Contributions of the ADC NP Cores in facilitating research beyond the AD Centers

Lewy body dementia, a major Alzheimer Disease Related Dementia

Neuropathology of Lewy body dementia

Evolution of neuropathologic assessment/criteria for Lewy body dementia

- **1961 Okazaki**
  - Okazaki H, et al. Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion. *J Neuropathol Exp Neurol* 1961;20:237-244
- **1984 Kosaka**
  - Kosaka K, et al. Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree. A new disease? *Clin Neuropathol* 1984;3:185–192.

- **2003 Braak**
  - Braak H, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197-211.
- **2009 Beach**
  - Beach TG, et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol* 2009;117:613-34.
- **2017 McKeith**
  - McKeith IG, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017;89:88-100

Consortium on Dementia with Lewy Bodies (CDLB); Newcastle, UK, 1995

Neuropathologists: Bergeron, Dickson, Hansen, Jellinger, Kosaka, Kuzuhara, Lippa, Lowe, Perry

Organized and led by Ian McKeith

Dementia with Lewy bodies – Early neuropathologic studies (USA)

1980's

UC San Diego
SCHOOL OF MEDICINE

Penn
UNIVERSITY of PENNSYLVANIA

University of Pittsburgh

CASE WESTERN RESERVE
EST. 1826 UNIVERSITY

UT Southwestern
Medical Center

Banner Sun Health
Research Institute

HARVARD
UNIVERSITY

JOHNS HOPKINS
MEDICINE

CLEVELAND
ALZHEIMER'S DISEASE
RESEARCH CENTER

MAYO
CLINIC

1990's

Neuropathology of Lewy body dementia

- **Neuropathologic criteria for Lewy body dementia have evolved, but retain basic principles**
  - The greater the density and wider distribution of Lewy related pathology, the more likely the patient had the DLB clinical syndrome.
  - Neuropathologic diagnosis of DLB is a probability statement that is *directly* related to the severity of Lewy related pathology and *inversely* related to the severity of Alzheimer type pathology.

Collaborations – Autopsy PD GWAS

ARTICLES

PARK10 is a major locus for sporadic neuropathologically confirmed Parkinson disease

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ABSTRACT

Objective: To minimize pathologic heterogeneity in genetic studies of Parkinson disease (PD), the Autopsy-Confirmed Parkinson Disease Genetics Consortium conducted a genome-wide association study using both patients with neuropathologically confirmed PD and controls.

Methods: Four hundred eighty-four cases and 1,145 controls met neuropathologic diagnostic criteria, were genotyped, and then imputed to 3,922,209 variants for genome-wide association study analysis.

Results: A small region on chromosome 1 was strongly associated with PD (rs10788972; $p = 6.2 \times 10^{-8}$). The association peak lies within and very close to the maximum linkage peaks of 2 prior positive linkage studies defining the *PARK10* locus. We demonstrate that rs10788972 is in strong linkage disequilibrium with rs914722, the single nucleotide polymorphism defining the *PARK10* haplotype previously shown to be significantly associated with age at onset in PD. The region containing the *PARK10* locus was significantly reduced from 10.6 megabases to 100 kilobases and contains 4 known genes: *TCEANC2*, *TMEM59*, *miR-4781*, and *LDLRAD1*.

Conclusions: We confirm the association of a *PARK10* haplotype with the risk of developing idiopathic PD. Furthermore, we significantly reduce the size of the *PARK10* region. None of the candidate genes in the new *PARK10* region have been previously implicated in the biology of PD, suggesting new areas of potential research. This study strongly suggests that reducing pathologic heterogeneity may enhance the application of genetic association studies to PD.

Neurology® 2015;84:972–980

GLOSSARY

ADGC = Alzheimer Disease Genetics Consortium; **APDGC** = Autopsy-Confirmed Parkinson Disease Genetics Consortium; **CIDR** = Center for Inherited Disease Research; **GWAS** = genome-wide association study; **LD** = linkage disequilibrium; **MAF** = minor allele frequency; **OR** = odds ratio; **PCA** = principal component analysis; **PC1** = principal component 1; **PD** = Parkinson disease; **QC** = quality control; **SNP** = single nucleotide polymorphism.

Family studies have identified multiple Parkinson Disease (PD) genes: α-synuclein (*SNCA*), parkin (*PARK2*), DJ1 (*PARK7*), PTEN induced putative kinase 1 (*PINK1*), and leucine-rich repeat kinase 2 (*LRRK2*); association studies have identified up to 28 loci meeting genome-wide significance.[1–7] However, much of the heritability of PD remains unexplained.

One reason may be the amount of neuropathologic heterogeneity. PD is defined using clinical criteria that can include heterogeneous neuropathologic features, each of which may have a

NCRAD

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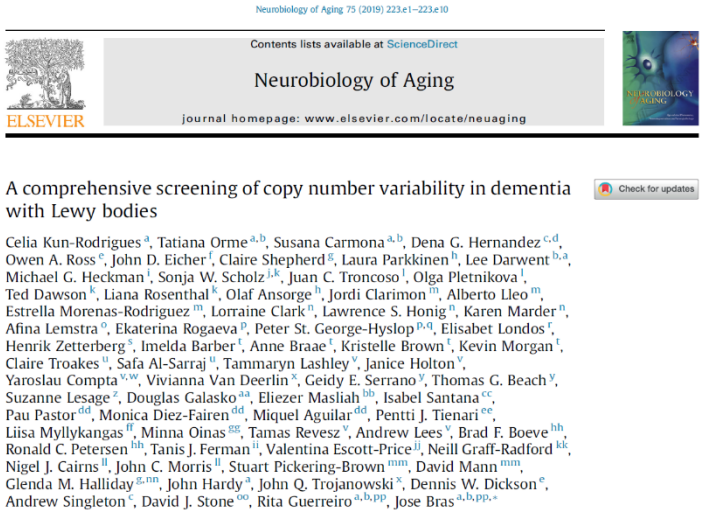
NIAGADS

Miami, Mayo, Penn, Indiana, Columbia, Sun Health, Hopkins, Harvard, UCLA, Cleveland Clinic, etc.

International DLB Genetics Consortium

- NINDS/NIA – University College London
- Mayo Clinic
- Johns Hopkins
- Columbia University
- University of Pennsylvania
- Banner Sun Health Research Institute
- University of California San Diego
- Washington University



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A comprehensive screening of copy number variability in dementia with Lewy bodies

Check for updates

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Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study

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Heritability and genetic variance of dementia with Lewy bodies

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Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases

CrossMark

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