Dementias in the Genomic Era:

Current Understanding of Lewy Body Dementia

Demystifying Medicine Lecture

NIH Campus, Bethesda, MD

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National Institutes of Health

Turning Discovery Into Health

Disclosures

- No conflicts of interest

Learning Objectives

- To understand the clinicopathological features of Lewy body dementia
- To review current genetic understanding of Lewy body dementia
- To delineate how genetic knowledge can be leveraged to advance the precision medicine paradigm

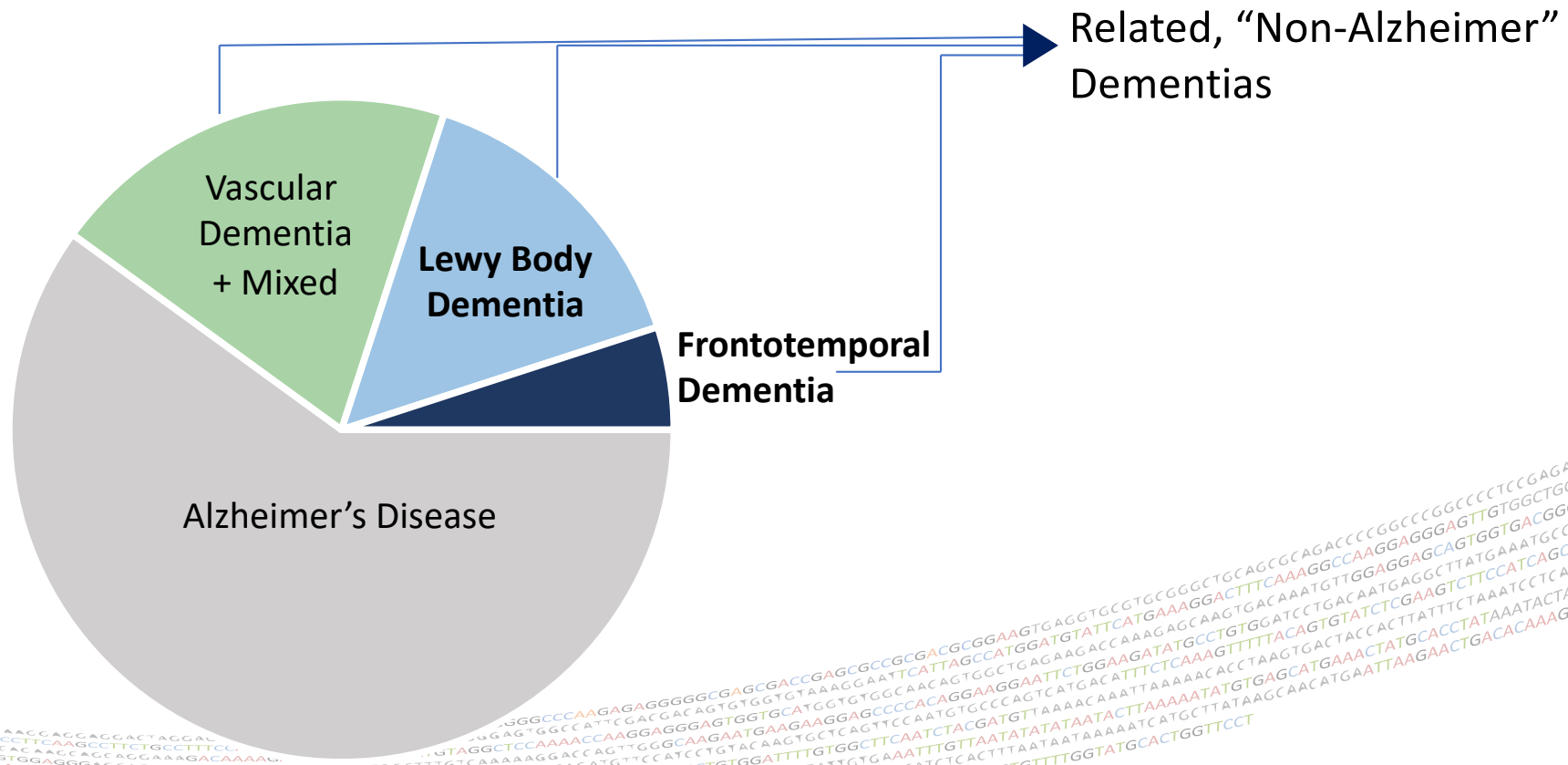
Overview

1 Background

2 Current Genetics

3 Future Directions

Age-Related Dementias



Definitions

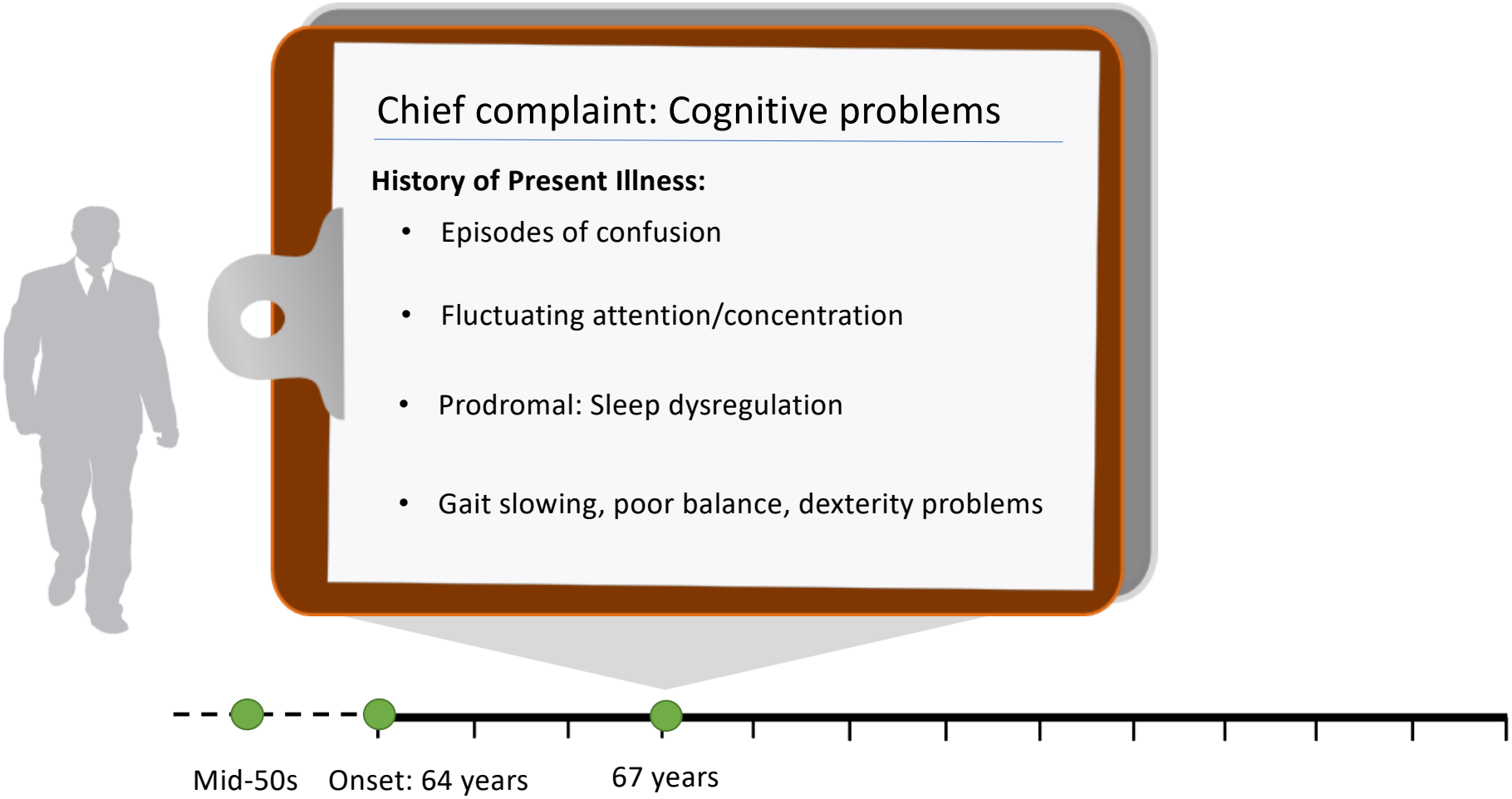
Parkinson's Disease

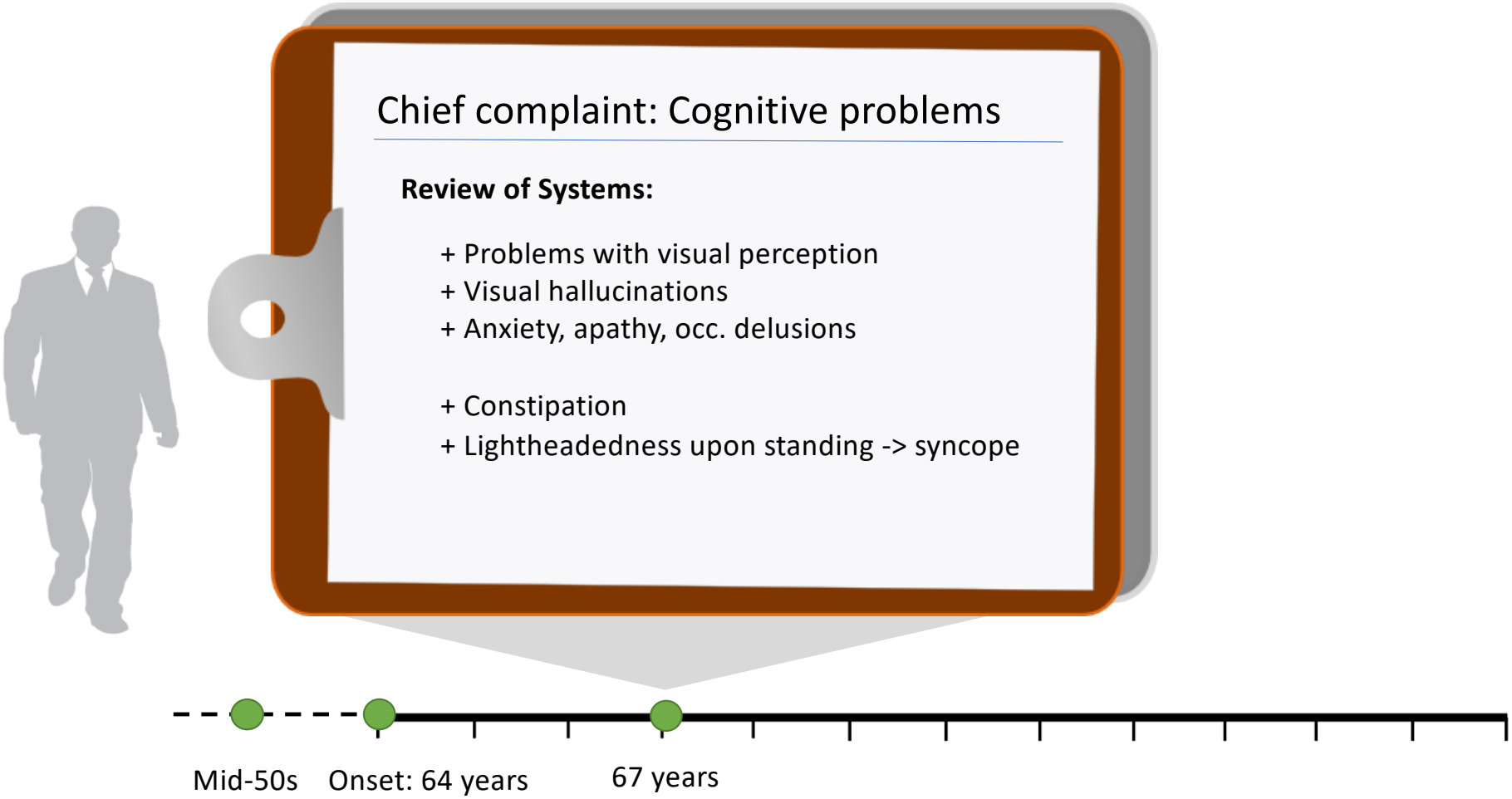
Lewy Body Dementia (LBD)

Parkinson Disease Dementia

Dementia with Lewy Bodies

1 year

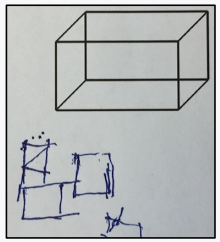

Chief complaint: Cognitive problems
History of Present Illness:
Episodes of confusion
Fluctuating attention/concentration
Prodromal: Sleep dysregulation
Gait slowing, poor balance, dexterity problems
Mid-50s
Onset: 64 years
67 years

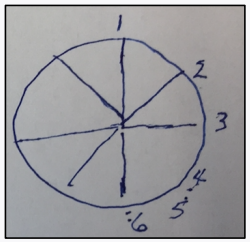

Chief complaint: Cognitive problems
Review of Systems:
+ Problems with visual perception
+ Visual hallucinations
+ Anxiety, apathy, occ. delusions
+ Constipation
+ Lightheadedness upon standing -> syncope
Mid-50s
Onset: 64 years
67 years

Chief complaint: Cognitive problems

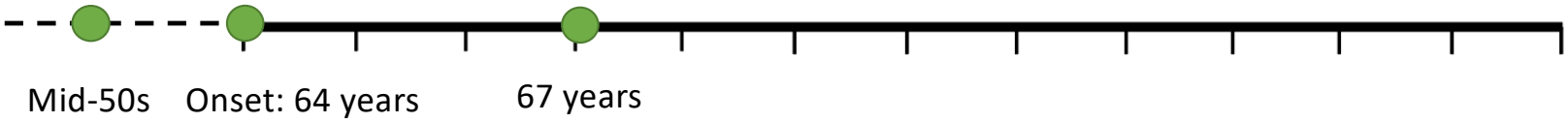
Neurological Examination:

- MOCA 19/30





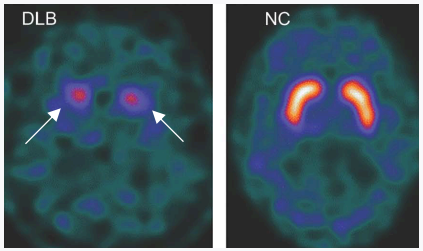
- Loss of smell
- Parkinsonism: rigidity, bradykinesia, stooped, soft voice, masked facies

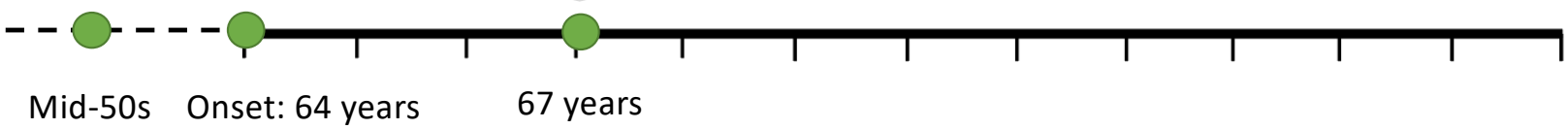


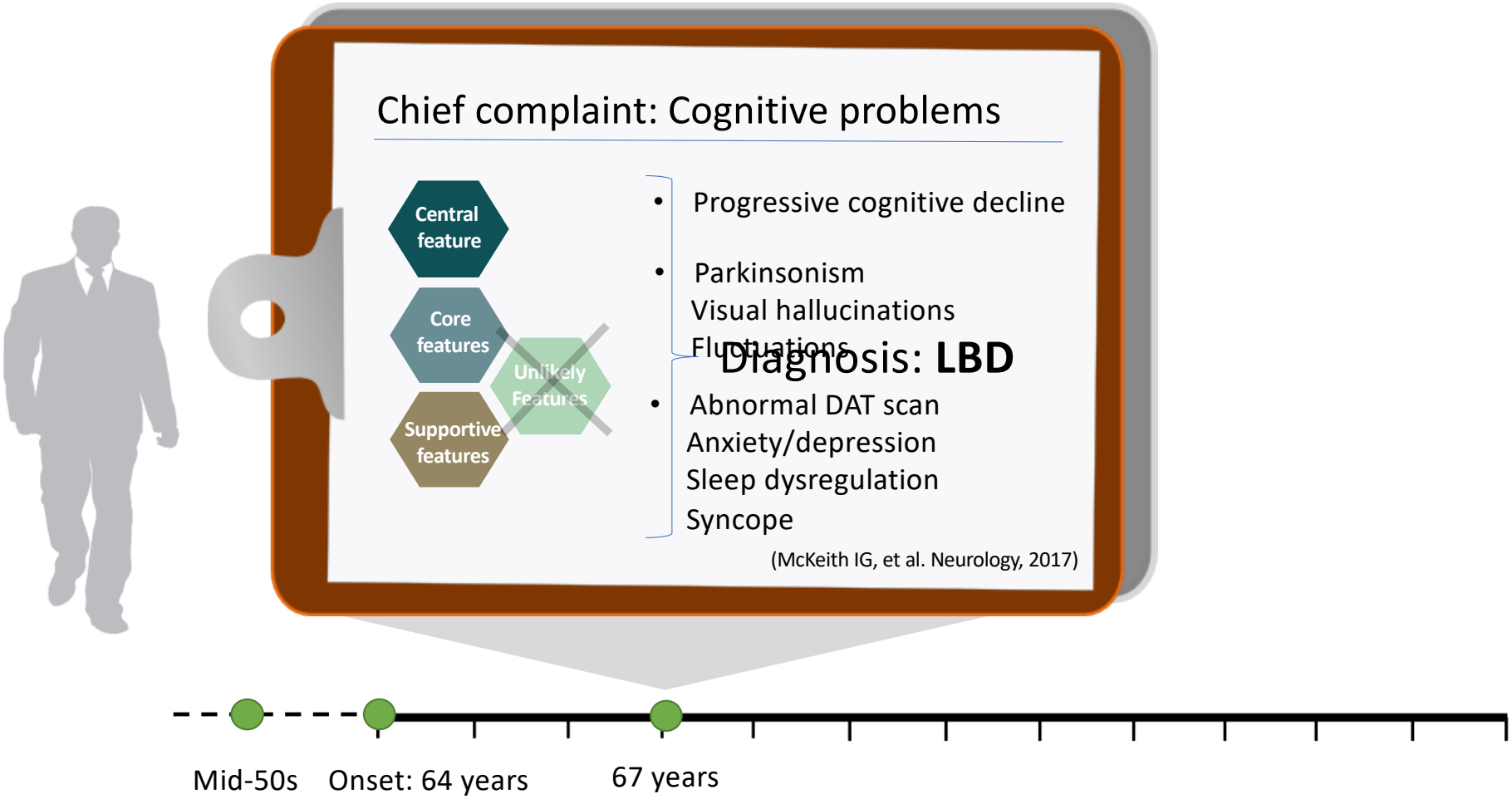
Chief complaint: Cognitive problems

Workup:

- Normal screening labs (CBC, CMP, TSH, B12)
- No acute abnormalities on MRI Brain
- DAT scan **abnormal**






Chief complaint: Cognitive problems
Central feature
Core features
Supportive features
Unlikely Features
Progressive cognitive decline
Parkinsonism
Visual hallucinations
Fluctuations
Abnormal DAT scan
Anxiety/depression
Sleep dysregulation
Syncope
Diagnosis: LBD
(McKeith IG, et al. Neurology, 2017)
Mid-50s
Onset: 64 years
67 years

Clinicopathological Features of LBD

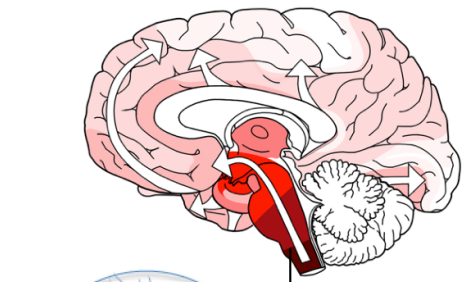
NEUROLOGICAL
Cognitive Impairment
Parkinsonism
Anosmia
Sleep dysregulation

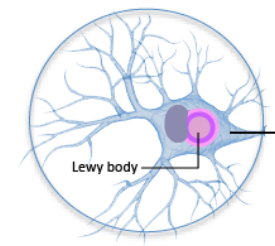
CARDIOVASCULAR
Ortho. Hypotension
Heart Rate Variability
Syncope

PSYCHIATRIC
Visual Hallucinations
Delusions
Anxiety/Depression
Fluctuating Attention
Neuroleptic Sensitivity

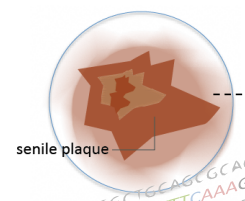
GASTROINTESTINAL
Gastroparesis
Constipation

GENITOURINARY
Urinary Incontinence
Erectile Dysfunction





NEOCORTICAL
LIMBIC SYSTEM
BRAINSTEM

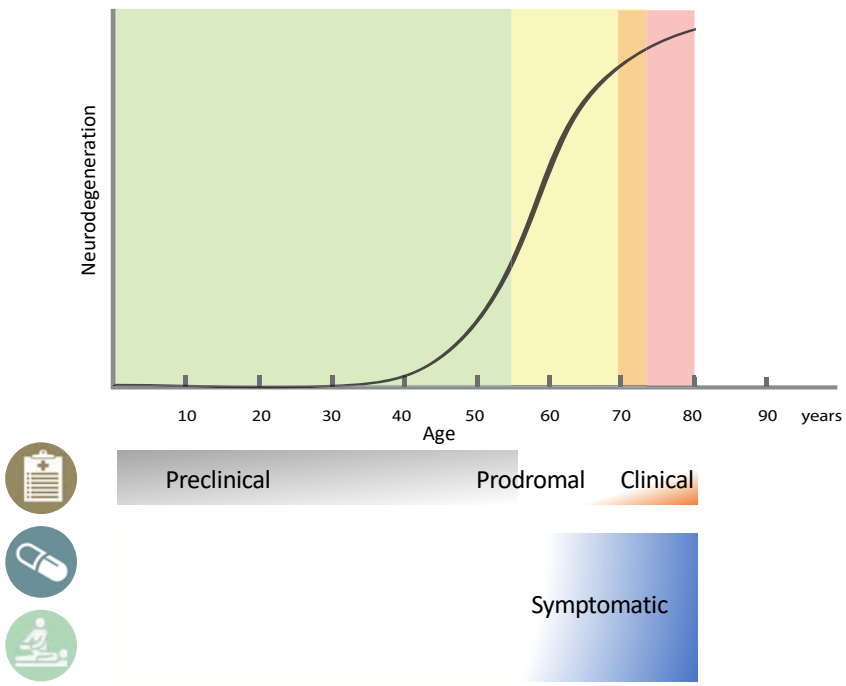


Adapted from H. Braak et al., *Cell Tissue Res* (2004)

Epidemiology

- 2nd most common neurodegenerative dementia
- 1.4 million people in the U.S.
- Men : Women = 3 : 1

Natural History



Age at onset ~ 70 years

Prodrome ~ 10-15 years

Progressive (8 years)

Treatment is supportive

Data source:
Williams, W Xiong, C et al. *Neurology* (2006)
McKeith, I Taylor, JP et al. *J Geriatr Psychiatry Neurol* (2016)

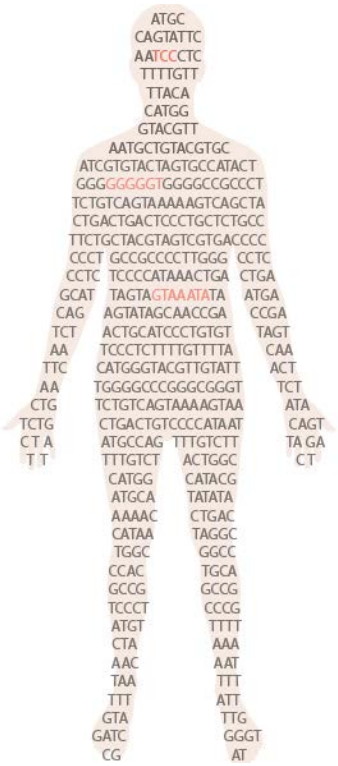
Overview

1 Background

2 Current Genetics

3 Future Directions

A Genetic Predisposition to LBD?



- Few families described
- Siblings have increased risk
- Heritability 30-60%

M.A. Denson et al. *Ann Neurology* (1997)
A. Ishikawa et al. *European Neurology* (1997)
K. Ohara et al. *Clin Neuropathology* (1997)
K. Wakabayashi et al. *Acta Neuropathologica* (1998)
S.W. Scholz et al. *Am Journal of Neurodegen Dis* (2015)
R. Guerreiro et al. *Neurobiol Dis* (2019)
R. Guerreiro et al. *Lancet Neurology* (2018)

Dissecting the Genetic Architecture of LBD

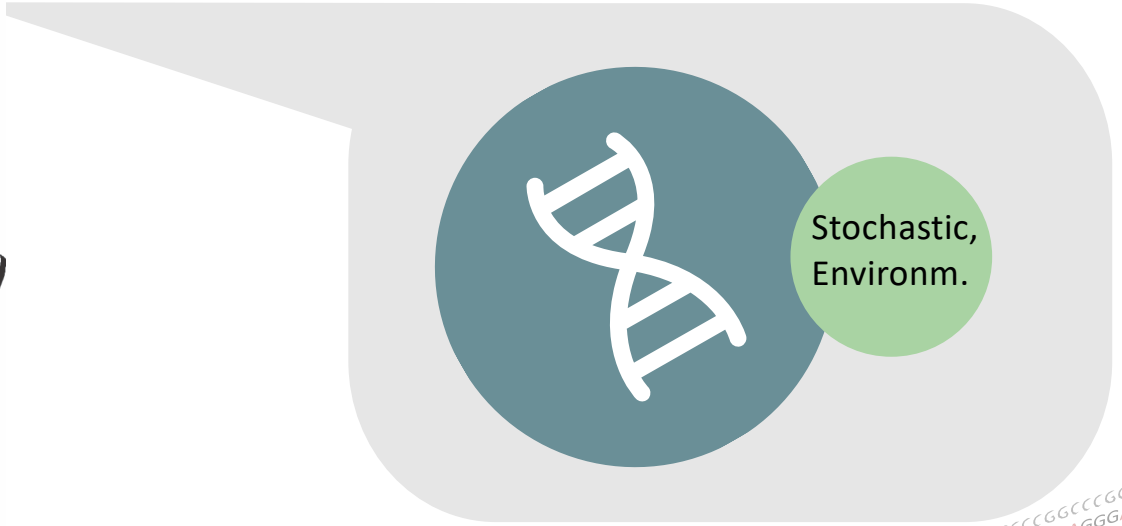
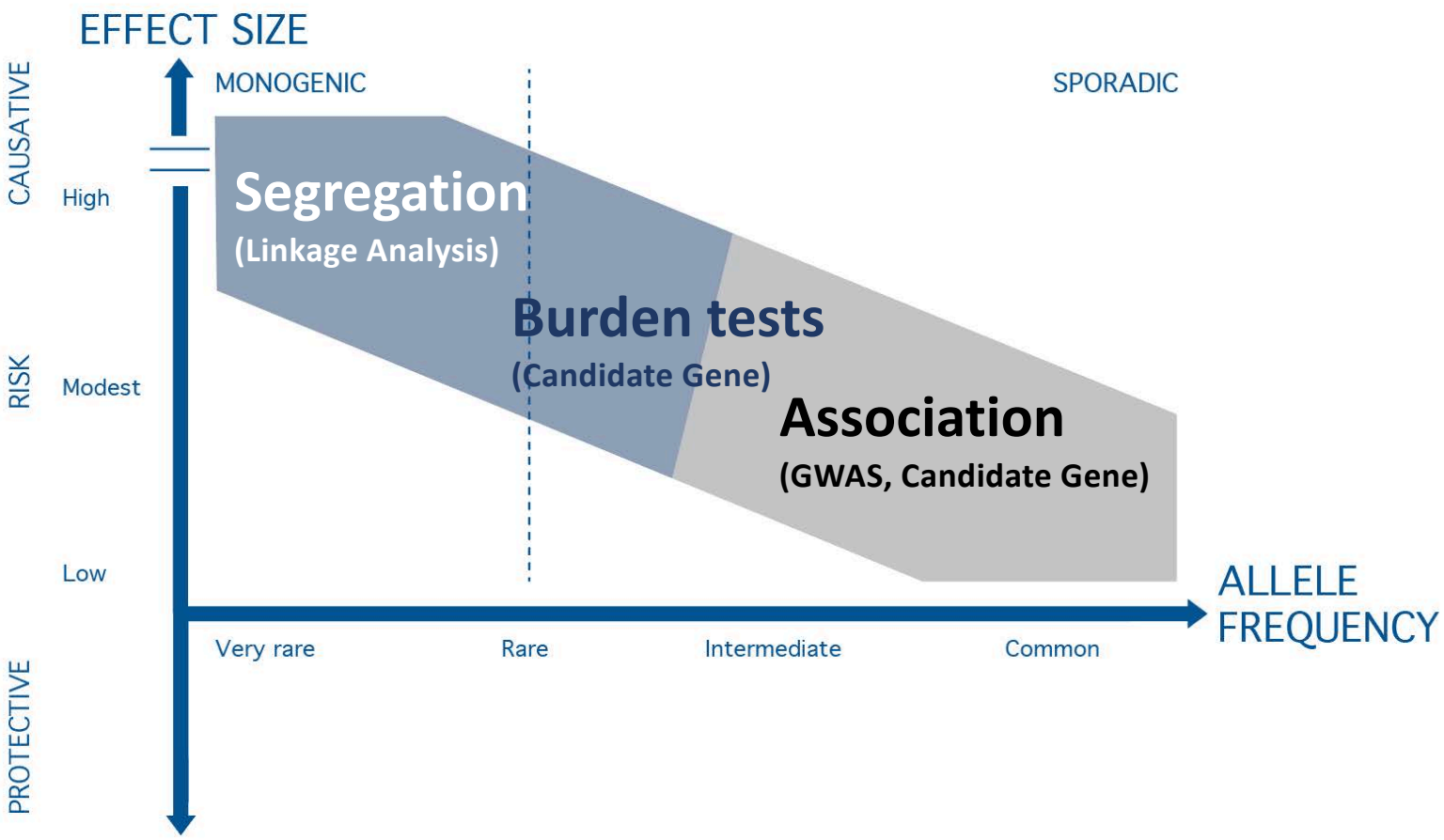


Image source: worldartsme.com

Tools to Dissect Complex Diseases



Dissecting the Genetic Architecture of LBD

1996 - 2005

Mendelian disease

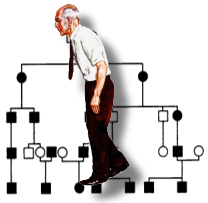
Dissecting the Genetic Architecture of LBD

1996 - 2005

Mendelian disease

Mutations in SNCA: a rare cause of familial LBD

Missense mutations in *SNCA*

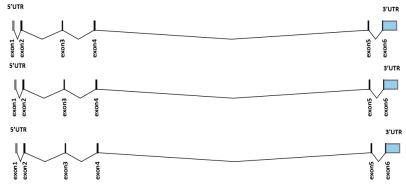


A30P E46K
A53T
G51D
A53V
A53E

Autosomal dominant

Early-onset

***SNCA* Triplication/Duplication**



Rare

Kruger, R et al., Nat Genet., 1998
Zarranz, JJ, et al., Ann Neurol., 2004
Proukakis, C et al., Neurology, 2013
Kiely, AP, et al., Acta Neuropath, 2013
Yoshino, H et al. Neurobiol Aging, 2017
Singleton, AB et al., Science, 2003
Chartier-Harlin, MC et al., Lancet, 2004

Dissecting the Genetic Architecture of LBD

1996 - 2005

Mendelian disease

Synucleinopathies: abnormal deposition α-synuclein

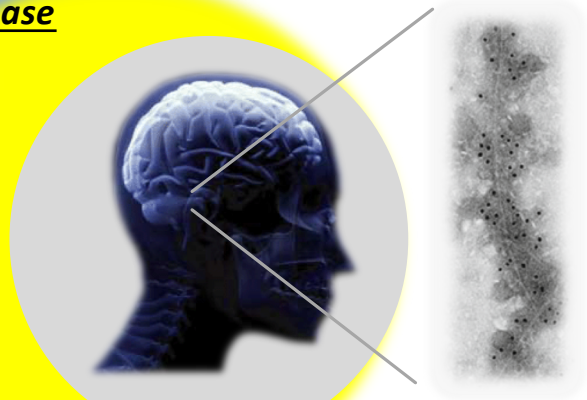
Parkinson's disease

Lewy Body Dementia

Multiple system atrophy

Pure autonomic failure

NBIA type I



EM image adapted from Goedert, M. Nat Rev Neurosci, 2001

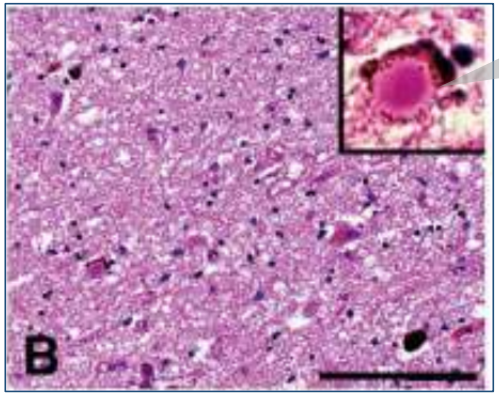
Dissecting the Genetic Architecture of LBD

1996 - 2005

Mendelian disease

Lewy body pathology in familial AD mutation cases

PSEN1 mutation carrier



Lewy body

A.Ishikawa et al., *Ann Neurol* (2005)
J.B. Leverenz et al., *Arch Neurol* (2006)

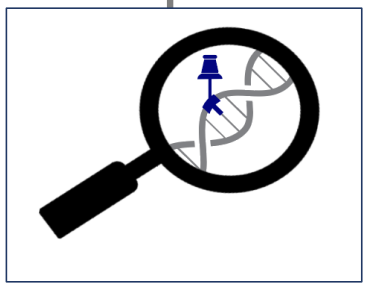
Dissecting the Genetic Architecture of LBD

Mendelian disease

1996 - 2005

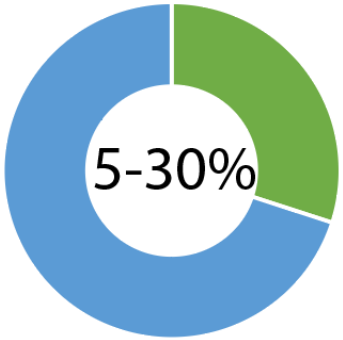
.....

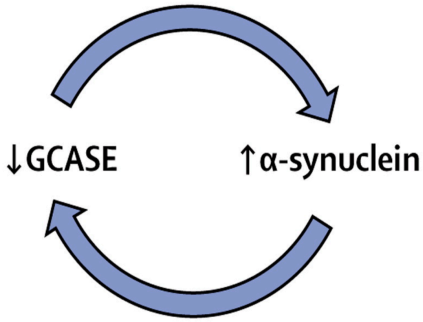
2005 - 2015



Candidate Genes

GBA mutations: autosomal dominant LBD

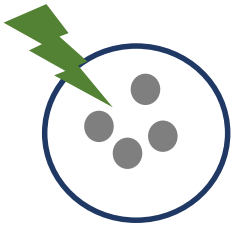




Loss of Function Mutations

I.F. Mata et al., *Arch Neurol* (2008)
M.A. Nalls et al., *JAMA Neurol* (2013)
A. Schapira et al., *Lancet* (2014)

Lysosomal Dysfunction in LBD

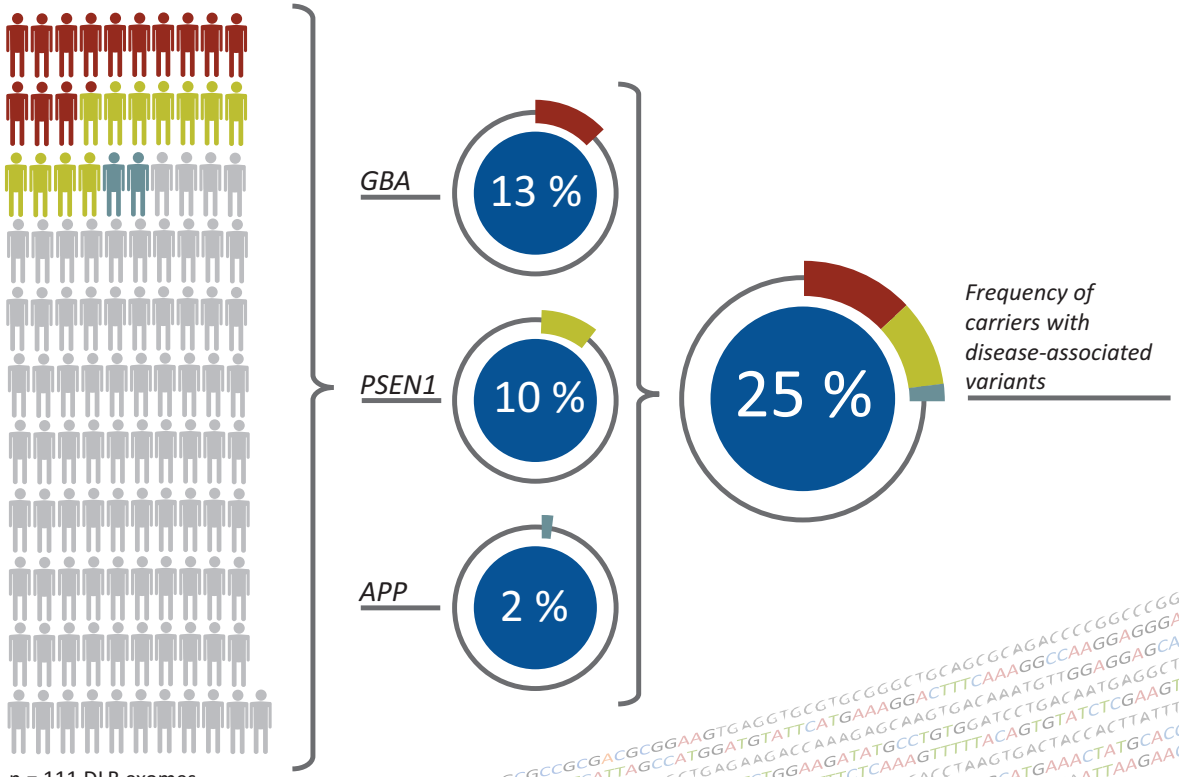


Excessive burden of mutations in lysosomal storage disorder genes (GBA, SPMD1)

Clinical trials: molecular chaperones
GCase enhancers

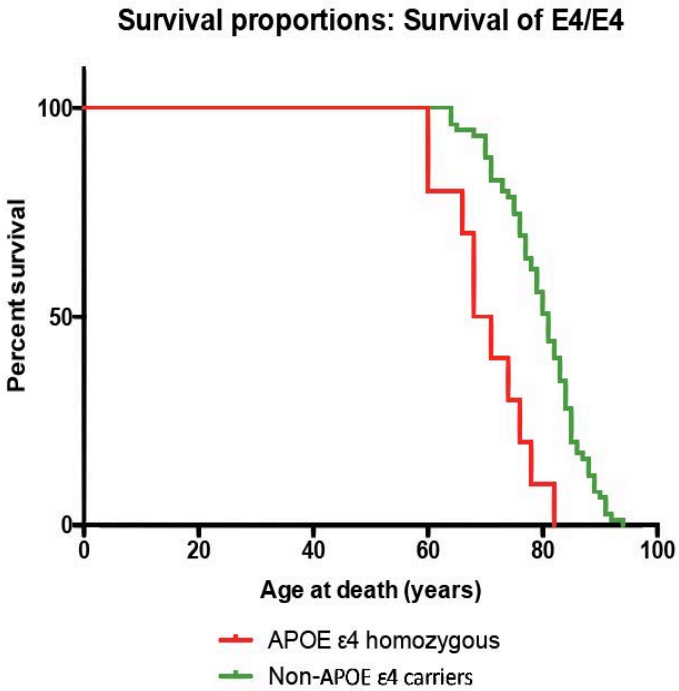
L.A. Robak et al., *Brain* (2017)
J.-N. Foo et al., *Neurobiol Aging* (2013)
Z. Gan-Or et al., *Parkinsonism Relat Disord* (2015)

A Pathological LBD Cohort



J.T. Geiger et al. *Neurobiology of Disease* (2016)

APOE ε4: a common risk variant for LBD



APOE ε4 is significantly associated with ↑risk for LBD
(*p*-value < 0.001)

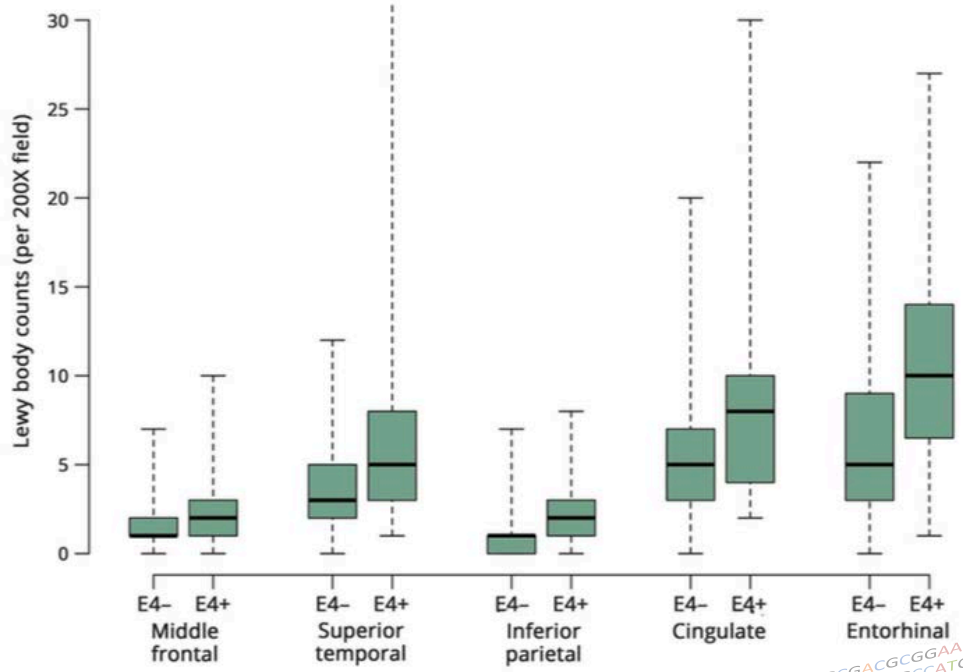
APOE ε4 decreases survival

APOE ε2 associated with ↓ disease risk

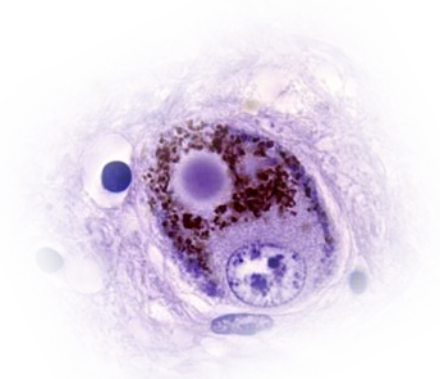
J.T. Geiger et al. *Neurobiol Disease* (2016)
M.S. Sabir et al. *Neuribiol Aging* (2019)

APOE ε4: a common risk variant for LBD

↑ Lewy body pathology in *APOE ε4* carriers (independent of Alzheimer pathology)



n=650 pathologically confirmed LBD cases

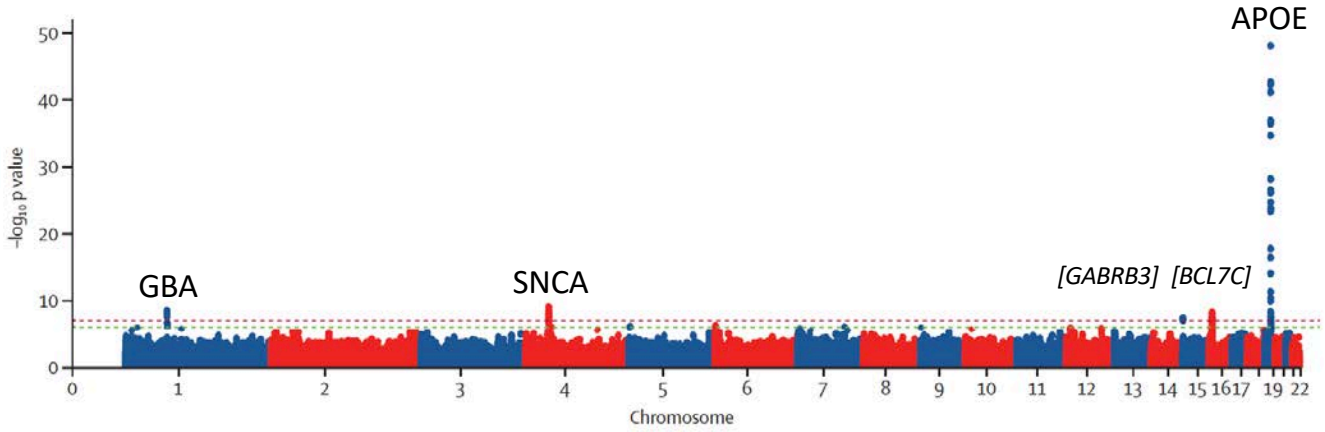


D.W. Dickson et al. *Neurology* (2018)

LBD GWAS

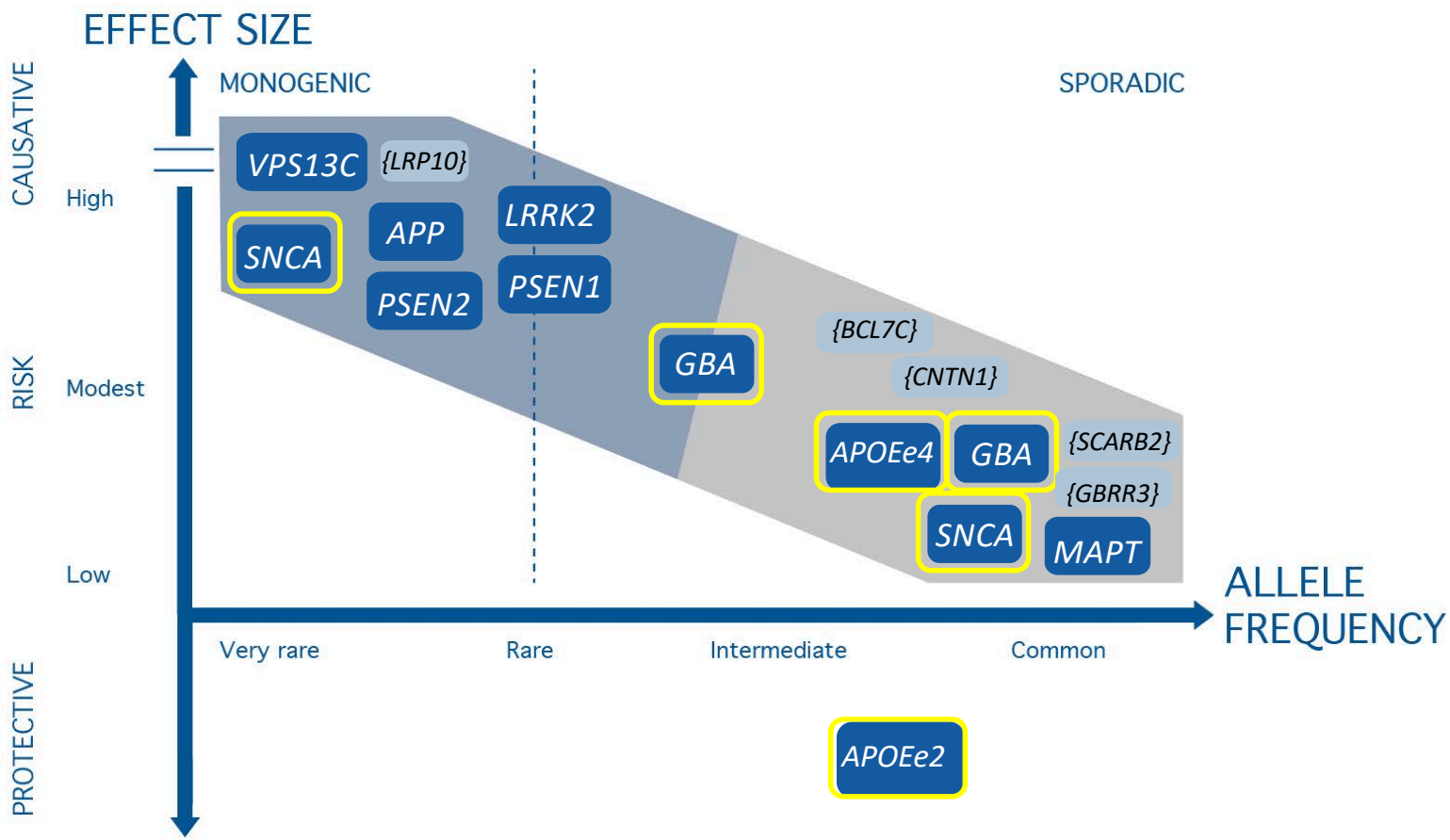
Multicenter, international LBD GWAS

(Discovery stage: n = 1,216 LBD cases, n = 3,791 controls)
(Replication stage: n = 527 LBD cases, n = 663 controls)

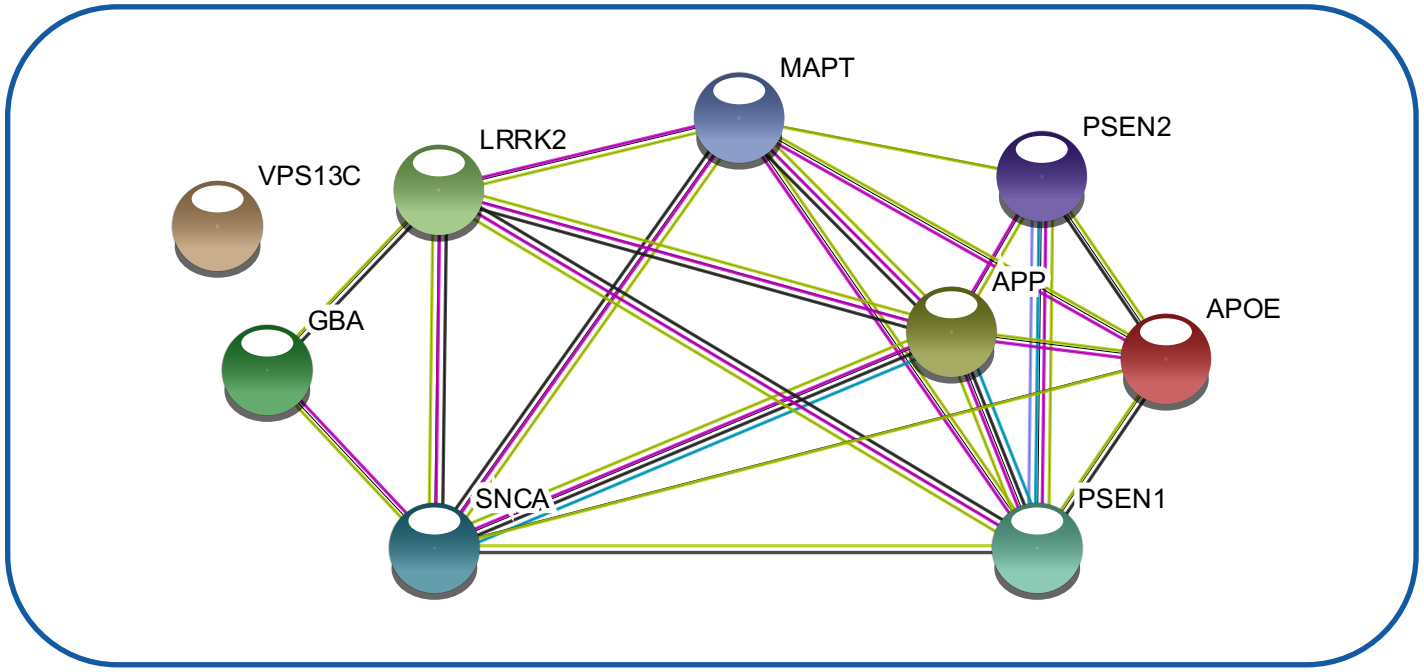


R. Guerreiro et al., *Lancet Neurol* (2018)

LBD Genetics: April 2019



Molecular Links to Alzheimer's and Parkinson's Disease



Parkinson's disease

Alzheimer's disease

Lewy body dementia risk genes

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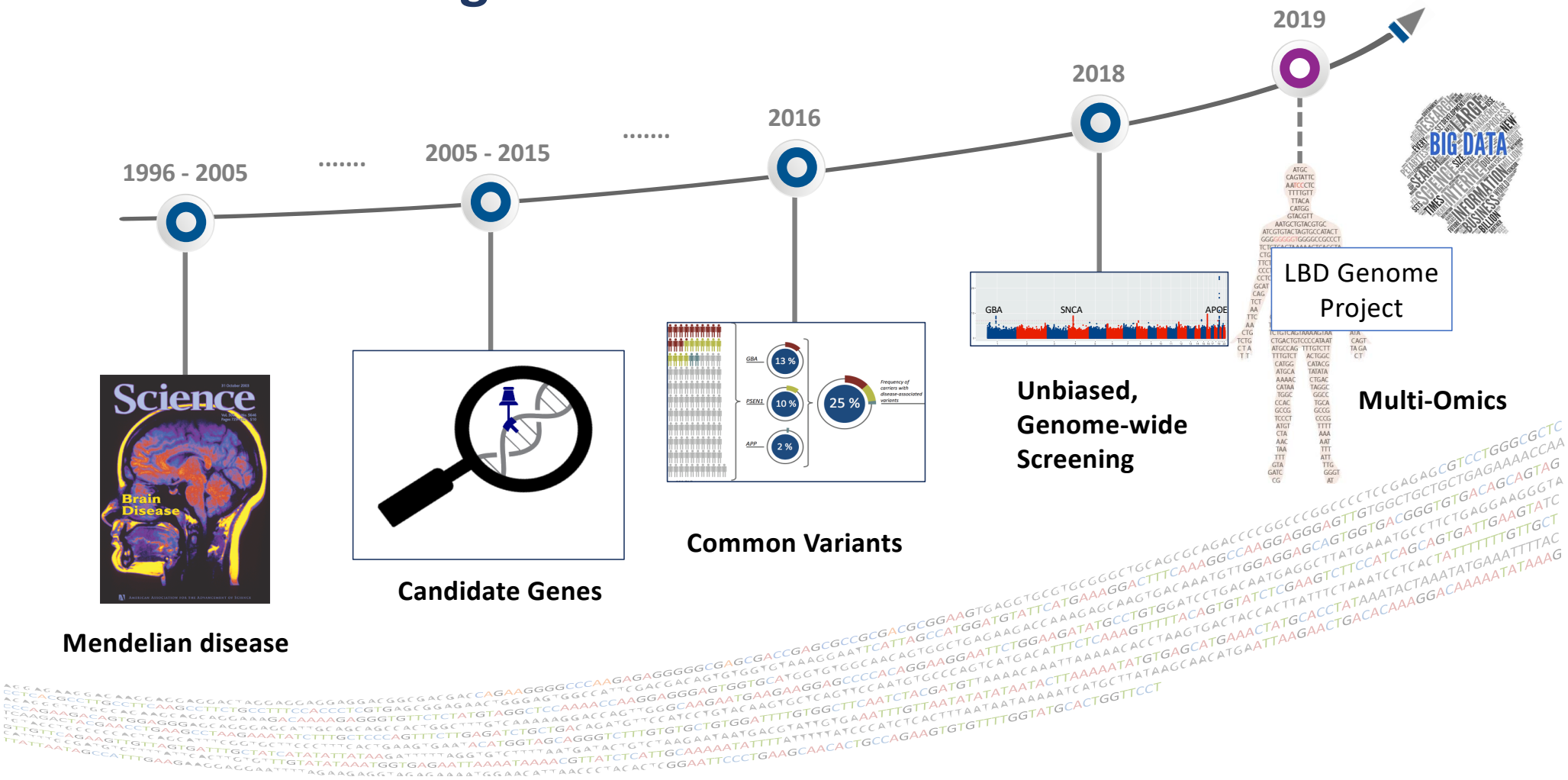
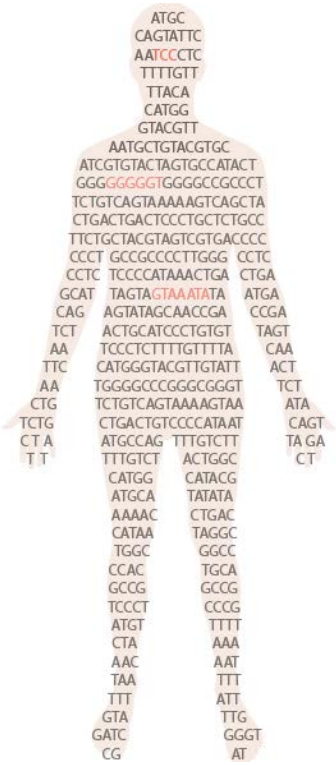
Dissecting the Genetic Architecture of LBD



Dementia Genome Sequencing Initiative

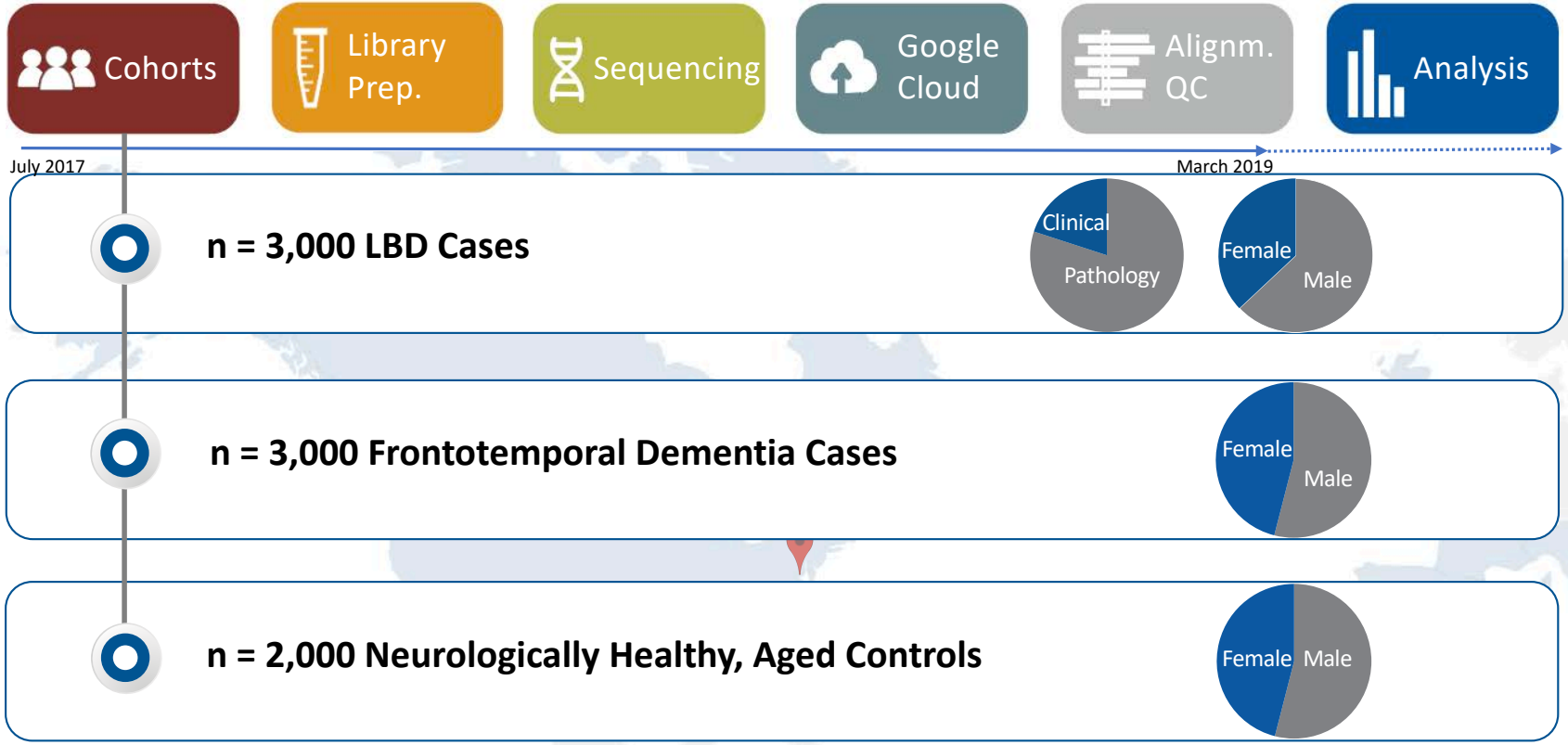


NIH Genome Sequencing Project:

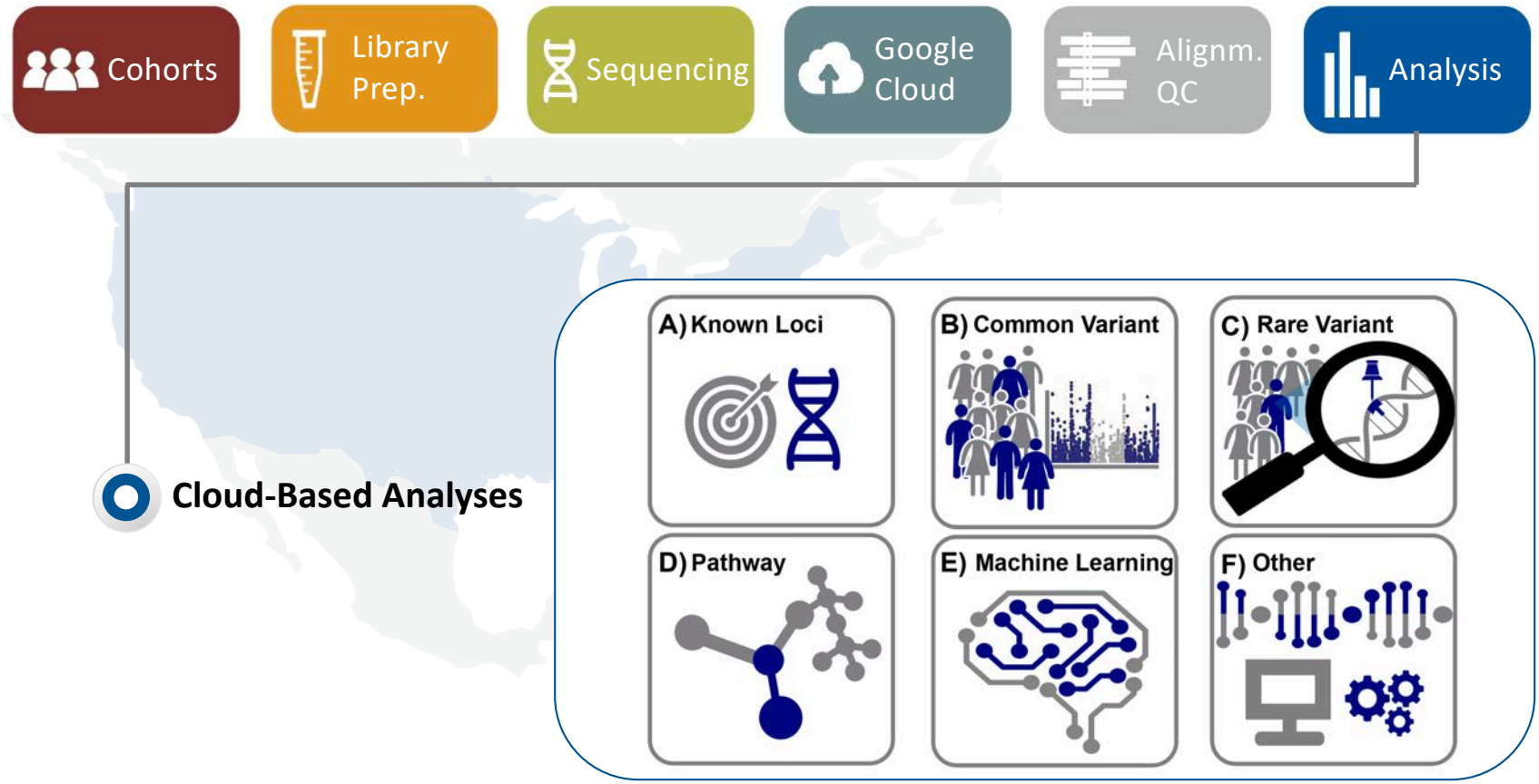
a) Lewy body dementia (LBD)
b) Frontotemporal dementia (FTD)
c) Neurologically Healthy, Aged Controls

Extend gene discovery efforts

Dementia Genome Sequencing Initiative



Dementia Genome Sequencing Initiative



Dementia Genome Sequencing Initiative

The Path to Precision Medicine

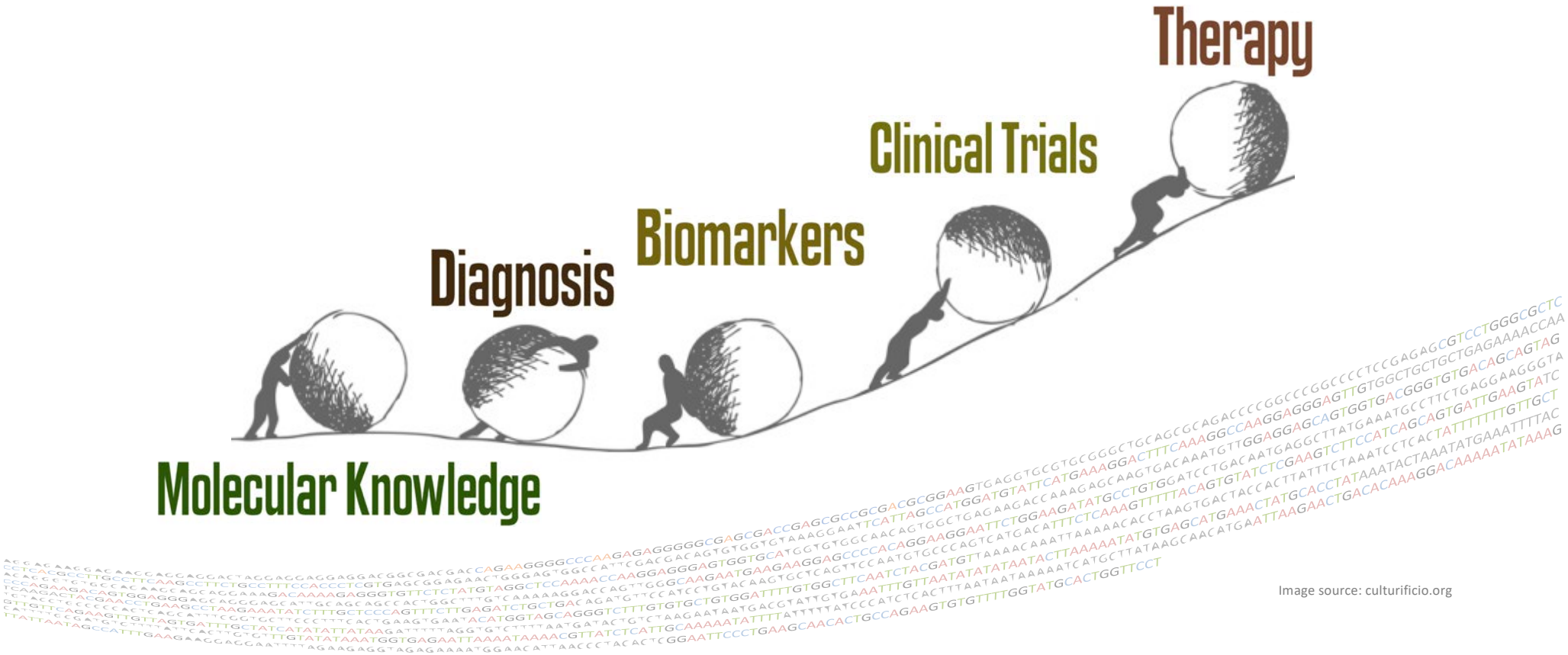


Image source: culturificio.org

Key Messages

- LBD is a common, complex neurodegenerative form of dementia
- Genetic factors are involved in the pathogenesis of LBD
- Genomics provides unprecedented opportunities
- Dementia genome sequencing initiative will generate a unique resource to accelerate the pace of discovery

Questions?