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Press information

A new factor of genetic susceptibility to Alzheimer's disease discovered through a study of a rare disease

A large-scale international study involving French researchers from the Inserm-Institut Pasteur Lille-Université Lille Nord de France "Public health and molecular epidemiology of ageing-related diseases" joint research unit led by Philippe Amouyel, has just discovered a gene for susceptibility to a rare disease that causes susceptibility to a common one, Alzheimer's disease, providing evidence of the heterogeneous aetiology of Alzheimer's disease. This whole-exome sequencing approach is explained in detail in *The New England Journal of Medicine* dated 14 November 2012.

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, or Nasu-Hakola disease, is a genetic disorder passed on by means of autosomal recessive transmission. The disease starts at the age of around 30 years with pains in the wrists or shoulders associated with swollen joints. Bone fractures can occur as a result of minor traumas. Bone x-rays show epiphyseal cysts. Slight personality changes then occur followed by frontal neurological signs (euphoria, loss of social inhibitions) evolving into early-onset dementia. The disorder has been associated with mutations of the TREM2 (Triggering Receptor Expressed on Myeloid cells 2) gene on chromosome 6.

British, American and French researchers have now shown that on this same region of chromosome 6, mutations of the TREM2 gene were associated with a five times greater risk of developing late-onset Alzheimer's disease. A complete sequencing was performed on 281 individuals with Alzheimer's disease and 504 controls. Analysis of the TREM2 gene showed excessive TREM2 mutations in those with the disease compared with the control subjects. Characterisation of one of these TREM2 mutations in very large sample populations of patients with Alzheimer's disease has allowed researchers to measure precisely the importance of this association between TREM2 mutations and the disease. Finally, a replication study was performed in another independent series of 1994 cases and 4602 controls, which confirmed this strong association (OR=4.97 CI 95% [2.42-10.21], P<6.10-6).

These results are also confirmed in the same edition of *The New England Journal of Medicine* by an Icelandic team, which also shows that this gene is a risk factor for Alzheimer's disease in the Finnish population and other European populations.

A pathological analysis of six individuals presenting variants of the TREM2 gene has revealed evidence of Alzheimer's-type brain lesions. The study of TREM2 gene expression in normal human brains has shown high levels in the white matter and in the hippocampus and cortex.

In a transgenic mouse model of Alzheimer's disease, an increase in TREM2 expression was observed in microglial cells surrounding the amyloid plaques and the neurons compared with normal mice. The TREM2 gene encodes a protein that participates in the activation of immune responses in macrophages and dendritic cells.

This discovery has two main consequences. Firstly, this observation provides a better understanding of the immune system's involvement in Alzheimer's disease in which the gene of complement receptor 1 (CR1) had already been implicated, in previous work by Inserm-Lille2-IPL UMR744[1]. Furthermore, this approach of whole-exome sequencing has allowed the discovery of a gene for susceptibility to a rare disease that causes susceptibility to a common disease, evidence of the heterogeneous aetiology of Alzheimer's disease. It is the loss of function of this gene in its homozygous or heterozygous variants that determines the nature of the disorder.

These results, which demonstrate how much progress has been made in understanding Alzheimer's disease, involved teams from LabEx DISTALZ, and were able to be produced partly through the support of the French Foundation for Scientific Cooperation on Alzheimer's and similar diseases, launched in February 2008.

Ever-increasing longevity among the human population means the number of patients suffering from Alzheimer's disease is also on the rise in France and throughout the world. Alzheimer's is the leading cause of memory and intellectual function disorders among elderly people and represents a major public health issue.

Alzheimer's disease is one of the main causes of dependency among the elderly. It results from neurodegeneration in different areas of the brain. Its symptoms include increasing impairment of memory and cognitive functions, and behaviour disorders that lead to a progressive loss of independence. In France, Alzheimer's disease affects more than 850,000 people and represents major social and economic costs.

Alzheimer's disease is characterized by the development of two types of lesion in the brain: amyloid plaques and neurofibrillary tangles. Amyloid plaques originate from the extracellular accumulation of a peptide, the β amyloid (Aβ) peptide, in specific areas of the brain. Neurofibrillary tangles are intraneuronal lesions caused by abnormal filamentary aggregation of a protein known as a tau protein.

Identifying the genes that participate in the incidence of Alzheimer's disease and its development will make it possible to tackle the physiopathological mechanisms behind this affliction more rapidly, to identify the target proteins and metabolic channels for new treatments, and to provide a means of identifying the individuals that are most at risk when effective preventive treatments become available.

For further information:

[1] ***Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease.*** Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fiévet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O; the European Alzheimer's Disease Initiative Investigators, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossù P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanché H, Dartigues JF, Tzourio C, Gut I, Van Broeckhoven C, Alpérovitch A, Lathrop M, Amouyel P. Nature Genetics 2009. 41: 1094-1099.

➢ **Source :**

"TREM2 Variants Predispose to Alzheimer's Disease."

Rita Guerreiro PhD[1,2], Aleksandra Wojtas MS[3*], Jose Bras PhD[1*], Minerva M. Carrasquillo PhD[3*], Ekaterina Rogaeva PhD[4,5*], Elisa Majounie PhD[2*], Carlos Cruchaga PhD[6*], Celeste Sassi MD [1,2], John S.K. Kauwe PhD[7], Michelle K Lupton PhD[8], Mina Ryten MD, PhD[1], Kristelle Brown PhD[9], the EADI Consortium, the GERAD Consortium, the UKBE Consortium, James Lowe DM[9], Perry G. Ridge MS[7,10], Monia B. Hammer MS[2], Yosuke Wakutani MD[5], Lilinaz Hazrati MD, PhD[5], Petroula Proitsi PhD[8], Stephen Newhouse PhD[8], Ebba Lohmann MD[11], Nihan Erginel-Unaltuna PhD[12], Christopher Medway PhD[8], Hasmet Hanagasi MD[11], Claire Troakes PhD[13], Hakan Gurvit MD[11], Basar Bilgic MD[11], Safa Al-Sarraj MD[14], Bruno Benitez MD[17], Breanna Cooper BS[17], David Carrell MS[17], Murat Emre MD[11], Fanggeng Zou PhD[3], Li Ma MS[3], Melissa E. Murray PhD[3], Dennis W. Dickson MD[3], Steven Younkin MD, PhD[3], Ronald C. Petersen PhD, MD[18], Christopher D. Corcoran ScD[15,16], Yefei Cai PhD[17], Catarina Oliveira MD, PhD[19,20], Maria Helena Ribeiro MS[21], Isabel Santana MD, PhD[20,21], JoAnn T. Tschanz PhD[16,22], J. Raphael Gibbs BSc[1,2], Maria C. Norton PhD[16,22,23], Iwona Kloszewska PhD[24], Patrizia Mecocci MD, PhD[25], Hilkka Soininen MD[26], Magda Tsolaki MD[27], Bruno Vellas MD, PhD[28], Ronald G. Munger PhD, MPH[16,29], David M.A. Mann PhD[30], Stuart Pickering-Brown PhD[31], Simon Lovestone PhD[32], Jonathan Beck BSc[33], Simon Mead MD[33], John Collinge MD[33], Linda Parsons MPhil[34], Jennifer Pocock PhD[35], John C. Morris MD[36], Tamas Revesz MD, FRCPath [34], Tammaryn Lashley PhD[34], Nick C. Fox MD[37], Martin N. Rossor MD[37], Benjamin Grenier-Boley MSc[38,39,40], Céline Bellenguez PhD[38,39,40], Valentina Moskvina PhD[41], Rebecca Sims PhD[41], Denise Harold PhD[41], Julie Williams PhD[41], Jean-Charles Lambert PhD[38,39,40], Philippe Amouyel MD, PhD[38,39,40,42], Neill Graff-Radford MBBCh, FRCP (London)[43], Alison Goate PhD[6], Rosa Rademakers PhD[3], Kevin Morgan PhD[9], John Powell PhD[8], Peter St George-Hyslop MD, FRCP(C)[4,5,44], Andrew Singleton PhD[2] and John Hardy PhD[1]

1- Department of Molecular Neuroscience, UCL Institute of Neurology, London WC1N 3BG, UK.
2- Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, United States of America
3- Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA
4- Department of Medicine, Division of Neurology, University of Toronto, Toronto, Canada
5- Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada
6- Department of Psychiatry, Hope Center for Neurological Disorders and Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St Louis, MO 63110, USA
7- Department of Biology, Brigham Young University, Provo, UT, USA
8- Institute of Psychiatry, King's College London, London, UK
9- Human Genetics and Cellular Pathology, School of Molecular Medical Sciences, University of Nottingham, Nottingham, NG7 2UH, UK.
10- ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT, USA
11- Department of Neurology, Faculty of Medicine, Istanbul University, Istanbul, Turkey
12- Department of Genetics, Institute for Experimental Medical Research, Istanbul University, Istanbul, Turkey
13- KHP Centre for Neurodegeneration Research, Institute of Psychiatry, King's College London, UK
14- KHP Centre for Neurodegeneration Research, Institute of Psychiatry, King's College London, UK and Department of Clinical Neuropathology, King's College Hospital, UK
15- Department of Mathematics and Statistics, Utah State University, Logan, UT
16- Center for Epidemiologic Studies, Utah State University, Logan, UT, USA
17- Department of Psychiatry, Washington University School of Medicine, St Louis, MO 63110, USA
18- Department of Neurology, Mayo Clinic, Rochester, MN, USA
19- CNC–Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal
20- Faculty of Medicine, University of Coimbra, Coimbra, Portugal
21- Neurology Service, Coimbra University Hospital, Coimbra, Portugal
22- Department of Psychology, Utah State University, Logan, UT, USA
23- Department of Family Consumer and Human Development, Utah State University, Logan, UT, USA
24- Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Lodz, Poland
25- Section of Gerontology and Geriatrics, Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy
26- Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland
27- Third Department of Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece
28- UMR INSERM 1027 Gerootopole and Department of Internal and Geriatrics Medicine, Hôpitaux de Toulouse, Toulouse, France
29- Department of Nutrition, Dietetics, and Food Sciences, Utah State University, Logan, UT, USA
30- Greater Manchester Centre for Neurosciences, University of Manchester Cerebral Function Unit, Hope Hospital, Salford, Manchester, M6 8HD, UK
31- Institute of Brain, Behaviour and Mental Health, Faculty of Human and Medical Sciences, University of Manchester, UK
32- King's College London, Department of Old Age Psychiatry, Institute of Psychiatry, Box PO70, De Crespigny Park, London, SE5 8AF, UK.
33- MRC Prion Unit and Department of Neurodegenerative Disease, UCL Institute of Neurology, London WC1N 3BG, UK.
34- Queen Square Brain Bank, UCL Institute of Neurology, London WC1N 3BG, UK
35- Department of Neuroinflammation, University College London Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ, UK
36- Department of Neurology, Hope Center for Neurological Disorders and Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St Louis, MO 63110, USA
37- Dementia Research Centre, UCL Institute of Neurology, London WC1N 3BG, UK
38- INSERM, U744, Lille, France
39- Institut Pasteur de Lille, Lille, France
40- Université Lille-Nord de France, Lille, France

41- Medical Research Council (MRC) Centre for Neuropsychiatric Genetics and Genomics, Neurosciences and Mental Health Research Institute, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Cardiff, UK.
42- CHRU de Lille, F-59000 Lille, France
43- Department of Neurology, Mayo Clinic, Jacksonville, FL, USA
44- Cambridge Institute for Medical Research, and the Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.

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➢ **Researcher contact**

Philippe Amouyel
Director of Inserm UMR 744 "Santé publique et épidémiologie moléculaire des maladies liées au vieillissement" (Public health and molecular epidemiology of ageing-related diseases) and LabEx DISTALZ
E-mail: philippe.amouyel@pasteur-lille.fr
Tel: 06 86 43 23 34

➢ **Press contact:**

presse@inserm.fr
Tel: 01 44 23 60 98