NEWSLETTER

GeneStroke | The Spanish Stroke Genetics Consortium

Diciembre 2016

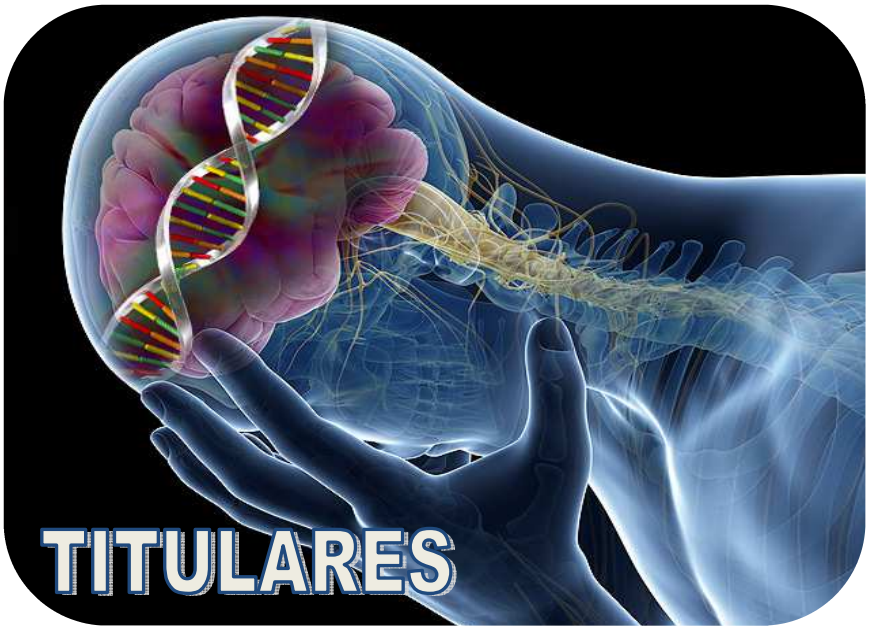
Nº 19

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:

new **Whole exome sequencing analysis reveals TRPV3 as a risk factor for cardioembolic stroke.**

Carrera C, Jiménez-Conde J, Derdak S, Rabionet K, Vives-Bauzá C, Soriano-Tárrega C, Giralt-Steinhauer E, Mola-Caminal M, Diaz-Navarro RM, Tur S, Muiño E, Gallego-Fabrega C, Beltran S, Roquer J, Ruiz A, Sotolongo-Grau O, Krupinski J, Lee JM, Cruchaga C, Delgado P, Malik R, Worrall BB, Seshadri S, Montaner J, Fernández-Cadenas I; Metastroke Consortium, **ISGC Consortium and Genestroke Consortium. Thromb Haemost. 2016 Nov.**

new **Ischemic stroke patients are biologically older than their chronological age.**

Soriano-Tárraga C, Giralt-Steinhauer E, Mola-Caminal M, Vivanco-Hidalgo RM, Ois A, Rodríguez-Campello A, Cuadrado-Godia E, Sayols-Baixeras S, Elosua R, Roquer J, Jiménez-Conde J. **Aging (Albany NY). 2016 Aug**.

new **Identification of additional risk loci for stroke and small vessel disease: a meta-analysis of genome-wideassociation studies.**

Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. Stroke Genetics Network (SiGN). **International Stroke Genetics Consortium (ISGC). Lancet Neurol. 2016 Jun.**

new **Genetic variants in CETP increase risk of intracerebral hemorrhage.**

Anderson CD, Falcone GJ, Phuah CL, Radmanesh F, Brouwers HB, Battey TW, Biffi A, Peloso GM, Liu DJ, Ayres AM, Goldstein JN, Viswanathan A, Greenberg SM, Selim M, Meschia JF, Brown DL, Worrall BB, Silliman SL, Tirschwell DL, Flaherty ML, Kraft P, Jagiella JM, Schmidt H, Hansen BM, Jimenez-Conde J, Giralt-Steinhauer E, Elosua R, Cuadrado-Godia E, Soriano C, van Nieuwenhuizen KM, Klijn CJ, Rannikmae K, Samarasekera N, Salman RA, Sudlow CL, Deary IJ, Morotti A, Pezzini A, Pera J, Urbanik A, Pichler A, Enzinger C, Norrving B, Montaner J, Fernandez-Cadenas I, Delgado P, Roquer J, Lindgren A, Slowik A, Schmidt R, Kidwell CS, Kittner SJ, Waddy SP, Langefeld CD, Abecasis G, Willer CJ, Kathiresan S, Woo D, Rosand J.**Global Lipids Genetics Consortium and International Stroke Genetics Consortium. Ann Neurol. 2016 Nov.**

PROYECTOS GENESTROKE EN ACTIVO

Actualmente tenemos estos proyectos en curso:

new ***Proyecto:*** **GERTRUDIS (Genètica i Epigenètica en la Recuperació i el TRactament sUbagut De l'IctuS)**
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: Pendiente de financiación (PERIS)

new ***Proyecto:*** **CADÓMICA (Estudios de integróMICA en CADASIL con el objetivo de encontrar tratamientos farmacológicos mediante el reposicionamiento de fármacos de forma personalizada)**
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: Pendiente de financiación (PERIS)

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

Proyecto: **EWAL (Estudio de Epigenome Wide Association en Leucoaraiosis)**
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: En fase de análisis

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: En fase de análisis

Proyecto: **miRO (miRNA associated to functional Outcome in Stroke)**
IP: Cristòfol Vives (Hospital Son Espases)
Estado: En fase de análisis

¿Quieres realizar un estudio y necesitas colaboraciones? ¡Envíanos tu propuesta! ¡PARTICIPA!

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: **GODS project (Genetic contribution to functional Outcome and Disability after Stroke)**
Coordinador: Jordi Jiménez Conde (Hospital del Mar).
Estado: En fase de publicación

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: Publicado

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

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 publicación

Proyecto: **GWALA!! (Bases genéticas de la leucoaraiosis)**
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: En fase de publicación

Para solicitar más información sobre los proyectos podéis contactar conmigo

Marina Mola
(mmola@imim.es)

NOVEDADES SOBRE GENÉTICA EN EL ICTUS:

ISGC **Identification of additional risk loci for stroke and small vessel disease: a meta-analysis of genome-wideassociation studies.**

Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. Stroke Genetics Network (SiGN). **International Stroke Genetics Consortium (ISGC).**
Lancet Neurol. 2016 Jun.

Abstract

BACKGROUND: Genetic determinants of stroke, the leading neurological cause of death and disability, are poorly understood and have seldom been explored in the general population. Our aim was to identify additional loci for stroke by doing a meta-analysis of genome-wide association studies.

METHODS: For the discovery sample, we did a genome-wide analysis of common genetic variants associated with incident stroke risk in 18 population-based cohorts comprising 84961 participants, of whom 4348 had stroke. Stroke diagnosis was ascertained and validated by the study investigators. Mean age at stroke ranged from 45·8 years to 76·4 years, and data collection in the studies took place between 1948 and 2013. We did validation analyses for variants yielding a significant association (at p<5 × 10(-6)) with all-stroke, ischaemic stroke, cardioembolic ischaemic stroke, or non-cardioembolic ischaemic stroke in the largest available cross-sectional studies (70 804 participants, of whom 19 816 had stroke). Summary-level results of discovery and follow-up stages were combined using inverse-variance weighted fixed-effects meta-analysis, and in-silico lookups were done in stroke subtypes. For genome-wide significant findings (at p<5 × 10(-8)), we explored associations with additional cerebrovascular phenotypes and did functional experiments using conditional (inducible) deletion of the probable causal gene in mice. We also studied the expression of orthologs of this probable causal gene and its effects on cerebral vasculature in zebrafish mutants.

FINDINGS: We replicated seven of eight known loci associated with risk for ischaemic stroke, and identified a novel locus at chromosome 6p25 (rs12204590, near FOXF2) associated with risk of all-stroke (odds ratio [OR] 1·08, 95% CI 1·05-1·12, p=1·48 × 10(-8); minor allele frequency 21%). The rs12204590 stroke risk allele was also associated with increased MRI-defined burden of white matter hyperintensity-a marker of cerebral small vessel disease-in stroke-free adults (n=21 079; p=0·0025). Consistently, young patients (aged 2-32 years) with segmental deletions of FOXF2 showed an extensive burden of white matter hyperintensity. Deletion of Foxf2 in adult mice resulted in cerebral infarction, reactive gliosis, and microhaemorrhage. The orthologs of FOXF2 in zebrafish (foxf2b and foxf2a) are expressed in brain pericytes and mutant foxf2b(-/-) cerebral vessels show decreased smooth muscle cell and pericyte coverage.

INTERPRETATION: We identified common variants near FOXF2 that are associated with increased stroke susceptibility. Epidemiological and experimental data suggest that FOXF2 mediates this association, potentially via differentiation defects of cerebral vascular mural cells. Further expression studies in appropriate human tissues, and further functional experiments with long follow-up periods are needed to fully understand the underlying mechanisms. approach to stroke prevention. In view of the subtype-specificity of the associations detected, the rich phenotyping data available in the Stroke Genetics Network (SiGN) are likely to be crucial for further genetic discoveries related to ischaemicstroke.

Ischemic stroke patients are biologically older than their chronological age.

Soriano-Tárraga C, Giralt-Steinhauer E, Mola-Caminal M, Vivanco-Hidalgo RM, Ois A, Rodríguez-Campello A, Cuadrado-Godia E, Sayols-Baixeras S, Elosua R, Roquer J, Jiménez-Conde J.

Aging (Albany NY). 2016 Aug.

Abstract

Ischemic stroke is associated with aging. It is possible to predict chronological age by measuring age-related changes in DNA methylation from multiple CpG sites across the genome, known as biological age. The difference between biological age and actual chronological age would indicate an individual's level of aging. Our aim was to determine the biological age of ischemic stroke patients and compare their aging with controls of the same chronological age. A total of 123 individuals, 41 controls and 82 patients with ischemic stroke were paired by chronological age, ranging from 39 to 82 years. Illumina HumanMethylation450 BeadChip array was used to measure DNA methylation in CpG sites in both groups, and biological age was estimated using methylation values of specific CpGs. Ischemic stroke patients were *biologically* an average 2.5 years older than healthy controls (p-value=0.010). Stratified by age tertiles, younger stroke patients (≤57 years old) were biologically older than controls (OR=1.19; 95%CI 1.00-1.41, p-value=0.046). The older groups showed no biological age differences between cases and controls, but were close to reaching the significance level. Ischemic stroke patients are *biologically* older than controls. Biological age should be considered as a potential new biomarker of stroke risk.

Genetic Risk Prediction of Atrial Fibrillation.

Lubitz SA, Yin X, Lin H, Kolek M, Smith JG, Trompet S, Rienstra M, Rost NS, Teixeira P, Almgren P, Anderson CD, Chen LY, Engström G, Ford I, Furie KL, Guo X, Larson MG, Lunetta K, Macfarlane PW, Psaty BM, Soliman EZ, Sotoodehnia N, Stott DJ, Taylor KD, Weng LC, Yao J, Geelhoed B, Verweij N, Siland JE, Kathiresan S, Roselli C, Roden DM, van der Harst P, Darbar D, Jukema JW, Melander O, Rosand J, Rotter JI, Heckbert SR, Ellinor PT, Alonso A, Benjamin EJ; **AFGen Consortium. Circulation. 2016 Oct.**

Abstract

BACKGROUND: Atrial fibrillation (AF) has a substantial genetic basis. Identification of individuals at greatest AF risk could minimize the incidence of cardioembolic stroke

METHODS: To determine whether genetic data can stratify risk for development of AF, we examined associations between AF genetic risk scores and incident AF in five prospective studies comprising 18,919 individuals of European ancestry. We examined associations between AF genetic risk scores and ischemic stroke in a separate study of 509 ischemic stroke cases (202 cardioembolic [40%]) and 3,028 referents. Scores were based on 11 to 719 common variants (≥5%) associated with AF at P-values ranging from $<1x10^{-3}$ to $<1x10^{-8}$ in a prior independent genetic association study.

RESULTS: Incident AF occurred in 1,032 (5.5%) individuals. AF genetic risk scores were associated with new-onset AF after adjusting for clinical risk factors. The pooled hazard ratio for incident AF for the highest versus lowest quartile of genetic risk scores ranged from 1.28 (719 variants; 95%CI, 1.13-1.46; $P=1.5x10^{-4}$) to 1.67 (25 variants; 95%CI, 1.47-1.90; $P=9.3x10^{-15}$). Discrimination of combined clinical and genetic risk scores varied across studies and scores (maximum C statistic, 0.629-0.811; maximum ΔC statistic from clinical score alone, 0.009-0.017). AF genetic risk was associated with stroke in age- and sex-adjusted models. For example, individuals in the highest versus lowest quartile of a 127-variant score had a 2.49-fold increased odds of cardioembolic stroke (95%CI, 1.39-4.58; $P=2.7x10^{-3}$). The effect persisted after excluding individuals (n=70) with known AF (odds ratio, 2.25; 95%CI, 1.20-4.40; P=0.01).

CONCLUSIONS: Comprehensive AF genetic risk scores were associated with incident AF beyond associations for clinical AF risk factors, though offered small improvements in discrimination. AF genetic risk was also associated with cardioembolic stroke in age- and sex-adjusted analyses. Efforts are warranted to determine whether AF genetic risk may improve identification of subclinical AF or help distinguish between stroke mechanisms.

Whole exome sequencing analysis reveals TRPV3 as a risk factor for cardioembolic stroke.

Carrera C, Jiménez-Conde J, Derdak S, Rabionet K, Vives-Bauzá C, Soriano-Tárrega C, Giralt-Steinhauer E, Mola-Caminal M, Diaz-Navarro RM, Tur S, Muiño E, Gallego-Fabrega C, Beltran S, Roquer J, Ruiz A, Sotolongo-Grau O, Krupinski J, Lee JM, Cruchaga C, Delgado P, Malik R, Worrall BB, Seshadri S, Montaner J, Fernández-Cadenas I. Metastroke Consortium, **ISGC Consortium and Genestroke Consortium.**
Thromb Haemost. 2016 Nov.

Abstract

Genetic studies suggest that hundreds of genes associated with stroke remain unidentified. Exome sequencing proves useful for finding new genes associated with stroke. We aimed to find new genetic risk factors for cardioembolic stroke by analysing exome sequence data using new strategies. For discovery, we analysed 42 cardioembolic stroke cases and controls with extreme phenotypes (cohort 1), and for replication, 32 cardioembolic stroke cases and controls (cohort 2) using the SeqCapExome capture kit. We then analysed the replicated genes in two new cohorts that comprised 834 cardioembolic strokes and controls (cohort 3) and 64,373 cardioembolic strokes and controls (cohort 4). Transcriptomic in-silico functional analyses were also performed. We found 26 coding regions with a higher frequency of mutations in cardioembolic strokes after correcting for the number of mutations found in the whole exome of every patient. The TRPV3 gene was associated with cardioembolic stroke after replication of exome sequencing analysis (p-value-discovery: 0.018, p-value-replication: 0.014). The analysis of the TRPV3 gene using polymorphisms in cohort 3 and 4 revealed two polymorphisms associated with cardioembolic stroke in both cohorts, the most significant polymorphism being rs151091899 (p-value: 3.1×10^{-05}; odds ratio: 5.4) in cohort 3. The genotype of one polymorphism of TRPV3 was associated with a differential expression of genes linked to cardiac malformations. In conclusion, new strategies using exome sequence data have revealed TRPV3 as a new gene associated with cardioembolic stroke. This strategy among others might be useful in finding new genes associated with complex genetic diseases.

Genetic variants in CETP increase risk of intracerebral hemorrhage.

Anderson CD, Falcone GJ, Phuah CL, et al. **Global Lipids Genetics Consortium and International Stroke Genetics Consortium.** **Ann Neurol. 2016 Nov.**

Abstract

OBJECTIVE: In observational epidemiologic studies, higher plasma high-density lipoprotein cholesterol (HDL-C) has been associated with increased risk of intracerebral hemorrhage (ICH). DNA sequence variants that decrease cholesteryl ester transfer protein (CETP) gene activity increase plasma HDL-C; as such, medicines that inhibit CETP and raise HDL-C are in clinical development. Here, we test the hypothesis that CETP DNA sequence variants associated with higher HDL-C also increase risk for ICH.

METHODS: We performed 2 candidate-gene analyses of CETP. First, we tested individual CETP variants in a discovery cohort of 1,149 ICH cases and 1,238 controls from 3 studies, followed by replication in 1,625 cases and 1,845 controls from 5 studies. Second, we constructed a genetic risk score comprised of 7 independent variants at the CETP locus and tested this score for association with HDL-C as well as ICH risk.

RESULTS: Twelve variants within CETP demonstrated nominal association with ICH, with the strongest association at the rs173539 locus (odds ratio [OR] = 1.25, standard error [SE] = 0.06, $p = 6.0 \times 10^{-4}$) with no heterogeneity across studies (I^2 = 0%). This association was replicated in patients of European ancestry (p = 0.03). A genetic score of CETP variants found to increase HDL-C by 2.85mg/dl in the Global Lipids Genetics Consortium was strongly associated with ICH risk (OR = 1.86, SE = 0.13, $p = 1.39 \times 10^{-6}$).

INTERPRETATION: Genetic variants in CETP associated with increased HDL-C raise the risk of ICH. Given ongoing therapeutic development in CETP inhibition and other HDL-raising strategies, further exploration of potential adverse cerebrovascular outcomes may be warranted. Ann Neurol 2016;80:730-740.

CONGRESOS Y REUNIONES DE INTERÉS 2017-2018

International Stroke Conference, February 22-24, 2017. Houston, Texas.

International Symposium on Cerebral Blood Flow, Metabolism and Function (Brain), April 1-4, 2017. Berlin, Germany.

American Academy of Neurology Annual Meeting (AAN), April 22-28, 2017. Boston, USA.

European Stroke Organisation Conference, May 16-18, 2017. Prague, Czeck Republic.

26th European Stroke Conference, May 24-26, 2017. Berlin, Germany.

The European Human Genetics Conference, May 27-30, 2017. Copenhagen, Denmark.

Canadian Stroke Congress, September 9-11, 2017. Calgary, Canada.

American Society of Human Genetics (ASHG), October 17-21, 2017. Orlando, USA.

Society for Neuroscience (SFN) Annual Meeting. November 11-15, 2017. Washington DC, USA.

LXVIII Reunión Anual de la Sociedad Española de Neurología, November 2017.

11th FENS Forum of Neuroscience, July 7-11, 2018. Berlin, Germany.

11th World Stroke Congress, October 17-20, 2018. Montreal, Canada.

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

GeneStroke