NEWSLETTER

Septiembre 2012

Nº 4

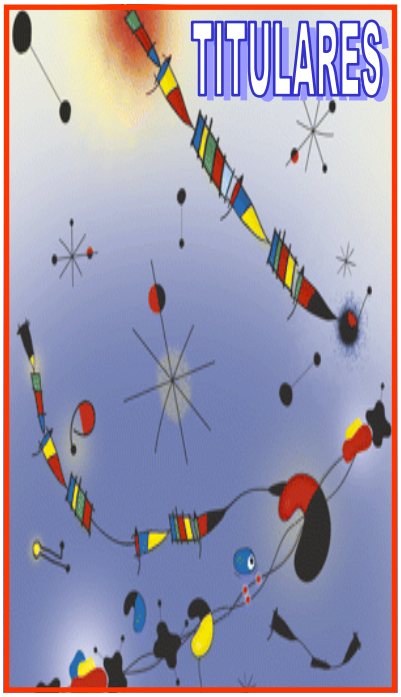
GeneStroke | The Spanish Stroke Genetics Consortium

Estimados compañeros

Os enviamos la Newsletter del consorcio GeneStroke, donde esperamos encontrareis información de vuestro interés, sobre las novedades del consorcio y de la genética en el ictus.

Equipo GeneStroke
www.GeneStroke.com

Contenido:



REUNIÓN ANUAL GENESTROKE

SOCIEDAD ESPAÑOLA DE NEUROLOGIA

SEN 2012 BARCELONA

22 de Noviembre 2012

¡¡¡Os esperamos a todos!!!

El Consorcio pone a vuestra disposición el *Servicio de extracción de DNA* y la participación en la *Colección de muestras Genestroke*.

OFERTA ANTICRISIS

EXTRACCIÓN DNA GRATIS

Publicaciones con participación de *Genestroke:*

Burden of Risk Alleles for Hypertension Increases Risk of Intracerebral Hemorrhage.
Falcone GJ, Biffi A, Devan WJ, Jagiella JM, Schmidt H, Kissela B, Hansen BM, **Jimenez-Conde J, Giralt-Steinhauer E, Elosua R, Cuadrado-Godia E, Soriano C,** Ayres AM, Schwab K, Pera J, Urbanik A, Rost NS, Goldstein JN, Viswanathan A, Pichler A, Enzinger C, Norrving B, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, **Montaner J, Fernandez-Cadenas I,** Delgado P, Broderick JP, Greenberg SM, **Roquer J**, Lindgren A, Slowik A, Schmidt R, Flaherty ML, Kleindorfer DO, Langefeld CD, Woo D, Rosand J; on behalf of the International Stroke Genetics Consortium. *Stroke. (2012)*

Role of the MMP9 gene in hemorrhagic transformations after t-PA treatment in stroke patients.
I. Fernández-Cadenas PhD; A. del Río-Espínola PhD; C. Carrera; S. Domingues-Montanari PhD; M. Mendióroz MD, PhD; P. Delgado MD, PhD; A. Rosell PhD; M. Ribó MD, PhD; D. Giralt; M. Quintana; M. Castellanos MD, PhD; V. Obach MD, PhD; S. Martínez MD, PhD; M.M. Freijo MD, J. Jiménez-Conde MD, PhD; J. Roquer MD, PhD; J. Martí-Fábregas MD, PhD; CA. Molina MD, PhD; J. Álvarez-Sabín MD, PhD; J. Montaner MD, PhD. *Stroke (2012)*

***TTC7B* emerges as a novel risk factor for ischemic stroke through the convergence of several genome-wide approaches.**
Krug, Tiago; Gabriel, João Paulo; Taipa, Ricardo; Fonseca, Maria B.; Domingues-Montanari, Sophie; Fernández Cadenas, Israel; Manso, Helena; Gouveia, Liliana; Sobral, João; Albergaria, Isabel; Gaspar, Gisela; Jiménez-Conde, Jordi; Rabionet, Raquel; Ferro, José; Montaner, Joan; Vicente, Astrid; Silva, Mário Rui; Matos, Ilda; Lopes, Gabriela; Oliveira, Sofia,. *Journal of Cerebral Blood Flow & Metabolism* (2012)

PROYECTOS GENESTROKE EN ACTIVO

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

Actualmente tenemos estos proyectos en curso:

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

Proyecto: **RICAD**
IP: Gavin Lucas (grupo de Investigación Cerebrovascular del Hospital del Mar)
Estado: Terminado. 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: Pendiente de resultados de genotipación.

Proyecto: **GWAs GenotPA**
IP: Israel Cadenas (Hospital Vall d'Hebron)
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: Se ha comenzado a genotipar las muestras. Pendiente de comenzar la secuenciación del exoma.

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

Proyecto: **GRECAS Project (**Genotyping Risk and Efficacy of Clopidogrel or Aspirin following Stroke)
IP: Israel Cadenas (Hospital Vall d'Hebron)
Estado: Fase de Replicación. Reclutamiento de pacientes.

Para solicitar más información sobre los proyectos, contactar con:

Carolina Soriano
(csoriano@imim.es)

Marina Mola
(mmola@imim.es)

NOVEDADES SOBRE GENÉTICA y EPIGENÉTICA EN EL ICTUS:

Common variants at 6p21.1 are associated with large artery atherosclerotic stroke.

Holliday EG, Maguire JM, Evans TJ, Koblar SA, Jannes J, Sturm JW, Hankey GJ, Baker R, Golledge J, Parsons MW, Malik R, McEvoy M, Biros E, Lewis MD, Lincz LF, Peel R, Oldmeadow C, Smith W, Moscato P, Barlera S, Bevan S, Bis JC, Boerwinkle E, Boncoraglio GB, Brott TG, Brown RD Jr, Cheng YC, Cole JW, Cotlarciuc I, Devan WJ, Fornage M, Furie KL, Grétarsdóttir S, Gschwendtner A, Ikram MA, Longstreth WT Jr, Meschia JF, Mitchell BD, Mosley TH, Nalls MA, Parati EA, Psaty BM, Sharma P, Stefansson K, Thorleifsson G, Thorsteinsdottir U, Traylor M, Verhaaren BF, Wiggins KL, Worrall BB; The Australian **Stroke** Genetics Collaborative; The International **Stroke** Genetics Consortium; The Wellcome Trust Case Control Consortium 2, Sudlow C, Rothwell PM, Farrall M, Dichgans M, Rosand J, Markus HS, Scott RJ, Levi C, Attia J. **Nat Genet**. 2012

Abstract

Genome-wide association studies (GWAS) have not consistently detected replicable genetic risk factors for ischemic stroke, potentially due to etiological heterogeneity of this trait. We performed GWAS of ischemic stroke and a major ischemic stroke subtype (large artery atherosclerosis, LAA) using 1,162 ischemic stroke cases (including 421 LAA cases) and 1,244 population controls from Australia. Evidence for a genetic influence on ischemic stroke risk was detected, but this influence was higher and more significant for the LAA subtype. We identified a new LAA susceptibility locus on chromosome 6p21.1 (rs556621: odds ratio (OR) = 1.62, P = 3.9 × 10(-8)) and replicated this association in 1,715 LAA cases and 52,695 population controls from 10 independent population cohorts (meta-analysis replication OR = 1.15, P = 3.9 × 10(-4); discovery and replication combined OR = 1.21, P = 4.7 × 10(-8)). This study identifies a genetic risk locus for LAA and shows how analyzing etiological subtypes may better identify genetic risk alleles for ischemic stroke.

Genetic variation in MDR1, LPL and eNOS genes and the response to atorvastatin treatment in ischemic stroke.

Munshi A. **Hum Genet.** 2012

Abstract

Statins reduce the risk of cardiovascular events by lowering the blood cholesterol. Many genes involved in the pharmacodynamic pathway of statins have been part of pharmacogenetic research in patients with hypercholesterolemia, with an emphasis on genes involved in the cholesterol pathway. The present study was carried out with an aim to evaluate the association between the genetic variants of lipoprotein lipase gene [HindIII (+/+)/HindIII (-/-)], multiple drug resistance gene (C3435T) and endothelial nitric oxide synthase gene (4a/4b) with clinical outcome including an increased risk of recurrent stroke or death in ischemic stroke patients on atorvastatin therapy. 525 stroke patients and 500 healthy controls were involved in the study. Follow-up telephone interviews were conducted with patients post-event to determine stroke outcome. Blood samples were collected and genotypes determined by polymerase chain reaction-restriction digestion technique. A significant association of MDR1 and LPL gene variants with bad outcome in stroke patients on atorvastatin therapy was found. However, there was no significant association of 27 bp VNTR polymorphism of eNOS gene with outcome. MDR analysis was carried out to analyze gene-gene interaction involving these gene variants contributing to clinical outcome of patients on stratin therapy but no significant interaction between these variants was observed. In conclusion the individuals with HindIII (-/-) genotype of LPL and CC genotype of MDR1 gene would benefit more from atorvastatin therapy.

Burden of isk Alleles for Hypertension Increases Risk of Intracerebral Hemorrhage.

Falcone GJ, Biffi A, Devan WJ, Jagiella JM, Schmidt H, Kissela B, Hansen BM, **Jimenez-Conde J, Giralt-Steinhauer E, Elosua R, Cuadrado-Godia E, Soriano C**, Ayres AM, Schwab K, Pera J, Urbanik A, Rost NS, Goldstein JN, Viswanathan A, Pichler A, Enzinger C, Norrving B, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, **Montaner J, Fernandez-Cadenas I**, Delgado P, Broderick JP, Greenberg SM, **Roquer J**, Lindgren A, Slowik A, Schmidt R, Flaherty ML, Kleindorfer DO, Langefeld CD, Woo D, Rosand J; on behalf of the International Stroke Genetics Consortium**. Stroke.** 2012

Abstract

BACKGROUND AND PURPOSE: Genetic variation influences risk of intracerebral hemorrhage (ICH). Hypertension (HTN) is a potent risk factor for ICH and several common genetic variants (single nucleotide polymorphisms [SNPs]) associated with blood pressure levels have been identified. We sought to determine whether the cumulative burden of blood pressure-related SNPs is associated with risk of ICH and pre-ICH diagnosis of HTN.

METHODS: We conducted a prospective multicenter case-control study in 2272 subjects of European ancestry (1025 cases and 1247 control subjects). Thirty-nine SNPs reported to be associated with blood pressure levels were identified from the National Human Genome Research Institute genome-wide association study catalog. Single-SNP association analyses were performed for the outcomes ICH and pre-ICH HTN. Subsequently, weighted and unweighted genetic risk scores were constructed using these SNPs and entered as the independent variable in logistic regression models with ICH and pre-ICH HTN as the dependent variables.

RESULTS: No single SNP was associated with either ICH or pre-ICH HTN. The blood pressure-based unweighted genetic risk score was associated with risk of ICH (OR, 1.11; 95% CI, 1.02-1.21; P=0.01) and the subset of ICH in deep regions (OR, 1.18; 95% CI, 1.07-1.30; P=0.001), but not with the subset of lobar ICH. The score was associated with a history of HTN among control subjects (OR, 1.17; 95% CI, 1.04-1.31; P=0.009) and ICH cases (OR, 1.15; 95% CI, 1.01-1.31; P=0.04). Similar results were obtained when using a weighted score.

CONCLUSIONS: Increasing numbers of high blood pressure-related alleles are associated with increased risk of deep ICH as well as with clinically identified HTN.

DNA methylation profiling in the clinic: applications and challenges.

Heyn H, Esteller M. **Nat Rev Genet.** 2012

Abstract

Knowledge of epigenetic alterations in disease is rapidly increasing owing to the development of genome-wide techniques for their identification. The ever-growing number of genes that show epigenetic alterations in disease emphasizes the crucial role of these epigenetic alterations - particularly DNA methylation - for future diagnosis, prognosis and prediction of response to therapies. This Review focuses on epigenetic profiling, which has started to be of clinical value in cancer and may in the future be extended to other diseases, such as neurological and autoimmune disorders.

ESPECIAL

Encyclopedia of DNA Elements

An integrated encyclopedia of DNA elements in the human genome.
The ENCODE Project Consortium. **Nature.** 2012

Abstract
The human genome encodes the blueprint of life, but the function of the vast majority of its nearly three billion bases is unknown. The Encyclopedia of DNA Elements (ENCODE) project has systematically mapped regions of transcription, transcription factor association, chromatin structure and histone modification. These data enabled us to assign biochemical functions for 80% of the genome, in particular outside of the well-studied protein-coding regions. Many discovered candidate regulatory elements are physically associated with one another and with expressed genes, providing new insights into the mechanisms of gene regulation. The newly identified elements also show a statistical correspondence to sequence variants linked to human disease, and can thereby guide interpretation of this variation. Overall, the project provides new insights into the organization and regulation of our genes and genome, and is an expansive resource of functional annotations for biomedical research.

Landscape of transcription in human cells.
Djebali S, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, Tanzer A, Lagarde J, Lin W, Schlesinger F, Xue C, Marinov GK, Khatun J, Williams BA, Zaleski C, Rozowsky J, Röder M, Kokocinski F, Abdelhamid RF, Alioto T, Antoshechkin I, Baer MT, Bar NS, Batut P, Bell K, Bell I, Chakrabortty S, Chen X, Chrast J, Curado J, Derrien T, Drenkow J, Dumais E, Dumais J, Duttagupta R, Falconnet E, Fastuca M, Fejes-Toth K, Ferreira P, Foissac S, Fullwood MJ, Gao H, Gonzalez D, Gordon A, Gunawardena H, Howald C, Jha S, Johnson R, Kapranov P, King B, Kingswood C, Luo OJ, Park E, Persaud K, Preall JB, Ribeca P, Risk B, Robyr D, Sammeth M, Schaffer L, See LH, Shahab A, Skancke J, Suzuki AM, Takahashi H, Tilgner H, Trout D, Walters N, Wang H, Wrobel J, Yu Y, Ruan X, Hayashizaki Y, Harrow J, Gerstein M, Hubbard T, Reymond A, Antonarakis SE, Hannon G, Giddings MC, Ruan Y, Wold B, Carninci P, Guigó R, Gingeras TR. **Nature.** 2012

Abstract
Eukaryotic cells make many types of primary and processed RNAs that are found either in specific subcellular compartments or throughout the cells. A complete catalogue of these RNAs is not yet available and their characteristic subcellular localizations are also poorly understood. Because RNA represents the direct output of the genetic information encoded by genomes and a significant proportion of a cell's regulatory capabilities are focused on its synthesis, processing, transport, modification and translation, the generation of such a catalogue is crucial for understanding genome function. Here we report evidence that three-quarters of the human genome is capable of being transcribed, as well as observations about the range and levels of expression, localization, processing fates, regulatory regions and modifications of almost all currently annotated and thousands of previously unannotated RNAs. These observations, taken together, prompt a redefinition of the concept of a gene.

CONGRESOS Y REUNIONES DE INTERÉS 2012-2013

3rd Canadian Stroke Congress, September 29-October 2nd, 2012. Calgary, Alberta.

8th World Stroke Congress, October 10-13, 2012. Brasilia, Brazil.

Society for Neuroscience (SFN) Annual Meeting: Neuroscience 2012, October 13-17, 2012. New Orleans, USA.

American Society of Human Genetics (ASHG) 62nd Annual Meeting, November 6-10, 2012. San Francisco, USA.

SEN 2012 - LXIV Reunión Anual de la Sociedad Española de Neurología, 20 al 24 de Noviembre de 2012. Barcelona.

International Stroke Conference, Febrary 6-8, 2013. Honolulu, Hawaii, USA

22nd European stroke conference, May 28-31, 2013. London, UK.

23 rd Meeting of European Neurological Society, June 8-11, 2013. Barcelona, Spain.

The European Human Genetics Conference, June 8-11, 2013. Paris, France.

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

GE, GE, GE…

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

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