association data sets to study the relationship between genetic influence on stroke with both age and sex.

METHODS: Using genomic-relatedness-matrix restricted maximum likelihood methods, we performed 4 analyses: (1) we calculated the genetic correlation between groups divided by age and (2) by sex, (3) we calculated the heritability of age-at-stroke-onset, and (4) we evaluated the evidence that heritability of stroke is greater in women than in men.

RESULTS: We found that genetic factors influence age at stroke onset (h(2) [SE]=18.0 [6.8]; P=0.0038), with a trend toward a stronger influence in women (women: h(2) [SE]=21.6 [3.5]; Men: h(2) [SE]=13.9 [2.8]). Although a moderate proportion of genetic factors was shared between sexes (rG [SE]=0.68 [0.16]) and between younger and older cases (rG [SE]=0.70 [0.17]), there was evidence to suggest that there are genetic susceptibility factors that are specific to sex (P=0.037) and to younger or older groups (P=0.056), particularly for women (P=0.0068). Finally, we found a trend toward higher heritability of stroke in women although this was not significantly greater than in men (P=0.084).

CONCLUSIONS: Our results indicate that there are genetic factors that are either unique to or have a different effect between younger and older age groups and between women and men. Performing large, well-powered genome-wide association study analyses in these groups is likely to uncover further associations.

Integrative Mouse and Human Studies Implicate ANGPT1 and ZBTB7C as Susceptibility Genes to Ischemic Injury.

Du R, Zhou J, Lorenzano S, Liu W, Charoenvimolphan N, Qian B, Xu J, Wang J, Zhang X, Wang X, Berndt A, Devan WJ, Valant VJ, Wang J, Furie KL, Rosand J, Rost N, Friedlander RM, Paigen B, Weiss ST. **Stroke 2015 Dec.**

Abstract

BACKGROUND AND PURPOSE: The extent of ischemic injury in response to cerebral ischemia is known to be affected by native vasculature. However, the nonvascular and dynamic vascular responses and their genetic basis are not well understood.

METHODS: We performed a genome-wide association study in 235 mice from 33 inbred strains using the middle cerebral artery occlusion model. Population structure and genetic relatedness were accounted for using the efficient mixed-model association method. Human orthologs to the genes associated with the significant and suggestive single-nucleotide polymorphisms from the mouse strain survey were examined in patients with M1 occlusions admitted with signs and symptoms of acute ischemic stroke.

RESULTS: We identified 4 genome-wide significant and suggestive single-nucleotide polymorphisms to be associated with infarct volume in mice (rs3694965, P=2.17×10(-7); rs31924033, P=5.61×10(-6); rs32249495, P=2.08×10(-7); and rs3677406, P=9.56×10(-6)). rs32249495, which corresponds to angiopoietin-1 (ANGPT1), was also significant in the recessive model in humans, whereas rs1944577, which corresponds to ZBTB7C, was nominally significant in both the additive and dominant genetic models in humans. ZBTB7C was shown to be upregulated in endothelial cells using both in vitro and in vivo models of ischemia.

CONCLUSIONS: Genetic variations of ANGPT1 and ZBTB7C are associated with increased infarct size in both mice and humans. ZBTB7C may modulate the ischemic response via neuronal apoptosis and dynamic collateralization and, in addition to ANGPT1, may serve as potential novel targets for treatments of cerebral ischemia.

CONGRESOS Y REUNIONES DE INTERÉS 2016-2017

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.

European Stroke Organisation Conference, May 10-12, 2016. Barcelona, Spain.

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

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

Canadian Stroke Congress, September 14-17, 2016. Québec City, Québec.

American Society of Human Genetics (ASHG), October 18-22, 2016. Vancouver, Canada.

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

Society for Neuroscience (SFN) Annual Meeting. November 12-16, 2016. San Diego, USA.

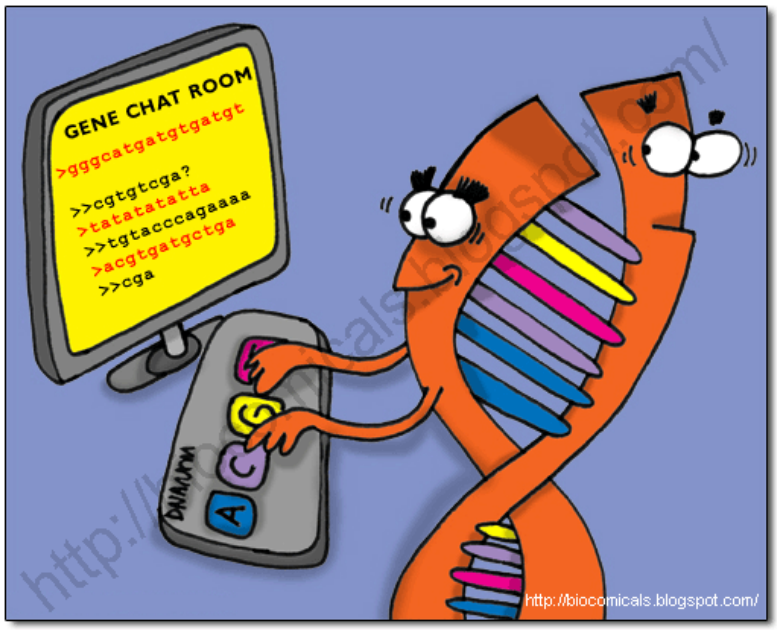
LXVIII Reunión Anual de la Sociedad Española de Neurología, November 2016. Valencia.

GE, GE, GE…

Sugerencias…
mmola@imim.es

Estamos en la web!
www.GeneStroke.com

GENE CHAT ROOM



GeneStroke