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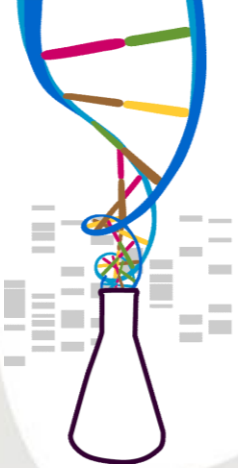
CAMPUS DE EXCELENCIA INTERNACIONAL
Universidad de Oviedo

Ad Futurum:

DEL XVII AL XXI: PROYECTANDO NUESTRA TRADICIÓN HACIA EL FUTURO



1608

2010

1ª JORNADA SECTORIAL: 02/02/11

L2: DESARROLLO Y DEGENERACIÓN CEREBRAL

Genética Molecular-HUCA

Coordinador / investigador responsable:
ELIECER COTO GARCIA
VICTORIA ALVAREZ MARTINEZ
Número de miembros: 8

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Líneas de investigación principales

GENÉTICA DE LA ENFERMEDAD DE PARKINSON
GENÉTICA DE LA ENFERMEDAD DE ALZHEIMER
GENÉTICA DE LA PARAPARESIA ESPÁSTICA

Mecanismos reguladores de la expresión génica en procesos neurodegenerativos:
microRNAs, promotores génicos

Laboratorio de referencia para estudios genéticos (asistencial)

Nombre de grupo

Coordinador / investigador responsable:
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VICTORIA ALVAREZ MARTINEZ
Número de miembros: 8

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Proyectos, contratos, patentes… en desarrollo o realizados

FIS PI02/0022(2003-2005) (Victoria Alvarez)
Genes del sistema parkina/alpha-sinucleína:análisis funcional de las variantes alélicas y su papel en la enf. de Parkinson

FIS PI05/008 (2006-2008) (Victoria Alvarez)

Enfermedad de Parkinson: nuevos marcadores genómicos y su relación con la genética mitocondrial.

FIS PI 08/0915 (Victoria Alvarez)
Enfermedad de Parkinson: Variación en microRNAS y regiones reguladores de la expresión de los genes PARK2, SNCA, LRRK2

Beca Asociación Parkinson Asturias (Cajastur)

Nombre de grupo

Coordinador / investigador responsable:
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VICTORIA ALVAREZ MARTINEZ
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Competencias y capacidades tecnológicas más relevantes

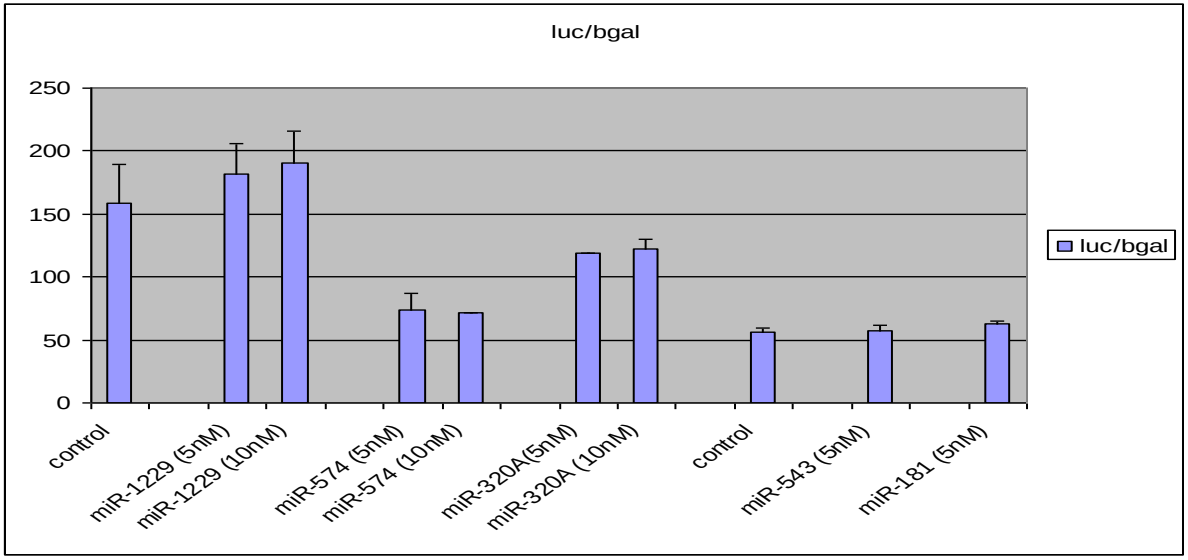
SECUENCIACIÓN AUTOMÁTICA
ABI3130 – 16 CAPILARES

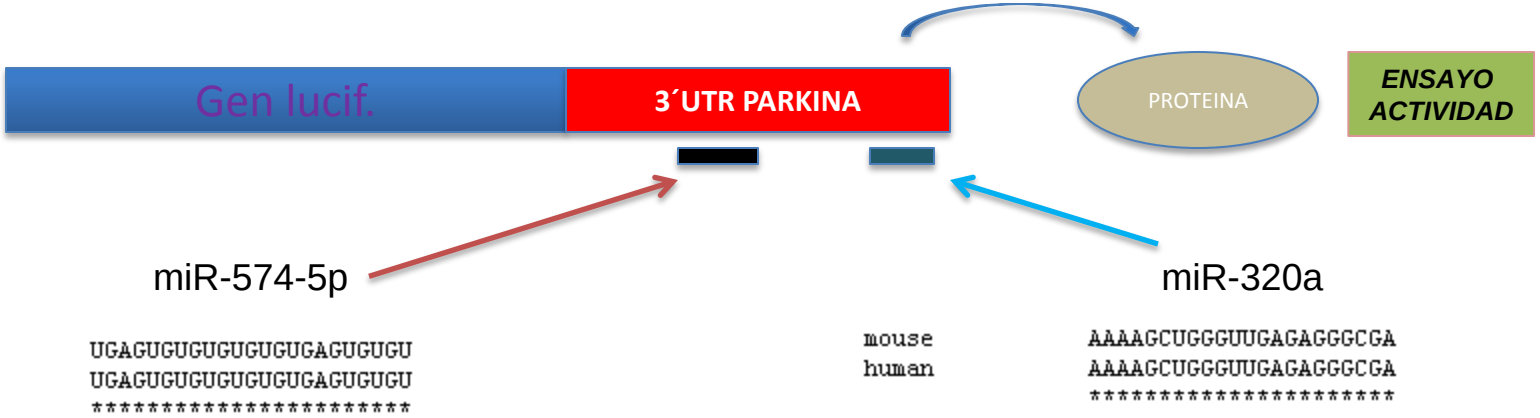
PCR EN TIEMPO REAL
ABI7500

Colaboración con el grupo de la Dra. L. Wang, Department of Medicine and Oncological Sciences, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City.

Estancia de Lorena de Mena, estudio de la regulación de PARK a través de su región 3´UTR.

MiReporter-mm-PARK2-3'UTR





Línea Enfermedad Alzheimer
Asistencial: estudio formas familiares, genes APP y Presenilinas
Genotipo APOE 2/3/4, todas las demencias: diagnóstico diferencial

Consentimineto Informado para inclusión en proyectos de investigación.
Colección ADN de pacientes Alzheimer (probable) + controles sanos

Estudios propios (>20 publicaciones, 2003-2010)
Colaboración internacional

FIS 00/0239 (2000-2002) (Victoria Alvarez)
Mediadores inflamatorios y enfermedad de alzheimer: papel de los polimorfismos genéticos en su progresión

Epistasis Project
Dirigido desde la Univ. de Oxford, financiado por el MRC
Dirigido a replicar la asociación e Interacción entre 100 genes/marcadores previamente relacionados con la EA

EADNI consortium (Europeo), iniciativa francesa (INSERM)
Estudios Genome Wide Association Enf. Alzheimer.

FIS PI02/0022(2003-2005) (Victoria Alvarez)

Genes del sistema parkina/alpha-sinucleína:análisis funcional de las variantes alélicas y su papel en la enfermedad de Parkinson

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Neuroscience Letters 380 (2005) 257–259

Neuroscience Letters

www.elsevier.com/locate/neulet

Homozygous partial genomic triplication of the parkin gene in early-onset parkinsonism

Ignacio F. Mata[a,b], Victoria Alvarez[b], Eliecer Coto[b], Marta Blazquez[c], Luis M. Guisasola[c], Carlos Salvador[c], Jennifer M. Kachergus[a], Sarah J. Lincoln[a], Matthew Farrer[a,*]

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Received 21 December 2004; received in revised form 10 January 2005; accepted 18 January 2005

Abstract

Autosomal recessive mutations in the parkin gene are the predominant cause of familial, early-onset parkinsonism; missense mutations involving one or a few nucleotides, exonic deletions and duplications have been described. Here we report a family with two affected brothers. Direct sequencing of parkin did not detect mutations, but semi-quantitative analysis identified a novel exonic rearrangement of exons 2–4. Both patients were homozygous for unique genomic triplications of the parkin gene.

Keywords: Parkin; Parkinson's disease; Triplication

European Journal of Neurology 2006, **13:** 391–394

LRRK2 mutations are a common cause of Parkinson's disease in Spain

I. F. Mata[a,b], O. A. Ross[a], J. Kachergus[a], C. Huerta[b], R. Ribacoba[c], G. Moris[c], M. Blazquez[d], L. M. Guisasola[d], C. Salvador[d], C. Martinez[e], M. Farrer[a] and V. Alvarez[b]

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Keywords:
G2019S, *LRRK2*, mutation, Parkinson's disease

Received 16 March 2005
Accepted 28 April 2005

Pathogenic mutations in the *leucine-rich repeat kinase 2* gene (*LRRK2*; PARK8) have been implicated in autosomal dominant, late-onset parkinsonism. The *LRRK2* 6055G > A (G2019S) mutation is the most common reported to date, and has been observed in a number of different European populations. So far, only the *LRRK2* 4321C > G (R1441G) mutation has been identified in the Spanish population. Herein we have assessed the frequency of G2019S in a referral-based series of 225 patients with Parkinson's disease (PD) from the region of Asturias, Northern Spain. The mutant allele was identified in five (2.7%) of the sporadic late-onset patients and was not present in control subjects. All carriers displayed genetic profiles consistent with the same haplotype, as previously reported for Lrrk2 G2019S-positive subjects. None of these patients presented with a family history of parkinsonism at the time of diagnosis. Thus, approximately 5% of sporadic patients with PD from the North of Spain have either Lrrk2 G2019S or R1441G substitutions.

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Neuroscience Letters 313 (2001) 108–110

Neuroscience Letters

www.elsevier.com/locate/neulet

Early-onset Parkinson's disease associated with a new parkin mutation in a Spanish family

Victoria Alvarez[a], Luis M. Guisasola[b], Vanessa G. Moreira[a], Carlos H. Lahoz[b], Eliecer Coto[a,*]

[a] *Genética Molecular, Hospital Central de Asturias, 33006 Oviedo, Spain*
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Received 17 July 2001; received in revised form 23 August 2001; accepted 23 August 2001

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Neuroscience Letters 382 (2005) 309–311

Neuroscience Letters

www.elsevier.com/locate/neulet

LRRK2 R1441G in Spanish patients with Parkinson's disease

Ignacio F. Mata[a,b], Julie P. Taylor[a], Jennifer Kachergus[a], Mary Hulihan[a], Cecilia Huerta[b], Carlos Lahoz[c], Marta Blazquez[c], Luis M. Guisasola[c], Carlos Salvador[c], Renee Ribacoba[d], Carmen Martinez[c], Matthew Farrer[a,*], Victoria Alvarez[b]

[a] *Departments of Neurology and Neuroscience, Mayo Clinic, Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224, USA*
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Received 3 February 2005; received in revised form 10 March 2005; accepted 15 March 2005

Neurogenetics (2009) 10:347–353
DOI 10.1007/s10048-009-0187-z

ORIGINAL ARTICLE

Lrrk2 R1441G-related Parkinson's disease: evidence of a common founding event in the seventh century in Northern Spain

Ignacio F. Mata · Carolyn M. Hutter · María C. González-Fernández · Marian M. de Pancorbo · Elena Lezcano · Cecilia Huerta · Marta Blazquez · Renee Ribacoba · Luis M. Guisasola · Carlos Salvador · Juan C. Gómez-Esteban · Juan J. Zarranz · Jon Infante · Joseph Jankovic · Hao Deng · Karen L. Edwards · Victoria Alvarez · Cyrus P. Zabetian

J Neurol Neurosurg Psychiatry 1999;67:733–736

Angiotensin converting enzyme and endothelial nitric oxide synthase DNA polymorphisms and late onset Alzheimer's disease

Ruth Alvarez, Victoria Alvarez, Carlos H Lahoz, Carmen Martínez, Joaquín Peña, José M Sánchez, Luis M Guisasola, Javier Salas-Puig, Germán Moris, José A Vidal, René Ribacoba, Bernardino B Menes, Dionisio Uría, Eliecer Coto

American Journal of Medical Genetics (Neuropsychiatric Genetics) 105:76–78 (2001)

Brief Research Communication

Variation in the LRP-Associated Protein Gene (LRPAP1) Is Associated With Late-Onset Alzheimer Disease

Lourdes Sánchez, Victoria Alvarez, Pelayo González, Ignacio González, Ruth Alvarez, and Eliecer Coto*

Laboratorio Genética Molecular, Instituto Reina Sofía Investigación Nefrológica, Hospital Central Asturias, Oviedo, Spain

BRIEF REPORT

The Sp1/Egr1-tandem Repeat Polymorphism in the 5-Lipoxygenase Gene Promoter is not Associated With Late Onset Alzheimer Disease

Victoria Alvarez, PhD, Pelayo González, PhD,* Ana I. Corao, BSc,* Manuel Menéndez, MD,† ‡ Carlos H. Lahoz, MD,‡ Carmen Martínez, MD,§ Maite Calatayud, MD,‡ Blanca Morales, PhD,* and Eliecer Coto, PhD**

Abstract: Arachidonate 5-lipoxygenase plays an important role in the synthesis of leukotrienes. Leukotrienes are inflammatory mediators, and inflammation has been implicated in the pathogenesis of Alzheimer disease. A polymorphism in the ALOX5 promoter consisting on 3 to 6 tandem-repeats of a Sp1/Egr1 binding motif (GGGCGG)n, has been related with the amount of gene expression. To verify the association between this polymorphism and the risk for late-onset Alzheimer disease we genotyped a total of 291 patients (mean age 74 ± 7 y) and 300 controls (mean age 73 ± 8 y). We found alleles of 3 to 6 repeats, and allele and genotype frequencies did not differ between patients and controls. These frequencies did not differ between patients according to the APOE genotype (ε34 + ε44 vs. ε23 + ε33). Together, our results indicate that the Sp1/Egr1-repeat polymorphism in the ALOX5 promoter is not a genetic marker for the risk of developing late-onset Alzheimer disease.

Key Words: arachidonate 5-lipoxygenase, Alzheimer disease, gene polymorphism, genetic association

(*Alzheimer Dis Assoc Disord* 2008;22:177–180)

polymorphisms in the 5-LOX gene (ALOX5) could contribute to the risk of developing late-onset Alzheimer disease (LOAD).[7,8] A promoter polymorphism consisting in 3, 4, 5, or 6 tandem Sp1/Egr1 binding motifs (GGGCGG)n, modified transcription activity and was recently associated with carotid intimal-medial thickness, a measure of atherosclerosis.[9,10] This polymorphism was also related with ALOX5 mRNA expression and leukotriene production, and with the response to antiasthma treatments.[11,12] To analyze the effect of this ALOX5-promoter polymorphism on LOAD-risk, we genotyped a cohort of LOAD patients and controls.

METHODS

Patients and Controls

The study included 291 patients (182 women, 109 men; mean age 74 ± 7 y; range: 60 to 97 y) who fulfilled the National Institutes of Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ARDA) criteria for clinical prob-

American Journal of Medical Genetics (Neuropsychiatric Genetics) 114:574–577 (2002)

Association Between the TNFα-308 A/G Polymorphism and the Onset-Age of Alzheimer Disease

Victoria Alvarez,[1]* Ignacio F. Mata,[1] Pelayo González,[1] Carlos H. Lahoz,[2] Carmen Martínez,[3] Joaquín Peña,[2] Luis M. Guisasola,[2] and Eliecer Coto[1]

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[3]*Servicio Neurología, Hospital Cabueñes, Gijón, Spain*

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Neuroscience Letters 411 (2007) 47–51

LETTERS

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Myocyte enhancing factor-2A in Alzheimer's disease: Genetic analysis and association with MEF2A-polymorphisms

Pelayo González[a], Victoria Álvarez[a], Manuel Menéndez[b], Carlos H. Lahoz[b], Carmen Martínez[c], Ana I. Corao[a], María T. Calatayud[b], Joaquín Peña[b], Mónica García-Castro[a], Eliecer Coto[a,*]

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Received 16 May 2006; received in revised form 13 September 2006; accepted 14 September 2006

Journal of Alzheimer's Disease 13 (2008) 275–280
IOS Press

Mitochondrial Transcription Factor A (TFAM) Gene Variation and Risk of Late-Onset Alzheimer's Disease

Victoria Alvarez[a], Ana I. Corao[a], Cristina Alonso-Montes[a], Elena Sánchez-Ferrero[a], Lorena De Mena[a], Blanca Morales[a], Mónica García-Castro[a] and Eliecer Coto[a,b,*]

[a] *Genética Molecular, Hospital Universitario Central de Asturias, Oviedo, Spain*
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nature genetics

Received 12 May; accepted 31 July; published online 6 September 2009; doi:10.1038/ng.439

Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease

Jean-Charles Lambert[1–3], Simon Heath[4], Gael Even[1,2], Dominique Campion[5], Kristel Sleegers[6,7], Mikko Hiltunen[8], Onofre Combarros[9], Diana Zelenika[4], Maria J Bullido[10], Béatrice Tavernier[11], Luc Letenneur[12], Karolien Bettens[6,7], Claudine Berr[13], Florence Pasquier[3,14], Nathalie Fiévet[1,2], Pascale Barberger-Gateau[12], Sebastiaan Engelborghs[7,15], Peter De Deyn[7,15], Ignacio Mateo[9], Ana Franck[16], Seppo Helisalmi[8], Elisa Porcellini[17], Olivier Hanon[18], the European Alzheimer's Disease Initiative Investigators[19], Marian M de Pancorbo[20], Corinne Lendon[21], Carole Dufouil[22,23], Céline Jaillard[24], Thierry Leveillard[24], Victoria Alvarez[25], Paolo Bosco[26], Michelangelo Mancuso[27], Francesco Panza[28], Benedetta Nacmias[29], Paola Bossù[30], Paola Piccardi[31], Giorgio Annoni[32], Davide Seripa[33], Daniela Galimberti[34], Didier Hannequin[5], Federico Licastro[17], Hilkka Soininen[8], Karen Ritchie[13], Hélène Blanché[35], Jean-François Dartigues[12], Christophe Tzourio[22,23], Ivo Gut[4], Christine Van Broeckhoven[6,7], Annick Alpérovitch[22,23], Mark Lathrop[4,35] & Philippe Amouyel[1–3,14]

Markers outside APOE with suggestive evidence of association ($P < 10^{-5}$) were examined in collections from Belgium, Finland, Italy and Spain totaling 3,978 Alzheimer's disease cases and 3,297 controls. Two loci gave replicated evidence of association: one within *CLU* (also called *APOJ*), encoding clusterin or apolipoprotein J, on chromosome 8 (rs11136000, OR = 0.86, 95% CI 0.81–0.90, $P = 7.5 \times 10^{-9}$ for combined data) and the other within *CR1*, encoding the complement component (3b/4b) receptor 1, on chromosome 1 (rs6656401, OR = 1.21, 95% CI 1.14–1.29, $P = 3.7 \times 10^{-9}$ for combined data). Previous biological studies support roles of *CLU* and *CR1* in the clearance of β amyloid (Aβ) peptide, the principal constituent of amyloid plaques, which are one of the major brain lesions of individuals with Alzheimer's disease.