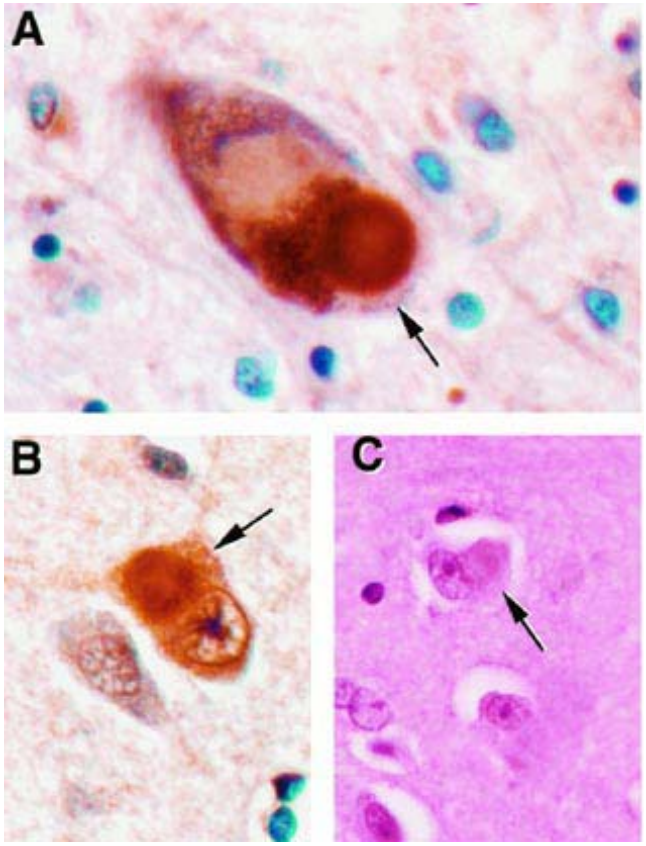
Epidemiology & Genetics of Dementia with Lewy Bodies

Richard Mayeux
Columbia University
Taub Institute/Sergievsky Center

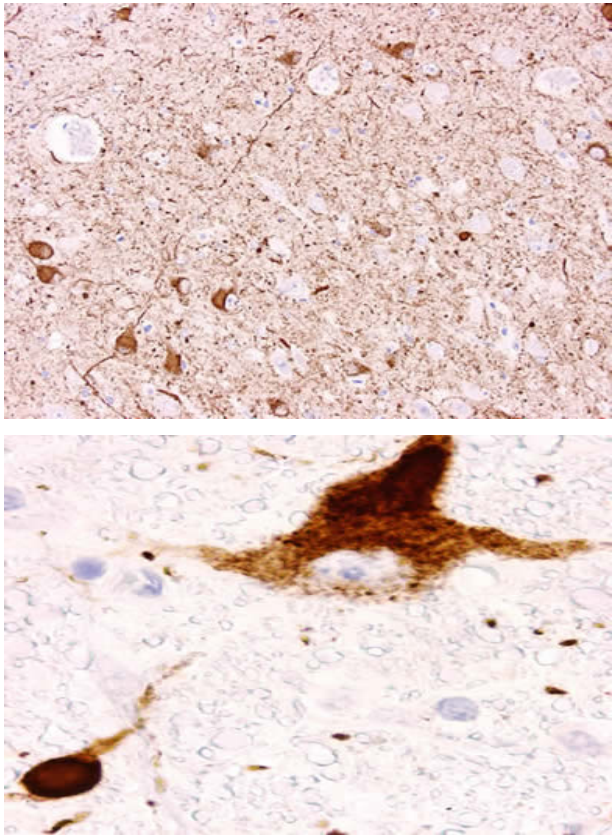
Epidemiology & Genetics of DLB

- Frequency
  - Pathological diagnosis
  - How accurate is the clinical diagnosis?
  - Rates uncertain without a uniform definition
- Risk factors
  - Misclassification of diagnosis
- Genetic influences
  - Families multiply affected
  - Cohort studies

Lewy Body Pathology



A. Lewy body in substantia nigra
B. & C. Lewy body in cortical neuron
Ubiquitin Stain



A. & B. Lewy body in cortical neuron
Immunostained for α synuclein

Clinical Criteria for DLB

Table 1 *Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)*

1. *Central feature* (essential for a diagnosis of possible or probable DLB)

   Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.

2. *Core* features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)

   Fluctuating cognition with pronounced variations in attention and alertness

   Recurrent visual hallucinations that are typically well formed and detailed

   Spontaneous features of parkinsonism

3. *Suggestive features* (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)

   REM sleep behavior disorder

   Severe neuroleptic sensitivity

   Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

4. *Supportive features* (commonly present but not proven to have diagnostic specificity)

   Repeated falls and syncope

   Transient, unexplained loss of consciousness

   Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence

   Hallucinations in other modalities

   Systematized delusions

   Depression

   Relative preservation of medial temporal lobe structures on CT/MRI scan

   Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity

   Abnormal (low uptake) MIBG myocardial scintigraphy

   Prominent slow wave activity on EEG with temporal lobe transient sharp waves

5. A diagnosis of DLB is *less likely*

   In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging

   In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture

   If parkinsonism only appears for the first time at a stage of severe dementia

6. *Temporal sequence* of symptoms

   DLB should be diagnosed when dementia [illegible] parkinsonism (if it is present). The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

McKeith, I. G. et al. 2005

Likelihood of Pathologic Findings Reflect DLB Clinical Syndrome

Table 3 *Assessment of the likelihood that the pathologic findings are associated with a DLB clinical syndrome*

	Alzheimer type pathology		
	NIA-Reagan Low (Braak stage 0–II)	NIA-Reagan Intermediate (Braak stage III–IV)	NIA-Reagan High (Braak stage V–VI)
Lewy body type pathology			
Brainstem-predominant	Low	Low	Low
Limbic (transitional)	High	Intermediate	Low
Diffuse neocortical	High	High	Intermediate

DLB = dementia with Lewy bodies; NIA = National Institute on Aging.

McKeith, I. G. et al. 2005

Antemortem Prediction of LBD

Table 2 Frequency of clinical features in patient groups

	DLB (n = 23)	AD (n = 94)	P-value*
Visual hallucinations	5 (22)	1 (1)	0.001
Extrapyramidal signs	6 (26)	15 (16)	0.3
Visuospatial impairment on DRS-C	17 (74)	42 (45)	0.011
Wrong MMSE pentagon copy	7 (30)	15 (16)	0.1

Table 3 Sensitivity, specificity, predictive values, and odds ratios of clinical variables for distinguishing DLB from Alzheimer's disease

	Sensitivity	Specificity	PPV	NPV	Odds ratio (95% CI)
Visual hallucinations	0.22	0.99	0.83	0.84	25.8 (2.8–234.6)
Extrapyramidal signs	0.26	0.82	0.26	0.82	1.6 (0.5–4.7)
Visuospatial impairment on DRS-C	0.74	0.55	0.29	0.90	3.5 (1.3–9.7)
Wrong MMSE pentagon copy	0.30	0.84	0.32	0.83	2.3 (0.8–6.6)

PPV = positive predictive value, NPV = negative predictive value. Other abbreviations are as in Table 1.

Tiraboshi P, et al 2006

Table 1. Comparison of Clinical Signs and Symptoms Among LBP-Positive and LBP-Negative Participants

Parkinsonism	*LBP Positive (n = 80) n (%)*	*LBP Negative (n = 72) n (%)*	P *Value*a
Tremor	9 (11.3)	7 (9.7)	.76
Rigidity	9 (11.3)	5 (6.9)	.36
Bradykinesia	**15 (18.8)**	**5 (6.9)**	**.03**
Postural/gait	**23 (28.8)**	**13 (18.1)**	**.12**
Masked facies	**8 (10.0)**	**3 (4.2)**	**.17**
Postural instability	**15 (18.8)**	**8 (11.1)**	**.19**
Shuffling gait	**15 (18.8)**	**6 (8.3)**	**.06**
Multiple falls	**22 (27.5)**	**13 (18.1)**	**.17**
Neuropsychiatric symptoms			
Delusions	49 (61.3)	44 (61.1)	.99
Hallucinations	**48 (60.0)**	**24 (33.3)**	**.001**
Agitation	56 (70.0)	50 (69.4)	.94
Depression	51 (63.8)	44 (61.1)	.74
Anxiety	53 (66.3)	51 (70.8)	.54
Apathy	56 (70.0)	45 (62.5)	.33
Disinhibition	**12 (15.0)**	**6 (8.3)**	**.20**
Irritability	**40 (50.0)**	**43 (59.7)**	**.23**
Lability	35 (43.8)	29 (40.3)	.67
Aberrant motor behavior	54 (67.5)	46 (63.9)	.64
Hypersomnia	16 (20.0)	13 (18.1)	.76

Note: Signs and symptoms that differ between the 2 groups with $P < .20$ are in bold.
a. Chi-square statistic with one degree of freedom.

Tsuang D, et al 2008

Frequency of DLB by Clinical Criteria

Table 2. Distribution of dementia etiologies in patients evaluated at the Alzheimer's Disease Research Centers of California, 1992–2002

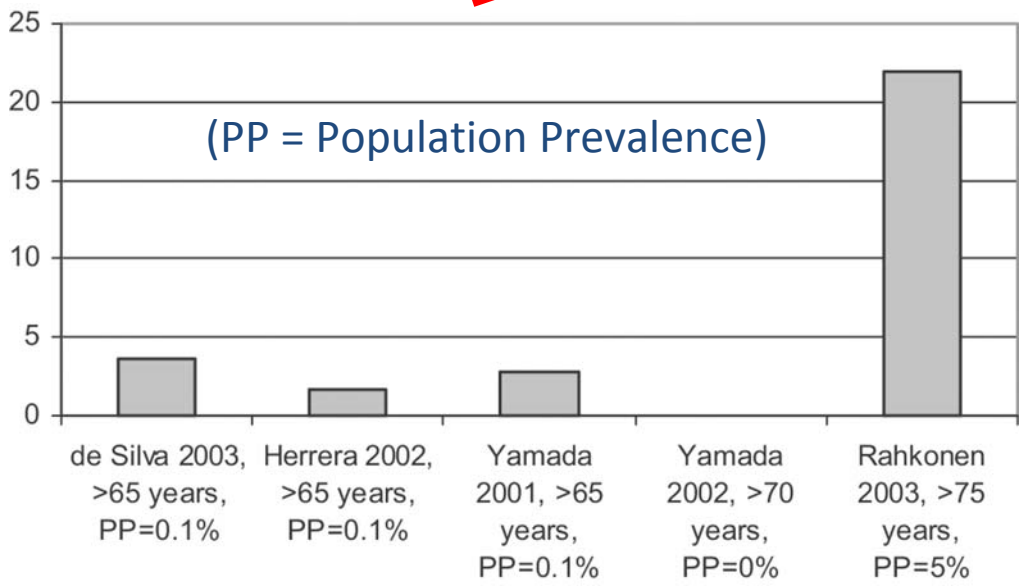
	API (n = 452)	Black (n = 472)	Latino (n = 675)	White (n = 4,926)	Total (n = 6,525)	p value
Alzheimer disease	351 (77.7)	381 (80.7)	557 (82.5)	4,037 (82.0)	5,326 (81.6)	0.13
Vascular dementia	60 (13.3)	68 (14.4)	71 (10.5)	364 (7.4)	563 (8.6)	<0.001
Dementia with Lewy bodies	10 (2.2)	12 (2.5)	20 (3.0)	242 (4.9)	284 (4.4)	<0.01
Frontotemporal lobar degeneration	19 (4.2)	7 (1.5)	16 (2.4)	231 (4.7)	273 (4.2)	<0.01
Parkinson disease	5 (1.1)	3 (0.6)	8 (1.2)	30 (0.6)	46 (0.7)	0.27
Progressive supranuclear palsy	7 (1.5)	1 (0.2)	3 (0.4)	22 (0.4)	33 (0.5)	<0.05

Figures in parentheses are percentages.

Population-Based Estimates of DLB

Table 2. Prevalence and incidence of DLB in population-based studies

Study	Numbers screened	Age	Dementia/population	DLB/population	DLB/dementia
Prevalence					
De Silva (2003)	703	>65	4.0% (28/703)	0.1% (1/703)	3.6% (1/28)
Herrera (2002)	1656	>65	7.1% (118/1656)	0.1% (2/1656)	1.7% (2/118)
Rahkonen (2003)	601	>75	22.8% (137/601)	5.0% (30/601)	21.9% (30/137)
Stevens (2002)	1085	>65	6.6% (72/1085)	2.0% (22/1085)	30.5% (22/72)
Yamada (2001)	3715	>65	3.8% (142/3715)	0.1% (4/3715)	2.8% (4/142)
Yamada (2002)	157	>70	12.1% (19/157)	0% (0)	0% (0)
Incidence					
Miech (2002)	5092	>65	3.6% a year (185/5092)	0.1% a year (6/5092)	3.2% a year (6/185)



Zaccai, J. et al 2005

Lewy Bodies -Healthy Elderly

Table 2 *Selected pathologic characteristics of subjects without cognitive impairment in the Religious Orders Study (ROS) and the Memory and Aging Project (MAP)*

Pathologic characteristics	ROS	MAP
CERAD AD		
Not present	40 (40.8)	17 (47.2)
Possible	13 (13.3)	3 (8.3)
Probable	36 (36.7)	14 (38.9)
Definite	9 (9.2)	2 (5.6)
Braak Score		
0	3 (3.1)	1 (2.8)
I	19 (19.4)	7 (19.4)
II	18 (18.4)	9 (25.0)
III	26 (26.5)	10 (27.8)
IV	27 (27.6)	9 (25.0)
V	5 (5.1)	0
VI	0	0
NIA-Reagan AD		
Not present	2 (2.0)	5 (13.9)
Low likelihood	59 (60.2)	18 (50.0)
Intermediate likelihood	35 (35.7)	13 (36.1)
High likelihood	2 (2.0)	0
Infarcts		
Not present	75 (76.5)	30 (83.3)
Present	23 (23.5)	6 (14.7)
Lewy bodies		
Not present	84 (83.6)	32 (88.9)
Nigral	7 (7.1)	1 (2.8)
Limbic	5 (5.1)	2 (5.6)
Neocortical	2 (2.0)	1 (2.8)

Values are n (%).

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; AD = Alzheimer disease.

12 to 16%

Bennett, D. A. et al. Neurology 2006

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Cerebrovascular contributions to DLB

	Total	Dementia	No dementia
Any cerebrovascular risk factor	72 (55)	47 (36)	25 (19)
Coronary heart disease	9 (6.9)	3	6
Atrial fibrillation	1 (0.8)	1	0
Heart failure*	9 (6.9)	6	3
Stroke/TIA	2 (1.5)	1	1
Hypertension	16 (12.3)	4	12
Diabetes mellitus	3 (2.3)	0	3
Smoking	45 (34.6)	15	30
No cerebrovascular risk factors	58 (45)	18	40

Values in parentheses are in percentage. Chi-square tests used. Two-tailed *P* values. $*P < 0.05$.

Haugarvoll K, 2004

Variable	DLB ($n = 25$)	AD ($n = 63$)
Age at death (years)	80.8 ± 6.6	83.2 ± 6.2
Age of onset (years)	75.1 ± 6.9	75.4 ± 7.4
Duration (months)	69.4 ± 50.5	92.8 ± 55.1
Hypertension	11 (44%)	27 (43%)
Hyperlipidemia	2 (8%)	2 (3%)
Heart disease	4 (16%)	11 (17%)
Diabetes mellitus	2 (8%)	10 (16%)
Tobacco use	10 (40%)	18 (29%)
Brain weight	1164 ± 124	1048 ± 118
Gross hemorrhage	5 (20%)	7 (11%)
Gross infarction	9 (36%)	25 (40%)
Microscopic hemorrhage	3 (12%)	4 (6%)
Microscopic infarction	10 (40%)	43 (68%)

Isojima D, et al 2006

Family History of Dementia as a Risk Factor for LBD

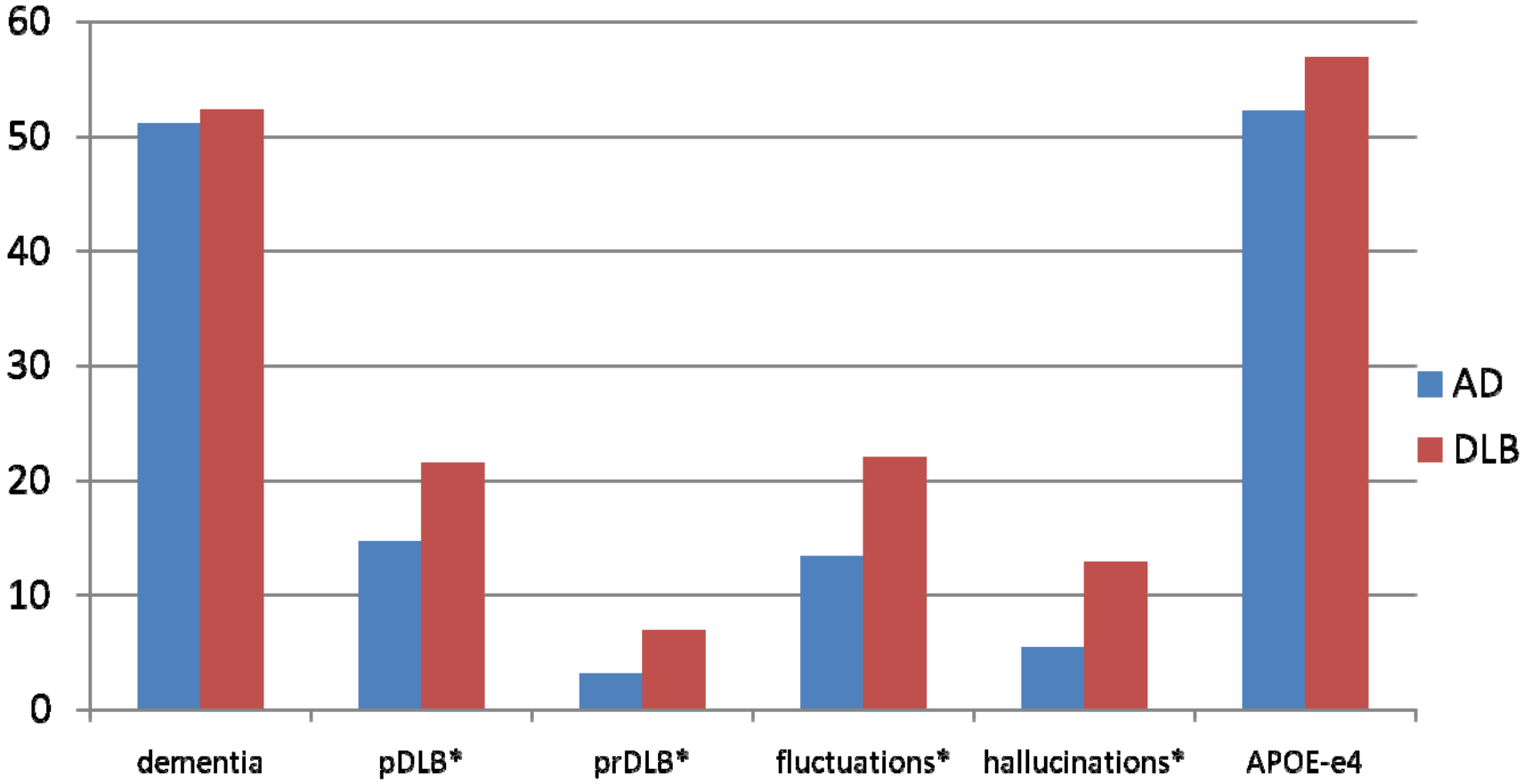
Table 2 *Patient characteristics*

Diagnosis type	No. of patients	% with family history of dementia (95% CI)	Median Braak stage (range)	% of all alleles that are E4 (95% CI)
AD	70	49 (36–61)	5.5 (4.0–6.0)	33 (24–44)
LBD	18	67 (41–87)	3.0 (0.0–4.0)	15 (4–35)
Controls	60	13 (6–25)	NA	9 (4–16)

AD = Alzheimer disease; LBD = Lewy body dementia (Braak stage ≤ 4); NA = not applicable.

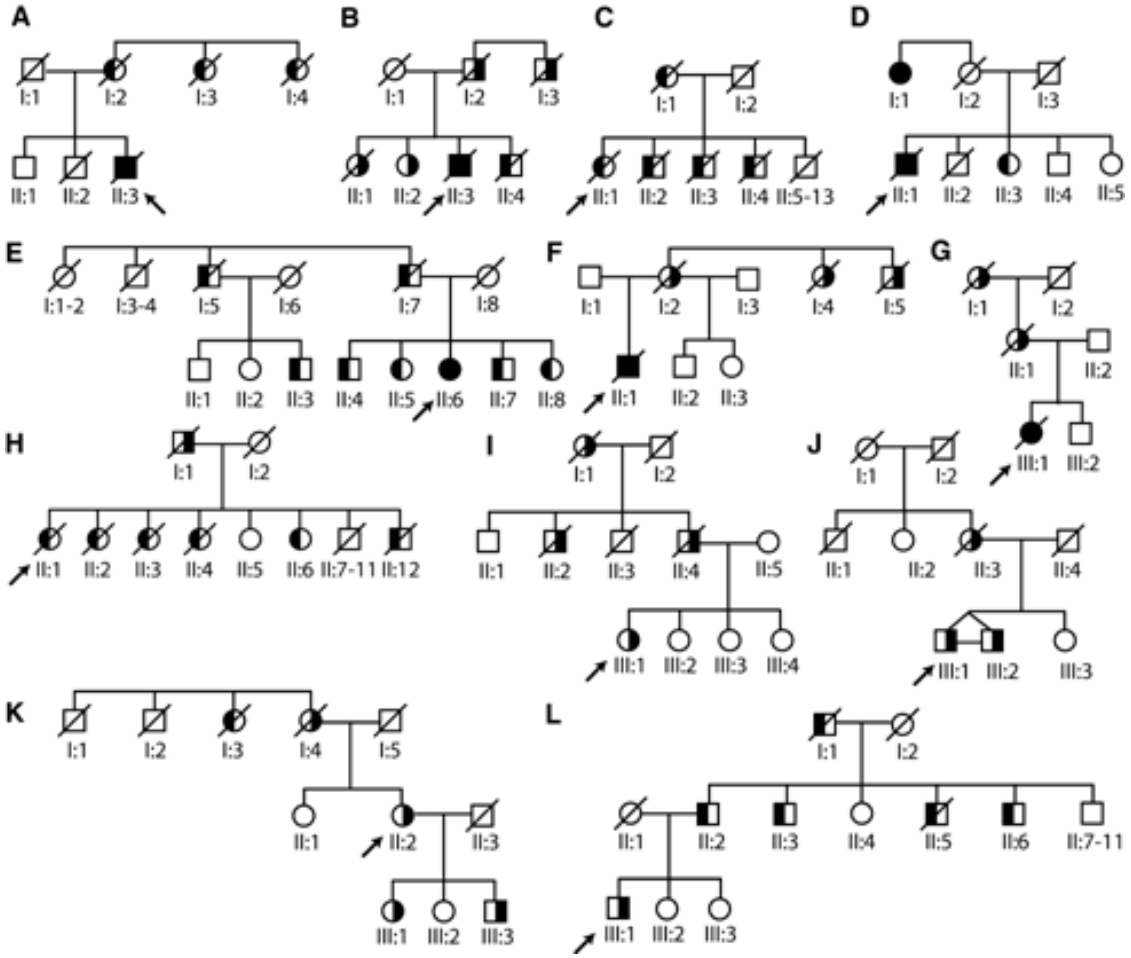
Woodruff, B. K. et al. 2006

Familial Aggregation of Clinically Diagnosed DLB



Nervi A, et al 2008

Families with Cortical Lewy Bodies and Dementia



Left = dementia, Right = PD, Full = both

Harding AJ, et al 2004

DLB Kindreds and APOE

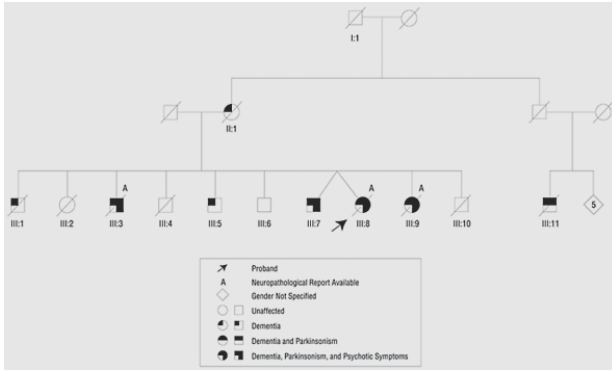


Table 1. Clinical Characteristics, Source of Information, and *APOE* Genotypes in Families 1 and 2*

Subject No.	Age of Onset, y	Dementia	Parkinsonism	Psychosis	Source of Information	*APOE* Genotype
			Family 1			
I:1	. . .	–	–	–	Hx	NA
II:1	72	+	–	–	Hx	NA
III:1	67	+	–	–	Hx and Med Rec	NA
III:3	73	+	+	+	Hx and Med Rec	ε3/ε4
III:5	79	+	–	–	Hx	ε3/ε4
III:6	. . .	–	–	–	Hx	ε3/ε4
III:7	77	+	+	+	Hx	ε3/ε4
III:8	67	+	+	+	Hx and Med Rec	ε3/ε4
III:9	63	+	+	+	Hx and Med Rec	ε3/ε4
III:11	69	+	+	–	Hx and Med Rec	ε4/ε4
			Family 2			
I:1	83	+	+	–	Hx, Med Rec, and PE	ε3/ε4
I:2	76	+	+	–	Hx, Med Rec, and PE	ε4/ε4
I:3	80	+	+	–	Hx and Med Rec	ε4/ε4
I:4	63	+	+	–	Hx, Med Rec, and PE	ε4/ε4
I:5	58	+	–	–	Hx and Med Rec	NA
I:7	59	+	–	–	Hx and Med Rec	NA

*APOE indicates apolipoprotein E; –, absent; Hx, clinical history; +, present; Med Rec, medical records; PE, face-to-face physical examination; NA, data not available; and ellipses, data not applicable.

Table 2. Clinical and Neuropathological Characteristics in 2 Families With DLB*

		Clinical Features			Neuropathological Findings				
					Braak Staging† (AD Changes)		LBs		
							SN		
Subject No.	Age of Onset, y	Dementia	PD	Psychosis	NFTs	SPs	H&E Staining	AS Staining	Amygdala (AS Staining)
				Family 1					
III:3	73	+	+	+	III	B	+	+	+
III:8	67	+	+	+	V	C	–	–	+
III:9	63	+	+	+	III	C	+	NA	NA
				Family 2					
I:5	58	+	–	–	III	C	+	+	+
I:7	59	+	–	–	VI	C	–	–	+

*DLB indicates dementia with Lewy bodies; PD, parkinsonism; AD, Alzheimer disease; LB, Lewy body; NFT, neurofibrillary tangle; SP, senile plaque; SN, substantia nigra; H&E, hematoxylin-eosin; AS, α-synuclein; +, present (in "Clinical Features" column) or positive (in "Neuropathological Findings" column); –, absent (in "Clinical Features" column) or negative (in "Neuropathological Findings" column); and NA, data not available.
†For Braak staging, see Braak and Braak.[31]

Tsuang, D. W. et al. 2002.

GBA Mutation Carriers and Parkinson's Disease

Study	*Population*	*GBA mutations analyzed*	*Mutation Frequency*	*Most Common Mutation*	*Control Group*	*Significance*
Lwin et al 2004[12]	57 brain bank samples from N. American PD patients	Complete gene sequencing	12 patients (21%). 2 homozygotes (N370S/N370S) and 10 heterozygotes	N370S, 2 homozygotes and 5 heterozygotes	Control group of 44 brain samples from adults without PD. 2 carried E326K. No other mutations identified.	Significant p=0.02
Aharon-Peretz et al 2004[56]	99 Israeli Jewish PD patients	6 mutations genotyped: N370S, L444P, 84insGG, IVS2+1g>a, V394L and R496H	31 patients (31%). 3 homozygotes and 28 heterozygotes	N370S, 3 homozygous and 23 heterozygous	Non-matched n=1543	Significant P<0.001
Clark et al 2007[2]	278 PD N. American patients	Complete gene sequencing	38 patients (13.7%). 3 homozygous, 34 heterozygous and 1 compound heterozygous	N370S. 2 homozygotes and 15 heterozygote	179 clinically screened matched controls. 4.5% of controls carried a mutation	Significant OR=3.4, 95% CI:1.5, 7.4)
Clark et al 2005[1]	160 New York Jewish PD patients	1 mutation genotyped: N370S	17 patients (11%). 2 homozygotes and 15 heterozygotes	N370S 2 homozygotes and 15 heterozygotes	Matched Jewish controls. Clinically screened Mutation frequency=4%	Not significant p=0.2
Toft et al 2006[57]	311 Norwegian PD pateints	2 mutations genotyped: N370S and L444P	7 patients (2.3%). All heterozygous.	N370S	N=474. Mutation frequency 1.7%	Not significant P=0.58
Wu et al 2007[7]	331 chinese PD patients	Genotyped 2 mutations N370S and L444P	8 patients (2.4%). All heterozygous for L444P	L444P	Matched controls n=347. No mutations identified in controls	Significant P=0.003
Spitz et al 2007[8]	65 Brazilian PD patients	Genotyped 3 mutations N370S, L444P and G377S	2 patients (3%). All heterozygous.	L444P	Matched controls. N=267	Significant p=0.0379
Wu et al 2007b[7]	518 PD Taiwanese patients	Genotyped 3 mutations R120W, L444P and RecNciI	16 patients (3.1%) All heterozygous.	L444P	Matched controls. N=339	Not significant p=0.0703
De Marco et al 2007[10]	395 PD patients from Southern Italy	Genotyped 2 mutations N370S and L444P	11 patients (2.8%). All heterozygous	L444P	Matched Controls N=483	Significant P=0.0018
Bras et al 2007[9]	230 PD patients from Portugal	Complete gene sequencing	-	-	Matched Controls N=430	Significant
Sato et al 2005[58]	88 Canadian patients	7 mutations genotypes: N370S, L444P, 84insGG, IVS2+1g>a, K198T, R329C and RecNciI	5 patients (5.6%). All heterozygous	RecNciI	N=122. Mutation frequency 0.8%	Marginally significant p=0.048
Eblan et al 2006[15]	33 Venezuelan PD patients	Complete gene sequencing	4 patients (12%). All heterozygotes	RecNciI	N=31. Mutation frequency 3.2%	Not significant p=0.35%
Ziegler et al 2007[6]	92 chinese PD patients from Taiwan	Complete gene sequencing	4 patients (4.3%). All heterozygotes	None 1 of each different mutation	92 clinically screened matched controls. Mutation frequency 1.1%	Not signficicant P=0.159

GBA Mutation Carriers

Table 1. Frequency of *GBA* Mutation Carriers Among Patients and Control Subjects

Mutation	Patients With PD, No. (%) (n=721)	Patients With DLB, No. (%) (n=57)	Control Subjects, No. (%) (n=554)
N370S	11 (1.5)	1 (1.8)	2 (0.4)
L444P	10 (1.4)	1 (1.8)	0
N370S or L444P	21 (2.9)[a]	2 (3.5)[b]	2 (0.4)
Wild type	700 (97.1)	55 (96.5)	552 (99.6)

Table 2. Clinical Characteristics of Patients With PD Heterozygous for *GBA* Mutations

Patient No.	Age at Last Assessment, y/ Sex/Age at Onset, y	Family History of PD	Resting Tremor	Rigidity	Bradykinesia	Asymmetric Onset	Hoehn and Yahr Stage	Response to Levodopa	Dementia
N370S									
IPD238	66/F/47	–	+	+	+	+	3	+	+
IPD260	82/M/65	–	–	+	+	+	3	+	+
IPD348	58/F/54	–	+	+	+	+	2	+	
IPD365	54/M/52	+	+	+	+	+	2	+	–
IPD419	64/M/58	–	+	+	+	+	3	+	–
IPD428	84/M/73	+	–	+	+	+	5	+	+
IPD461	50/F/43	–	–	+	+	–	2.5	+	–
IPD468	52/F/48	–	+	+	+	+	2	I	–
IPD648	61/F/50	–	+	+	+	+	2.5	+	–
IPD722	66/M/60	+	+	+	+	+	2	+	–
IPD763	84/M/82	–	+	+	+	+	2.5	+	–
L444P									
IPD254	57/M/48	–	–	+	+	+	3	+	–
IPD359[a]	62/F/60	–	+	+	+	+	2	+	–
IPD471	75/M/72	–	–	+	+	+	3	+	–
IPD495	62/M/57	–	–	+	+	–	2.5	+	–
IPD507	61/F/51	–	+	+	+	+	2	+	–
IPD632[a]	75/M/64	–	+	+	+	+	2	+	–
IPD769	54/M/42	–	+	+	+	–	3	+	–
IPD815	62/M/61	–	+	+	+	+	2.5	I	
IPD816[a]	66/M/64	–	+	+	+	+	2.5	+	+
PD24602	68/M/36	+	+	+	+	+	4	+	+

Abbreviations: I, inadequate trial; PD, Parkinson disease; +, positive; –, negative.
[a] Rec 1 allele carrier (L444P, A456P, and V460V).

Mata, I. F. et al. 2008

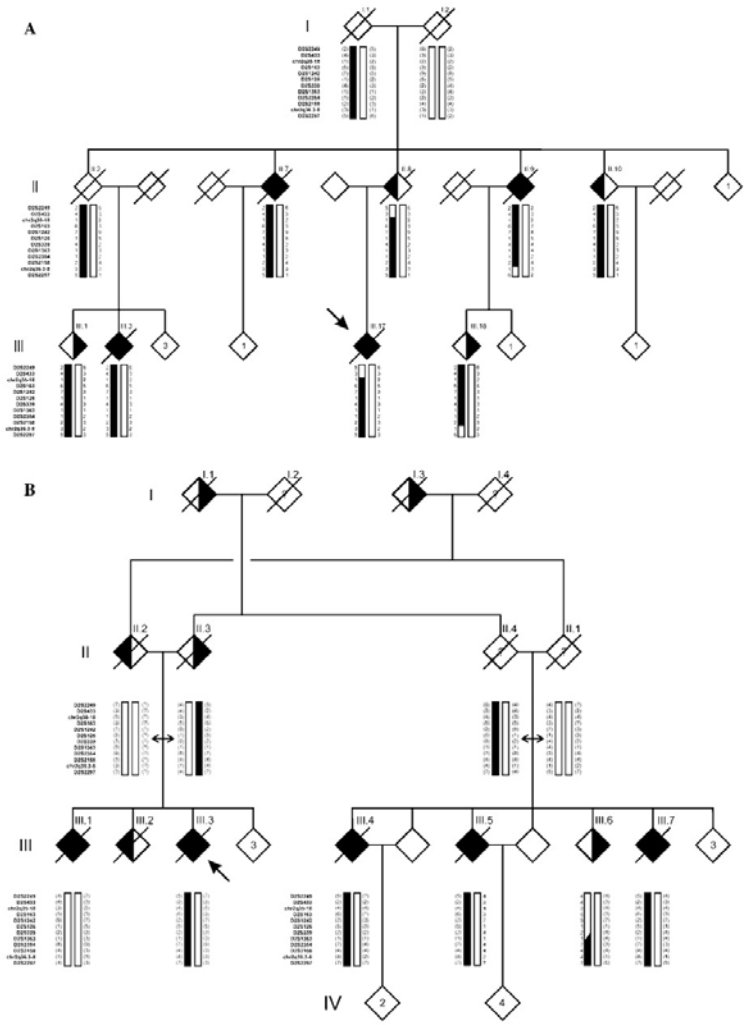
Neuropathological Studies

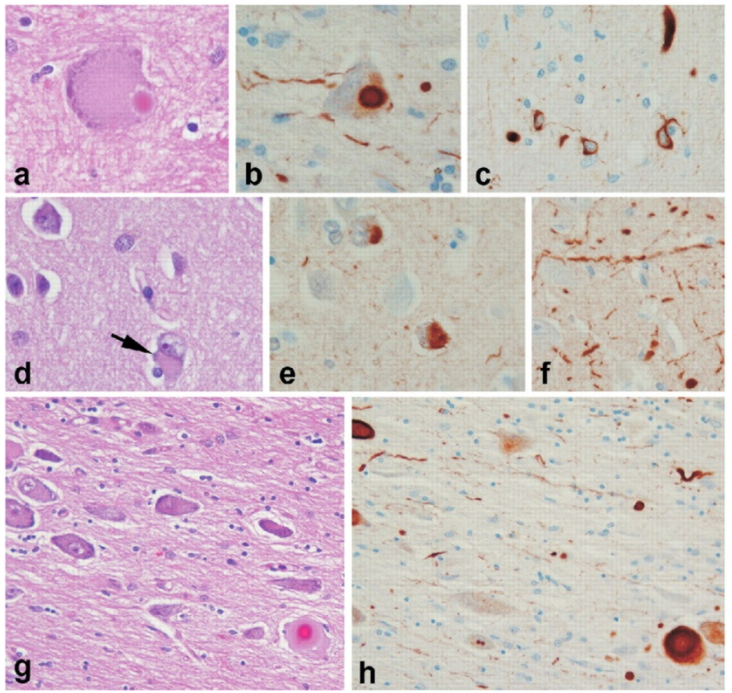
- Tayebi et al (2003) 4 autopsies of patients with Gaucher disease and parkinsonism. All had marked loss of pigmented neurons and numerous Lewy bodies in substantia nigra and two had Lewy bodies in brain regions affected by Gaucher, including the CA2-CA4 hippocampal regions.

- Goker-Alpan et al (2006) GBA in autopsy specimens with different synucleinopathies (35 DLBD, 29 PD and 12 MSA) and identified mutations in 23% of cases of DLBD, 4% of PD and 0% of MSA patients.

- Mata et al (2008) 54/57 with postmortem confirmed DLB and identified mutations in 3.5% of cases. Full gene sequencing was not performed and only 2 mutations, N370S and L444P, were genotyped.

Pedigrees Linked to 2q35-q36*





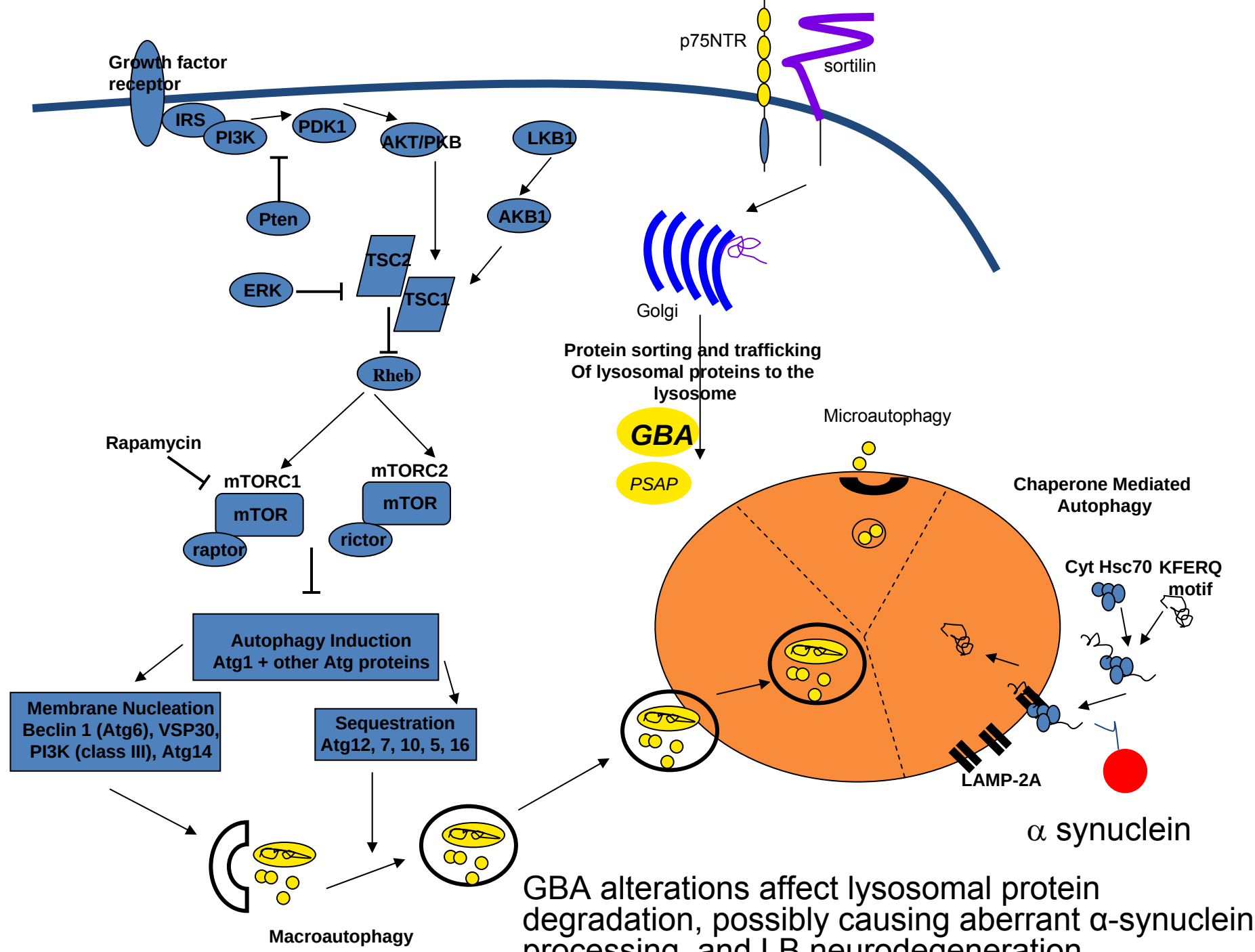
Age at onset 70.7 yrs (62 to 80 yrs)
Duration of disease 11.5 yerars
Excluded: *PSEN1/2, APP, PRNP, MAPT, SNCA, Parkin, DJ1, LRRK2*

* 77 genes in 9.2Mb candidate region

Bogaerts, V. et al. 2007

Conclusions

- Refinement of the clinical and pathological diagnostic criteria will improve
- At present it is difficult to know proportion of clinically diagnosed DLB
- No major risk factors reflects misclassification of diagnosis (favors null)
- Genetic influences robust
  - APOE
  - GBA mutations not associated with Alzheimer's disease pathology, thus mutation status could be used biomarker for the clinical diagnosis of LB disorders.
  - Candidate loci



GBA alterations affect lysosomal protein degradation, possibly causing aberrant α-synuclein processing, and LB neurodegeneration.

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