

Sex Differences for Clinical Presentations and Co-Pathologies in 4R Tauopathies

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Background

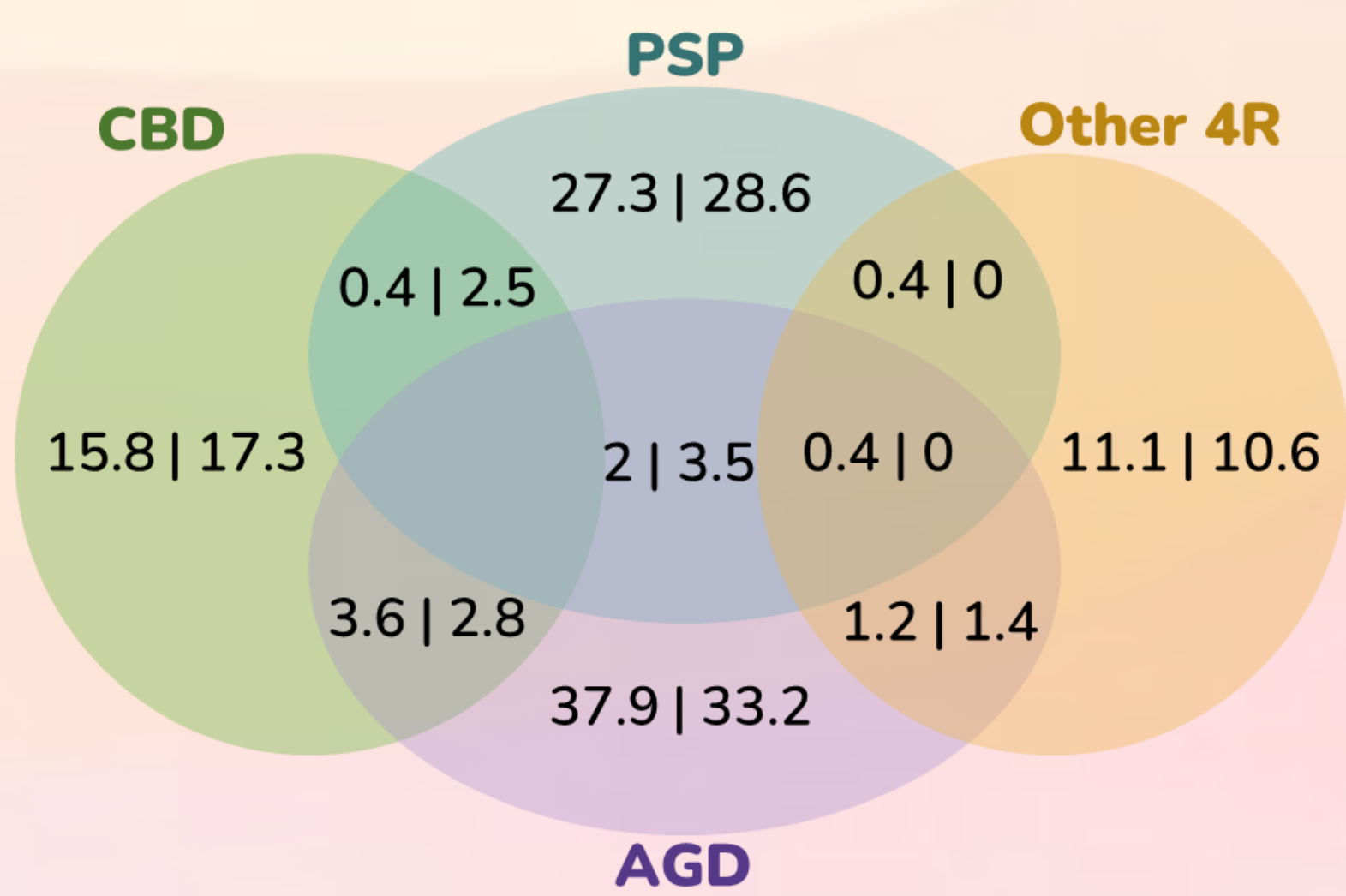
- Four-repeat (4R)-tauopathies include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), globular glial tauopathies (GGT), and FTLN-4R tau due to MAPT mutation.
- These pathologies are associated with various and overlapping clinical phenotypes, including frontotemporal dementias (FTD), Alzheimer’s disease (AD), and Lewy body diseases (LBD).
- Variable presentations may be differentially affected by sex and co-pathologies.

Methods

National Alzheimer’s Coordinating Center for 536 individuals (253 females, 283 males) with pathologically defined 4R-tauopathy:

- PSP: 77 females, 98 males
- CBD: 50 females, 64 males
- AGD: 114 females, 116 males
- Other 4R-tauopathy: 33 females, 34 males

% of 253 Females | 283 Males across groups



Sex differences assessed with generalized linear models in overall cohort and groups for

- co-pathologies (FTLD-3R tau, TDP-43, amyotrophic lateral sclerosis/motor neuron disease, other FTLN, hippocampal sclerosis, ischemic/hemorrhagic/vascular pathology, aging-related tau astrogliopathy, AD pathology [Thal score, Braak stage, CERAD neuritic and diffuse plaque scores], Lewy body pathology, substantia nigra neuron loss, cerebral amyloid angiopathy) correcting for age at death
- clinical diagnoses, behavioral, motor symptoms and onset age correcting for age at last visit,
- cognitive symptoms and onset age correcting for age at last visit and education

Results

In general, females (F) were less likely to have cognitive decline, apathy, and motor symptoms; and were older at cognitive and behavioral symptom onset than males (M).

	Overall	PSP	CBD	AGD	Other 4R
Demographics	F>M: Older at last visit, death M>F: Married, higher years of education, female co-participants	M>F: Married, higher years of education, female co-participants	F>M: Older at last visit M>F: Female co-participants	M>F: Married, higher years of education, female co-participants	M>F: Married, higher years of education, female co-participants
Pathology	M>F: CTE, Lewy body; Lewy body pathology increased clinical LBD phenotype			M>F: Lewy body; Lewy body pathology increased clinical LBD phenotype	
Cognitive	M>F: Dementia, cognitive fluctuations, memory, judgment decline, younger at cognitive decline onset	M>F: Memory, orientation, judgment, attention decline; dementia severity		M>F: Cognitive fluctuations	M>F: Younger at cognitive decline onset
Behavioral	M>F: Apathy, younger at behavioral symptom onset		M>F: Apathy, younger at behavioral symptom onset	F>M: Depression M>F: Younger at behavioral symptom onset, more severe behavioral symptoms	
Motor	M>F: Gait disorder, falls, tremor		M>F: Tremors	M>F: Gait disorder	M>F: Gait disorder, tremors, bradykinesia
Clinical diagnosis	Most common: FTD, AD M>F: LBD	Most common: PSP	Most common: Unspecified FTD	Most common: AD M>F: LBD	Most common: AD

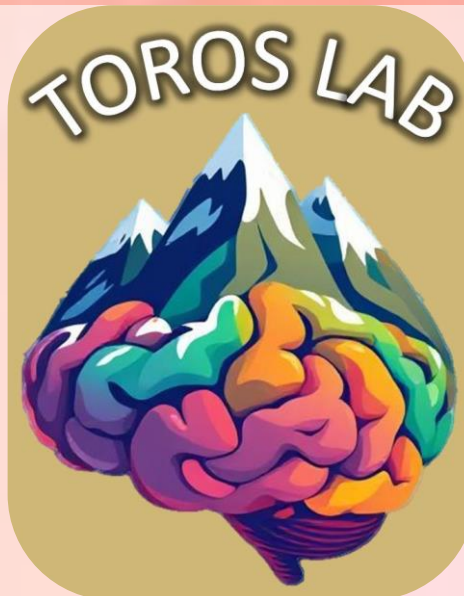
Most common clinical diagnosis for both females and males were PSP for PSP group, unspecified FTD for CBD group, AD for AGD & Other 4R groups.

	Overall (n=283)		PSP (n=175)		CBD (n=114)		AGD (n=230)		Other 4R (n=67)		Clinical diagnosis %
FTD	42.3%	48.4%	62.3%	58.2%	82.0%	90.6%	18.4%	24.1%	27.3%	38.2%	
PSP	14.6%	16.6%	42.9%	39.8%	8.0%	14.1%	2.6%	5.2%	0.0%	2.9%	
CBS	11.9%	9.2%	15.6%	9.2%	26.0%	23.4%	5.3%	3.4%	3.0%	0.0%	
bvFTD	4.7%	4.9%	3.9%	1.0%	14.0%	17.2%	1.8%	2.6%	3.0%	5.9%	
PPA	5.5%	5.7%	5.2%	3.1%	10.0%	14.1%	4.4%	6.0%	3.0%	0.0%	
FTD with MND	0.4%	0.7%	40.3%	1.0%	2.0%	34.4%	32.5%	0.0%	0.0%	2.9%	
Unspecified FTD	11.9%	20.1%	6.5%	18.4%	28.0%	42.2%	7.0%	11.2%	24.2%	26.5%	
AD	40.7%	40.6%	24.7%	33.7%	18.0%	15.6%	57.9%	56.0%	48.5%	47.1%	
LBD	4.7%	12.4%	10.4%	12.2%	0.0%	3.1%	3.5%	16.4%	0.0%	11.8%	
	Female (n=253)	Male (n=283)	Female (n=77)	Male (n=98)	Female (n=50)	Male (n=64)	Female (n=114)	Male (n=116)	Female (n=33)	Male (n=34)	

Conclusions

- Co-pathologies and clinical phenotypes may differ by sex for people with 4R tauopathies.
- Females had a clinical advantage with less symptoms and later onset.
- Males had more frequent chronic traumatic encephalopathy, worse Lewy body pathology, higher likelihood of LBD phenotype with Lewy body pathology.

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