NEWSLETTER

Enero 2012

GeneStroke | The Spanish Stroke Genetics Consortium

Estimados compañeros

Os enviamos la segunda 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:

GODS Project, Genetic contribution to functional Outcome and Disability after Stroke. **Concedido el proyecto presentado a *La Marató de TV3*.** Proyecto coordinado en el que participa el consorcio tanto en la fase de descubrimiento como de replicación.
(Coordinador: Jordi Jiménez Conde).

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

Más información en www.genestroke.com o contactad con *csoriano@genestroke.com*

Publicaciones con participación de *Genestroke:*

Variants at APOE influence risk of deep and lobar intracerebral hemorrhage.

Biffi A, Sonni A, Anderson CD, Kissela B, Jagiella JM, Schmidt H, Jimenez-Conde J, Hansen BM, Fernandez-Cadenas I, Cortellini L, Ayres A, Schwab K, Juchniewicz K, Urbanik A, Rost NS, Viswanathan A, Seifert-Held T, Stoegerer EM, Tomás M, Rabionet R, Estivill X, Brown DL, Silliman SL, Selim M, Worrall BB, Meschia JF, Montaner J, Lindgren A, Roquer J, Schmidt R, Greenberg SM, Slowik A, Broderick JP, Woo D, Rosand J; International Stroke Genetics Consortium. Ann Neurol. 2010 Dec;68(6):934-43.

APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study.

Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, Jimenez-Conde J, Pires CR, Ayres AM, Schwab K, Cortellini L, Pera J, Urbanik A, Romero JM, Rost NS, Goldstein JN, Viswanathan A, Pichler A, Enzinger C, Rabionet R, Norrving B, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, Broderick JP, Greenberg SM, Roquer J, Lindgren A, Slowik A, Schmidt R, Woo D, Rosand J; on behalf of the International Stroke Genetics Consortium. *Lancet Neurol.* 2011 Aug;10(8):702-709.

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)*

PROYECTOS GENESTROKE EN ACTIVO

Actualmente tenemos estos proyectos en curso:

Propuestas de proyectos!
¿Necesitas muestras?
¡¡PARTIPIPAD!!

Proyecto: **Replicación CONIC**
IP: Sophie Domingues-Montanari (Hospital Vall d'Hebron)
Estado: Se han genotipado y esta en fase de análisis.

Proyecto: **RICAD**
IP: Gavin Lucas (grupo de Investigación Cerebrovascular del Hospital del Mar)
Estado: Se han genotipado y esta en fase de análisis.

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 comenzar la genotipación de las muestras.

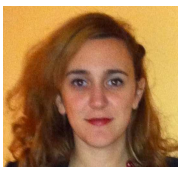
Proyecto: **GWAs GenotPA**
IP: Israel Cadenas (Hospital Vall d'Hebron)
Estado: En la fase inicial, este año se espera tener los resultados del GWAs.

Proyecto: **GODS project** (Genetic contribution to functional Outcome and Disability after Stroke)
IP: Jordi Jiménez Conde (Hospital del Mar).
Estado: Concedido el proyecto presentado a *La Marató de TV3*.

Proyecto: **METICUS** (Patrón de METilación como marcador de inestabilidad de placa carotídea en pacientes con ICtUS isquémico)
IP: Israel Cadenas (Hospital Vall d'Hebron)
Estado: Pendiente financiación. Se ha solicitado a la *Fundación Ramón Areces* (XVI Concurso Nacional para la Adjudicación de Ayudas a la Investigación en Ciencias de la Vida y de la Materia).

Para solicitar más información sobre los proyectos, contactar con:

Carolina Soriano
(csoriano@genestroke.com)



Sophie Domingues
(sdomingues@genestroke.com)

PROPUESTAS NUEVOS PROYECTOS:

Proyecto: **GLAM-Stroke** (GLobAl Methylation of ischemic stroke)
IP: Carolina Soriano (Hopital del Mar)
Contacto: (csoriano@genestroke.com)
Estado: Pendiente financiación.

NOVEDADES SOBRE GENÉTICA EN EL ICTUS:

Role of the MMP9 gene in hemorrhagic transformations after t-PA treatment in stroke patients.

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)

Genome-Wide Association Study of Vascular Dementia.

Schrijvers EM, Schürmann B, Koudstaal PJ, van den Bussche H, Van Duijn CM, Hentschel F, Heun R, Hofman A, Jessen F, Kölsch H, Kornhuber J, Peters O, Rivadeneira F, Rüther E, Uitterlinden AG, Riedel-Heller S, Dichgans M, Wiltfang J, Maier W, Breteler MM, Ikram MA.
Stroke. 2011 Nov 23. [Epub ahead of print]

Abstract
BACKGROUND AND PURPOSE: Most studies investigating the genetics of dementia have focused on Alzheimer disease, but little is known about the genetics of vascular dementia. The aim of our study was to identify new loci associated with vascular dementia.
METHODS: We performed a genome-wide association study in the Rotterdam Study, a large prospective population-based cohort study in the Netherlands. We sought to replicate genome-wide significant loci in 2 independent replication samples.
RESULTS: In the discovery analysis of 5700 dementia-free individuals, 67 patients developed incident vascular dementia over a mean follow-up time of 9.3±3.2 years. We showed genome-wide significance for rs12007229, which is located on the X chromosome near the androgen receptor gene (OR, 3.7; 95% CI, 2.3-5.8, per copy of the minor allele; P=1.3×10(-8)). This association was further confirmed in 2 independent populations (probability value of combined replication samples=0.024).
CONCLUSIONS: Our study shows a novel genetic locus for vascular dementia on the X chromosome. Further replication of this finding is required.

Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure

Wain LV, Verwoert GC, O'Reilly PF, Shi G, Johnson T, Johnson AD, Bochud M, Rice KM, Henneman P, Smith AV, Ehret GB, Amin N, Larson MG, Mooser V, Hadley D, Dörr M, Bis JC, Aspelund T, Esko T, Janssens AC, Zhao JH, Heath S, Laan M, Fu J, Pistis G, Luan J, Arora P, Lucas G, Pirastu N, Pichler I, Jackson AU, Webster RJ, Zhang F, Peden JF, Schmidt H, Tanaka T, Campbell H, Igl W, Milaneschi Y, Hottenga JJ, Vitart V, Chasman DI, Trompet S, Bragg-Gresham JL, Alizadeh BZ, Chambers JC, Guo X, Lehtimäki T, Kühnel B, Lopez LM, Polašek O, *et al.* *Nature Genetics* 2011 Sep 11;43(10):1005-11

Abstract

Numerous genetic loci have been associated with systolic blood pressure (SBP) and diastolic blood pressure (DBP) in Europeans. We now report genome-wide association studies of pulse pressure (PP) and mean arterial pressure (MAP). In discovery (N = 74,064) and follow-up studies (N = 48,607), we identified at genome-wide significance (P = 2.7 × 10 -8 to P = 2.3 × 10 -13) four new PP loci (at 4q12 near CHIC2, 7q22.3 near PIK3CG, 8q24.12 in NOV and 11q24.3 near ADAMTS8), two new MAP loci (3p21.31 in MAP4 and 10q25.3 near ADRB1) and one locus associated with both of these traits (2q24.3 near FIGN) that has also recently been associated with SBP in east Asians. For three of the new PP loci, the estimated effect for SBP was opposite of that for DBP, in contrast to the majority of common SBP- and DBP-associated variants, which show concordant effects on both traits. These findings suggest new genetic pathways underlying blood pressure variation, some of which may differentially influence SBP and DBP.

Genome-wide association studies of cerebral white matter lesion burden: The CHARGE consortium.

Fornage M, Debette S, Bis JC, Schmidt H, Ikram MA, Dufouil C, Sigurdsson S, Lumley T, Destefano AL, Fazekas F, Vrooman HA, Shibata DK, Maillard P, Zijdenbos A, Smith AV, Gudnason H, de Boer R, Cushman M, Mazoyer B, Heiss G, Vernooij MW, Enzinger C, Glazer NL, et al. *Ann Neurol.* 2011 Jun;69

Abstract

OBJECTIVE: White matter hyperintensities (WMHs) detectable by magnetic resonance imaging are part of the spectrum of vascular injury associated with aging of the brain and are thought to reflect ischemic damage to the small deep cerebral vessels. WMHs are associated with an increased risk of cognitive and motor dysfunction, dementia, depression, and stroke. Despite a significant heritability, few genetic loci influencing WMH burden have been identified.

METHODS: We performed a meta-analysis of genome-wide association studies (GWASs) for WMH burden in 9,361 stroke-free individuals of European descent from 7 community-based cohorts. Significant findings were tested for replication in 3,024 individuals from 2 additional cohorts.

RESULTS: We identified 6 novel risk-associated single nucleotide polymorphisms (SNPs) in 1 locus on chromosome 17q25 encompassing 6 known genes including WBP2, TRIM65, TRIM47, MRPL38, FBF1, and ACOX1. The most significant association was for rs3744028 (p (discovery) = 4.0 × 10(-9) ; p(replication) = 1.3 × 10(-7) ; p(combined) = 4.0 × 10(-15)). Other SNPs in this region also reaching genome-wide significance were rs9894383 (p = 5.3 × 10(-9)), rs11869977 (p = 5.7 × 10(-9)), rs936393 (p = 6.8 × 10(-9)), rs3744017 (p = 7.3 × 10(-9)), and rs1055129 (p = 4.1 × 10(-8)). Variant alleles at these loci conferred a small increase in WMH burden (4-8% of the overall mean WMH burden in the sample).

INTERPRETATION: This large GWAS of WMH burden in community-based cohorts of individuals of European descent identifies a novel locus on chromosome 17. Further characterization of this locus may provide novel insights into the pathogenesis of cerebral WMH.

APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study.

Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, Jimenez-Conde J, Pires CR, Ayres AM, Schwab K, Cortellini L, Pera J, Urbanik A, Romero JM, Rost NS, Goldstein JN, Viswanathan A, Pichler A, Enzinger C, Rabionet R, Norrving B, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, Broderick JP, Greenberg SM, Roquer J, Lindgren A, Slowik A, Schmidt R, Woo D, Rosand J; on behalf of the International Stroke Genetics Consortium.
Lancet Neurol. 2011 Aug;10(8):702-709.

Abstract

BACKGROUND: Carriers of APOE ε2 and ε4 have an increased risk of intracerebral haemorrhage (ICH) in lobar regions, presumably because of the effects of these gene variants on risk of cerebral amyloid angiopathy. We aimed to assess whether these variants also associate with severity of ICH, in terms of haematoma volume at presentation and subsequent outcome.

METHODS: We investigated the association of APOE ε2 and ε4 with ICH volume and outcomes in patients with primary ICH in three phases: a discovery phase of 865 individuals of European ancestry from the Genetics of Cerebral Hemorrhage on Anticoagulation study, and replication phases of 946 Europeans (replication 1) and 214 African-Americans (replication 2) from an additional six studies. We also assessed the association of APOE variants with ICH volume and outcomes in meta-analyses of results from all three phases, and the association of APOE ε4 with mortality in a further meta-analysis including data from previous reports. Admission ICH volume was quantified on CT scan. We assessed functional outcome (modified Rankin scale score 3-6) and mortality at 90 days. We used linear regression to establish the effect of genotype on haematoma volume and logistic regression to assess the effect on outcome from ICH.

FINDINGS: For patients with lobar ICH, carriers of the APOE ε2 allele had larger ICH volumes than did non-carriers in the discovery phase (p=2·5×10(-5)), in both replication phases (p=0·008 in Europeans and p=0·016 in African-Americans), and in the meta-analysis (p=3·2×10(-8)). In the meta-analysis, each copy of APOE ε2 increased haematoma size by a mean of 5·3 mL (95% CI 4·7-5·9; p=0·004). Carriers of APOE ε2 had increased mortality (odds ratio [OR] 1·50, 95% CI 1·23-1·82; p=2·45×10(-5)) and poorer functional outcomes (modified Rankin scale score 3-6; 1·52, 1·25-1·85; p=1·74×10(-5)) compared with non-carriers after lobar ICH. APOE ε4 was not associated with lobar ICH volume, functional outcome, or mortality in the discovery phase, replication phases, or meta-analysis of these three phases; in our further meta-analysis of 2194 patients, this variant did not increase risk of mortality (1·08, 0·86-1·36; p=0·52). APOE allele variants were not associated with deep ICH volume, functional outcome, or mortality.

INTERPRETATION: Vasculopathic changes associated with the APOE ε2 allele might have a role in the severity and clinical course of lobar ICH. Screening of patients who have ICH to identify the ε2 variant might allow identification of those at increased risk of mortality and poor functional outcomes.

FUNDING: US National Institutes of Health-National Institute of Neurological Disorders and Stroke, Keane Stroke Genetics Research Fund, Edward and Maybeth Sonn Research Fund, and US National Center for Research Resources.

CONGRESOS Y REUNIONES DE INTERÉS 2012

International Stroke Conference, Feb 1 - 3, 2012. New Orleans, USA.

21rt European stroke conference, 22-25 May, 2012. Lisbon, Portugal.

22nd Meeting of European Neurological Society. June 9-12, 2012. Prague, Czech Republic.

The European Human Genetics Conference 2012 in conjunction with the European Meeting on Psychosocial Aspects of Genetics 2012, June 23-26, 2012. Nuremberg, Germany.

6th EFNS Congress, September 08 - 11, 2012. Stockholm, Sweden.

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.

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Sugerencias...
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Estamos en la web!
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