NEWSLETTER

GeneStroke | The Spanish Stroke Genetics Consortium

Diciembre 2013

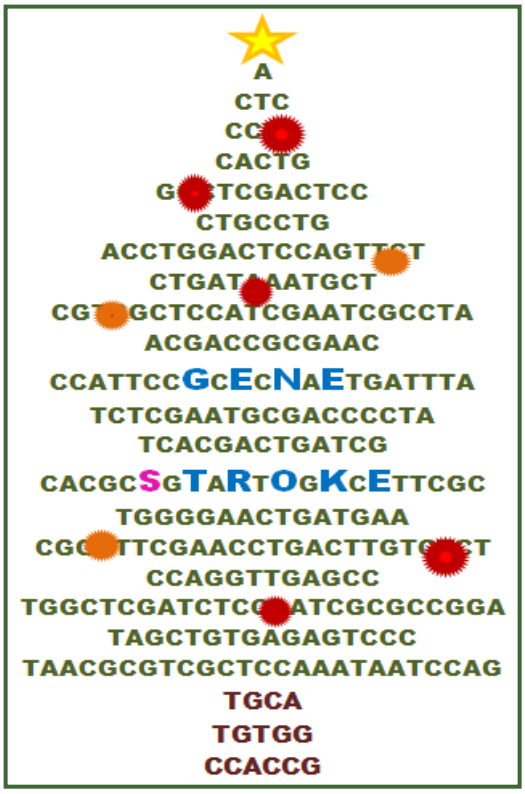
Nº 9

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:



TITULARES

Desde GeneStroke os deseamos FELICES FIESTAS!

Últimas publicaciones con participación de *GeneStroke:*

Stroke Genetics Network (SiGN) Study: Design and Rationale for a Genome-Wide Association Study of IschemicStroke Subtypes.
Meschia JF, Arnett DK, Ay H, Brown RD Jr, Benavente OR, Cole JW, de Bakker PI, Dichgans M, Doheny KF, Fornage M, Grewal RP, Gwinn K, Jern C, **Conde JJ**, Johnson JA, Jood K, Laurie CC, Lee JM, Lindgren A, Markus HS, McArdle PF, McClure LA, Mitchell BD, Schmidt R, Rexrode KM, Rich SS, Rosand J, Rothwell PM, Rundek T, Sacco RL, Sharma P, Shuldiner AR, Slowik A, Wassertheil-Smoller S, Sudlow C, Thijs VN, Woo D, Worrall BB, Wu O, Kittner SJ; on behalf of the **NINDS SiGN Study.** Stroke 2013 Sep 12.

Exploring the genetic basis of stroke. Spanish stroke genetics consortium.
Giralt-Steinhauer E, Jiménez-Conde J, Soriano Tárraga C, Mola M, Rodríguez-Campello A, Cuadrado-Godia E, Ois A, Fernández-Cádenas I, Carrera C,Montaner J, Díaz Navarro RM, Vives-Bauzá C, Roquer J. Neurología 2013 June 4.

Genes involved in hemorrhagic transformations that follow recombinant t-PA treatment in stroke patients.
Fernandez-Cadenas I, Rio-Espinola AD, Domingues-Montanari S, **Montaner J** et al. Pharmacogenomics. 2013 April.

DNA Isolation Method is a Source of Global DNA Methylation Variability Measured with LUMA. Experimental analysis and a systematic review.
Carolina Soriano-Tárraga, Jordi Jiménez-Conde, Eva Giralt-Steinhauer, Ángel Ois, Ana Rodríguez-Campello, Elisa Cuadrado-Godia, Israel Fernández-Cadenas, Joan Montaner, Gavin Lucas, Roberto Elosua and Jaume Roquer. PLOS ONE. 2013 April 9.

PROYECTOS GENESTROKE EN ACTIVO

Actualmente tenemos estos proyectos en curso:

Proyecto: **Replicación CONIC**
IP: Sophie Domingues-Montanari (Vall d'Hebron Institut de Recerca)
Estado: Terminado. En fase de publicación.

Proyecto: **GLAM-Stroke** (GLobAl Methylation of ischemic stroke)
IP: Carolina Soriano (Hospital del Mar)
Estado: Terminado. En fase de publicación

¿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 imputación con 1000 genomas

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)
IP: Jordi Jiménez Conde (Hospital del Mar)
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: Financiado. Pendiente de genotipado

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: Pendiente de financiación

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, contactar con:

Marina Mola
(mmola@imim.es)

NOVEDADES SOBRE GENÉTICA EN EL ICTUS:

NOTCH3 Variants and Risk of Ischemic Stroke.

Ross OA, Soto-Ortolaza AI, Heckman MG, Verbeeck C, Serie DJ, Rayaprolu S, Rich SS, Nalls MA, Singleton A, Guerreiro R, Kinsella E, Wszolek ZK, Brott TG, Brown RD Jr, Worrall BB, Meschia JF.
PLoS One. 2013 Sep 23.

Abstract

BACKGROUND: Mutations within the NOTCH3 gene cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL mutations appear to be restricted to the first twenty-four exons, resulting in the gain or loss of a cysteine amino acid. The role of other exonic NOTCH3 variation not involving cysteine residues and mutations in exons 25-33 in ischemic stroke remains unresolved.

METHODS: All 33 exons of NOTCH3 were sequenced in 269 Caucasian probands from the Siblings With Ischemic Stroke Study (SWISS), a 70-center North American affected sibling pair study and 95 healthy Caucasian control subjects. Variants identified by sequencing in the SWISS probands were then tested for association with ischemic stroke using US Caucasian controls collected at the Mayo Clinic (n=654), and further assessed in a Caucasian (n=802) and African American (n=298) patient-control series collected through the Ischemic Stroke Genetics Study (ISGS).

RESULTS: Sequencing of the 269 SWISS probands identified one (0.4%) with small vessel type stroke carrying a known CADASIL mutation (p.R558C; Exon 11). Of the 19 common NOTCH3 variants identified, the only variant significantly associated with ischemic stroke after multiple testing adjustment was p.R1560P (rs78501403; Exon 25) in the combined SWISS and ISGS Caucasian series (Odds Ratio [OR] 0.50, P=0.0022) where presence of the minor allele was protective against ischemic stroke. Although only significant prior to adjustment for multiple testing, p.T101T (rs3815188; Exon 3) was associated with an increased risk of small-vessel stroke (OR: 1.56, P=0.008) and p.P380P (rs61749020; Exon 7) was associated with decreased risk of large-vessel stroke (OR: 0.35, P=0.047) in Caucasians. No significant associations were observed in the small African American series.

CONCLUSION: Cysteine-affecting NOTCH3 mutations are rare in patients with typical ischemic stroke, however our observation that common NOTCH3 variants may be associated with risk of ischemic stroke warrants further study.

Shared Genetic Susceptibility to Ischemic Stroke and Coronary Artery Disease: A Genome-Wide Analysis of Common Variants.

Dichgans M, Malik R, König IR, Rosand J et al. The METASTROKE Consortium; the CARDIoGRAM consortium; the C4D consortium; the **International Stroke Genetics Consortium**. **Stroke**. 2013 Nov 21.

Abstract

BACKGROUND AND PURPOSE: Ischemic stroke (IS) and coronary artery disease (CAD) share several risk factors and each has a substantial heritability. We conducted a genome-wide analysis to evaluate the extent of shared genetic determination of the two diseases.

METHODS: Genome-wide association data were obtained from the METASTROKE, Coronary Artery Disease Genome-wide Replication and Meta-analysis (CARDIoGRAM), and Coronary Artery Disease (C4D) Genetics consortia. We first analyzed common variants reaching a nominal threshold of significance (P<0.01) for CAD for their association with IS and vice versa. We then examined specific overlap across phenotypes for variants that reached a high threshold of significance. Finally, we conducted a joint meta-analysis on the combined phenotype of IS or CAD. Corresponding analyses were performed restricted to the 2167 individuals with the ischemic large artery stroke (LAS) subtype.

RESULTS: Common variants associated with CAD at P<0.01 were associated with a significant excess risk for IS and for LAS and vice versa. Among the 42 known genome-wide significant loci for CAD, 3 and 5 loci were significantly associated with IS and LAS, respectively. In the joint meta-analyses, 15 loci passed genome-wide significance ($P<5\times10^{-8}$) for the combined phenotype of IS or CAD and 17 loci passed genome-wide significance for LAS or CAD. Because these loci had prior evidence for genome-wide significance for CAD, we specifically analyzed the respective signals for IS and LAS and found evidence for association at chr12q24/SH2B3 ($P_{IS}=1.62\times10^{-7}$) and ABO ($P_{IS}=2.6\times10^{-4}$), as well as at HDAC9 ($P_{LAS}=2.32\times10^{-12}$), 9p21 ($P_{LAS}=3.70\times10^{-6}$), RAI1-PEMT-RASD1 ($P_{LAS}=2.69\times10^{-5}$), EDNRA ($P_{LAS}=7.29\times10^{-4}$), and CYP17A1-CNNM2-NT5C2 ($P_{LAS}=4.9\times10^{-4}$).

CONCLUSIONS: Our results demonstrate substantial overlap in the genetic risk of IS and particularly the LAS subtype with CAD.

Association of E-selectin Gene Polymorphism (S128R) with Ischemic Stroke and Stroke Subtypes.

Roy S, Das S, Danaboina R, Sharma V, Kaul S, Jyothy A, Munshi A. **Inflammation**. 2013 Nov 19.

Abstract

E-selectin is an important inflammatory cytokine involved in the pathogenesis of various diseases such as atherosclerosis and stroke. We investigated the association of E-selectin gene polymorphism (S128R) with ischemic stroke and its subtypes. We studied 610 patients with ischemic stroke and 610 age- and sex-matched healthy controls. The ischemic stroke was classified according to Trial of Org10172 in Acute Stroke Treatment (TOAST). E-selectin gene polymorphism (S128R) was determined by polymerase chain reaction-restriction fragment length polymorphism technique. We found statistically significant difference in the genotypic distribution between patients and controls (for AC vs. AA, $\chi^2 = 49.5$; $p < 0.001$, odds ratio = 5.47(95 % CI, 3.25-9.21). A significant difference was observed in the frequency of C and A alleles in patients and controls (for C vs. A, $\chi^2 = 47.4$; $p < 0.001$, odds ratio = 5.13 (95 % CI, 3.06-8.57). Multiple logistic regression analysis revealed that the most predictive risk factor for stroke was AC genotype (adjusted odds ratio = 1.450 (95 % CI, 1.23-2.75) and p = 0.001), hypertension, smoking, and diabetes (p = 0.001 in each case). We also found a significant association of AC genotype with intracranial large artery atherosclerosis ($p < 0.01$, odds ratio = 9.37, (95 % CI, 5.31-16.5) and small artery occlusion ($p < 0.0001$, odds ratio = 9.81 (95 % CI, 4.94-19.4). Our results indicate that the individuals bearing AC genotype of E-selectin gene polymorphism (S128R) are more prone to stroke than AA genotype.

The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study protocol.

Woo D, Rosand J, Kidwell C, McCauley JL, Osborne J, Brown MW, West SE, Rademacher EW, Waddy S, Roberts JN, Koch S, Gonzales NR, Sung G, Kittner SJ, Birnbaum L, Frankel M, Testai FD, Hall CE, Elkind MS, Flaherty M, Coull B, Chong JY, Warwick T, Malkoff M, James ML, Ali LK, Worrall BB, Jones F, Watson T, Leonard A, Martinez R, Sacco RI, Langefeld CD. **Stroke**. 2013 Oct.

Abstract

BACKGROUND AND PURPOSE: Epidemiological studies of intracerebral hemorrhage (ICH) have consistently demonstrated variation in incidence, location, age at presentation, and outcomes among non-Hispanic white, black, and Hispanic populations. We report here the design and methods for this large, prospective, multi-center case-control study of ICH.

METHODS: The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study is a multi-center, prospective case-control study of ICH. Cases are identified by hot-pursuit and enrolled using standard phenotype and risk factor information and include neuroimaging and blood sample collection. Controls are centrally identified by random digit dialing to match cases by age (±5 years), race, ethnicity, sex, and metropolitan region.

RESULTS: As of March 22, 2013, 1655 cases of ICH had been recruited into the study, which is 101.5% of the target for that date, and 851 controls had been recruited, which is 67.2% of the target for that date (1267 controls) for a total of 2506 subjects, which is 86.5% of the target for that date (2897 subjects). Of the 1655 cases enrolled, 1640 cases had the case interview entered into the database, of which 628 (38%) were non-Hispanic black, 458 (28%) were non-Hispanic white, and 554 (34%) were Hispanic. Of the 1197 cases with imaging submitted, 876 (73.2%) had a 24 hour follow-up CT available. In addition to CT imaging, 607 cases have had MRI evaluation.

CONCLUSIONS: The ERICH study is a large, case-control study of ICH with particular emphasis on recruitment of minority populations for the identification of genetic and epidemiological risk factors for ICH and outcomes after ICH.

Two Novel Susceptibility SNPs for Ischemic Stroke Using Exome Sequencing in Chinese Han Population.

Zhang Y, Tong Y, Zhang Y, Ding H, Zhang H, Geng Y, Zhang R, Ke Y, Han J, Yan Z, Zhou L, Wu T, Hu FB, Wang D, Cheng J. **Molecular Neurobiology.** 2013 Oct 10.

Abstract

Genome-wide association studies (GWAS) of ischemic stroke (IS) have been performed on several cohorts of Caucasian or African population and Japanese, resulting in somewhat inconsistent conclusion. We aimed to identify susceptibility loci for IS by exome sequencing in a Chinese Han population. Exome sequencing was used to screen susceptibility loci among 100 cases and 100 matched controls. Significant SNPs from the first stage were verified in up to 3,554 participants from three hospital-based case-control studies. In the initial exome sequencing analysis, rs10489177 in c1orf156 gene located on chromosome 1q24 ($p < 1 \times 10^{-8}$) and rs17118 in XYLB gene located on chromosome 3p21 ($p < 1 \times 10^{-6}$) were found to be significantly associated with IS. In the following validation stage, significantly increased odds ratios were observed in individuals with rs10489177 GG (OR = 2.02, 95 % CI = 1.35-3.03) or rs17118 AA genotype (OR = 1.50, 95 % CI = 1.17-1.91). The rs10489177 GG genotype was associated with significantly increased risk for IS in individuals without hypertension (OR = 2.78, 95 % CI = 1.59-4.86) and in individuals without diabetes (OR = 1.93, 95 % CI = 1.27-2.94). In contrast, the rs17118 AA genotype may significantly increase the risk for IS, particularly for individuals with hypertension (OR = 1.73, 95 % CI = 1.08-2.78) and for individuals without diabetes (OR = 1.52, 95 % CI = 1.17-1.98) or non-smoker (OR = 1.59, 95 % CI = 1.16-2.19). Collectively, our study identified two novel loci (rs17118 and rs10489177) which were associated with an increased risk for IS in Chinese Han populations. Further studies are needed to confirm these associations in other populations and elucidate the biological mechanisms underlying the observed associations.

REUNIÓN ANUAL GeneStroke

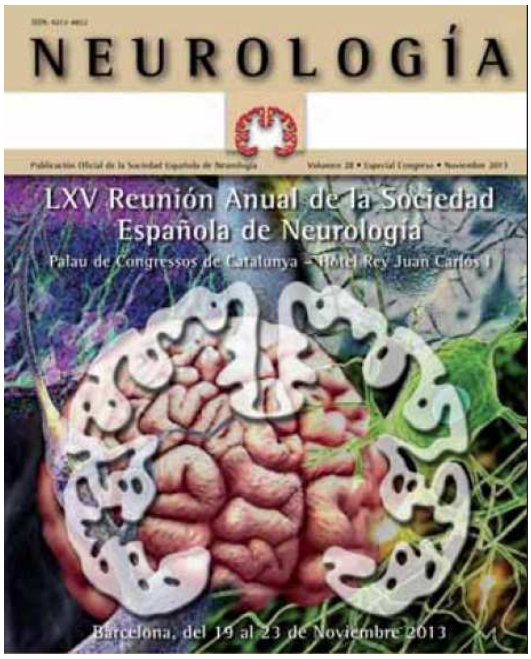
22 Noviembre 2013 Barcelona

LXV Reunión Anual SEN

La **Reunión Anual de GeneStroke** se celebró el pasado 22 de Noviembre en el ámbito de la SEN en Barcelona, donde también se presentaron un total de 5 comunicaciones.

Se presentaron los actuales proyectos del consorcio y se animó a los asistentes a participar activamente en la propuesta de nuevos proyectos, así como en la recogida de muestras de pacientes.

¡¡Gracias a los asistentes!!



Seminario — Sala Marenostrum A — Hotel Juan Carlos I

REUNIÓN DEL CONSORCIO ESPAÑOL PARA EL ESTUDIO GENÉTICO DEL ICTUS (CONSORCIO GENESTROKE)

16.00-18.00
Moderadores:
Dr. Israel Fernandez
Fundació per a Docència i Recerca Mútua Terrassa. Barcelona
Dr. Jordi Jimenez Conde
Unidad de Ictus, Servicio de Neurología, NEUVAS IMIM. Hospital del Mar. Barcelona
Dr. Jerzy Krupinski
Servicio de Neurología. Hospital Univ. Mútua Terrassa. Barcelona

16.00-16.15
Presentación consorcio Genestroke
Dr. Israel Fernandez y Dr. Jordi Jimenez Conde

16.15-16.45
Riesgo genético en la aparición de transformaciones hemorrágicas post-tPA. Analísis de genoma completo mediante GWAs
Dra. Caty Carrera
Laboratorio de Investigación Neurovascular
Hospital Universitari Vall d'Hebron. Barcelona

16.45-17.15
Exome sequencing: nuevas expectativas para el estudio genético del ictus
Dra. Marina Mola
Unidad de Neurología Hospital del Mar. Barcelona

CONGRESOS Y REUNIONES DE INTERÉS 2013-2014

International Stroke Conference, February 12-14, 2014. San Diego, U.S.

American Academy of Neurology Annual Meeting (AAN), April 26, 2014. Philadelphia.

23 European Stroke Conference, May 6-9, 2014. Nice, France.

The European Human Genetics Conference, May 31-June 3, 2014. Milan, Italy.

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. Barcelona.

XXII World Congress of Neurology, October 31- November 5, 2015. Santiago, Chile.

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

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