Primary Age-Related Tauopathy (PART): Genetic Sources of Resistance?

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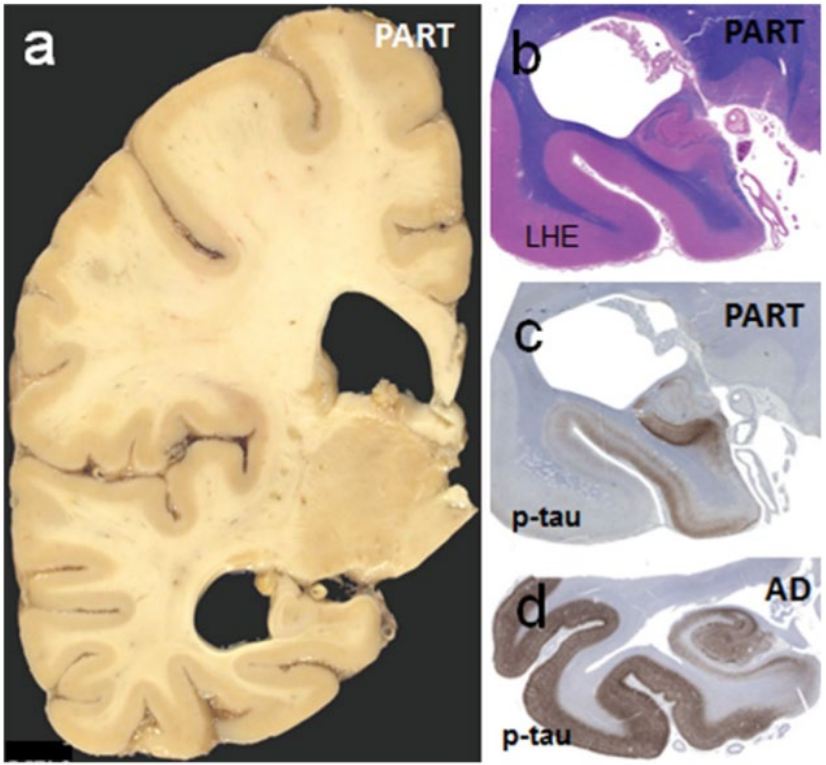
Neuropathology of Primary Age-Related Tauopathy (PART)



Neuropathological Criteria:

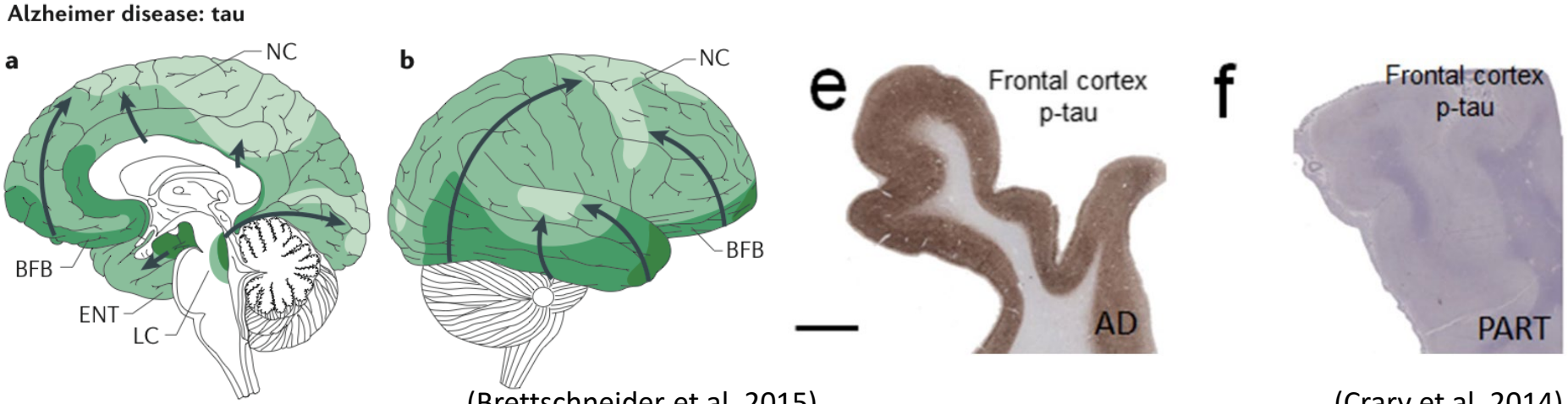
- Tau NFTs at Braak Stage I-IV
- *Definite PART*: No amyloid (CERAD=0)
- *Probable PART:* Minimal amyloid (CERAD=1)

There are no clinical criteria:

- Previously, “tangle-predominant senile dementia” (TPSD).
- But individuals could meet neuropathological criteria without dementia.

(Crary et al, 2014)

Braak Staging of Tau Pathology in AD & PART



(Brettschneider et al, 2015)

(Crary et al, 2014)

PART yields Braak Stage I-IV but rarely results in Braak Stage V-VI

Current Controversy of PART: Lumpers vs. Splitters

***Lumpers*:** "there is no way, neuropathologically, genetically, or clinically, to differentiate PART from early AD"

(Duyckaerts et al, 2014)

Splitters: PART constitutes a distinct neuropathological entity of age-related pathology.

Why is it Important To Study PART?

- Everyone agrees that age-related pathology is highly prevalent in the population.
- There are clinical consequences of PART
- PART provides a potential genetic model of amyloid resistance and tau risk, (mostly) independent of amyloid.

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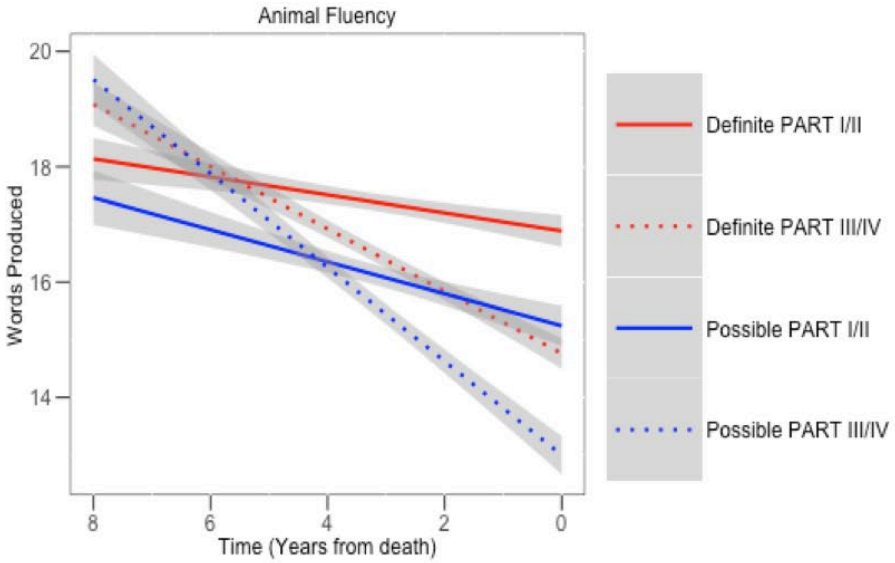
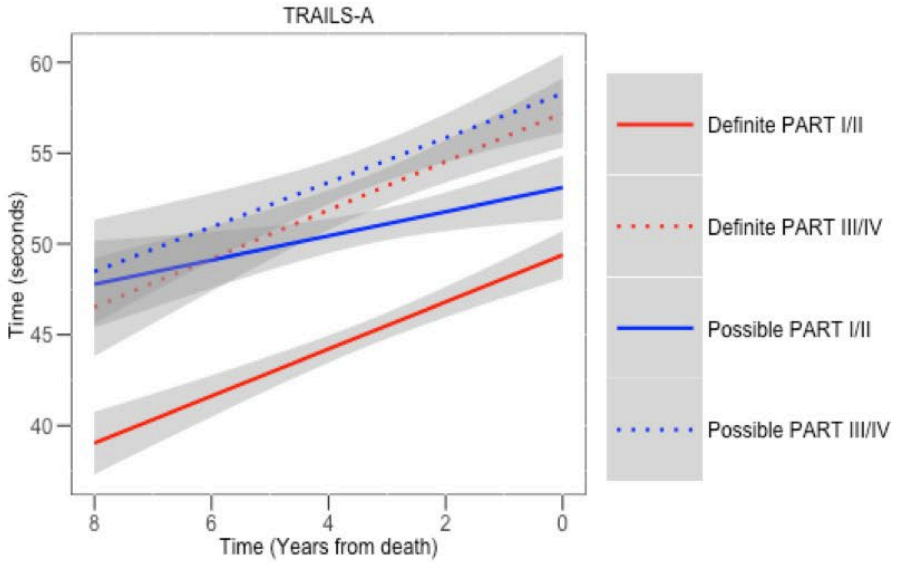
Clinical Features of PART from NACC





- **More tau, more decline:** Braak III/IV (dotted) faster cognitive decline than Braak I/II (solid).
  - category fluency, Trails, immediate memory, and digit-symbol – but not all domains.
- **Decline, relatively independent of amyloid:** Advanced Definite PART (III/IV) declines nearly as fast as Possible PART (red).

(Jefferson-George et al, 2017)

Clinical Features of PART from NACC

- Approximately 37-53% of Definite PART cases and 50-69% of Probable PART cases were rated as “cognitively impaired” by a physician.

(Jefferson-George et al, 2017)

- Cognitive impairment is present in both Definite PART (58%) and Probable PART (80%) cases. Severity of cognitive impairment is further related to:
  - Braak Stage, Stroke, and Depression for Definite PART
  - Braak Stage, Education, and Amyloid Angiopathy for Probable PART

(Besser et al, 2017)

- Domains of cognitive impairment differ across AD and PART, with Definite PART having relative memory sparing in early disease (CDR<1) and attention sparing in later disease (CDR≥2).

(Besser et al, 2019)

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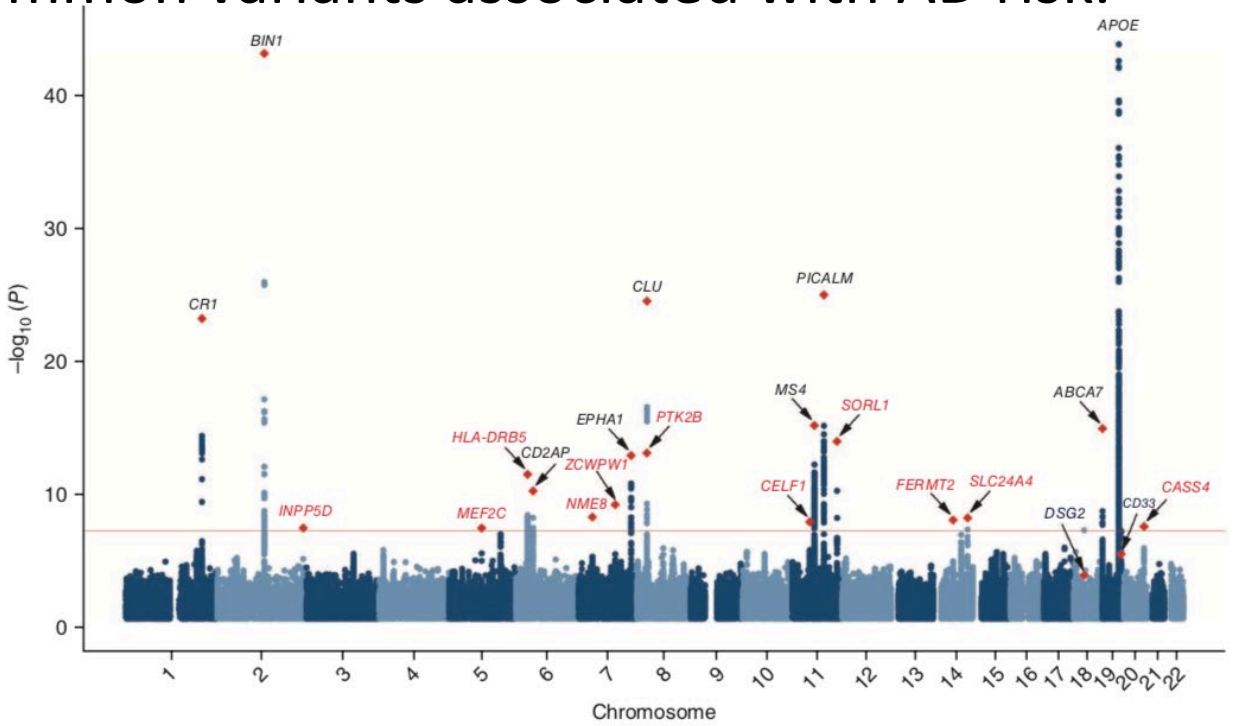
Alzheimer Disease Genetics

Large (N>74,000) case-control GWAS studies have now identified several common variants associated with AD risk.



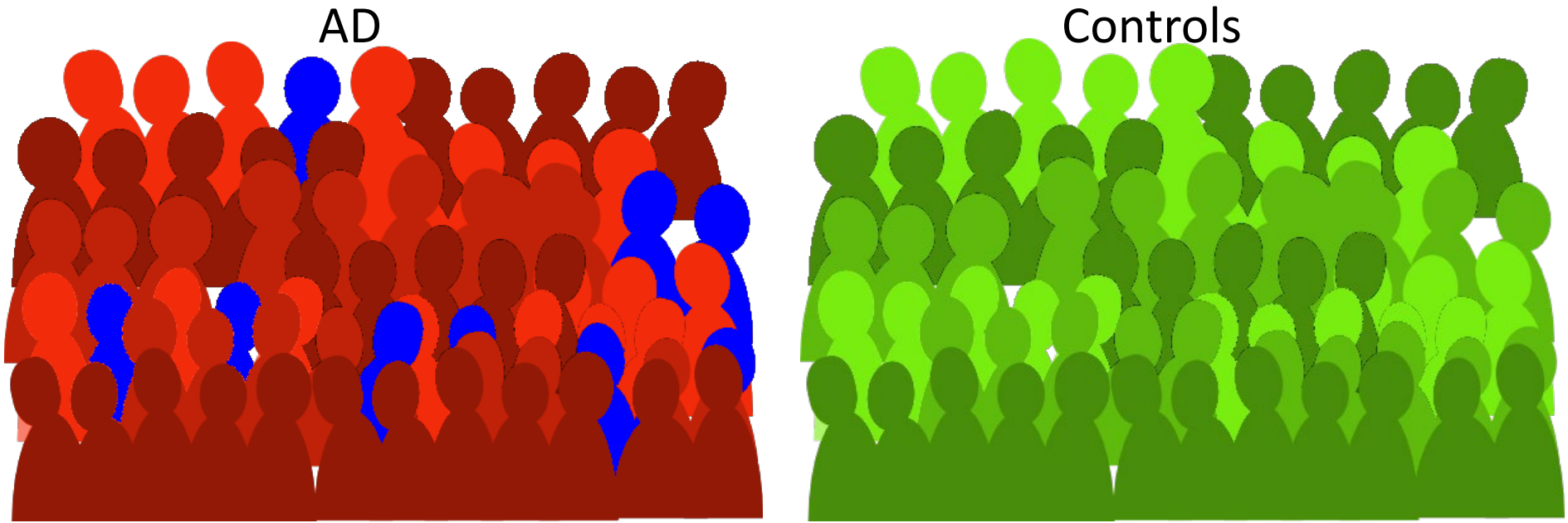
(Lambert et al, 2013)

Potential Limitations of Case-Control GWAS

AD

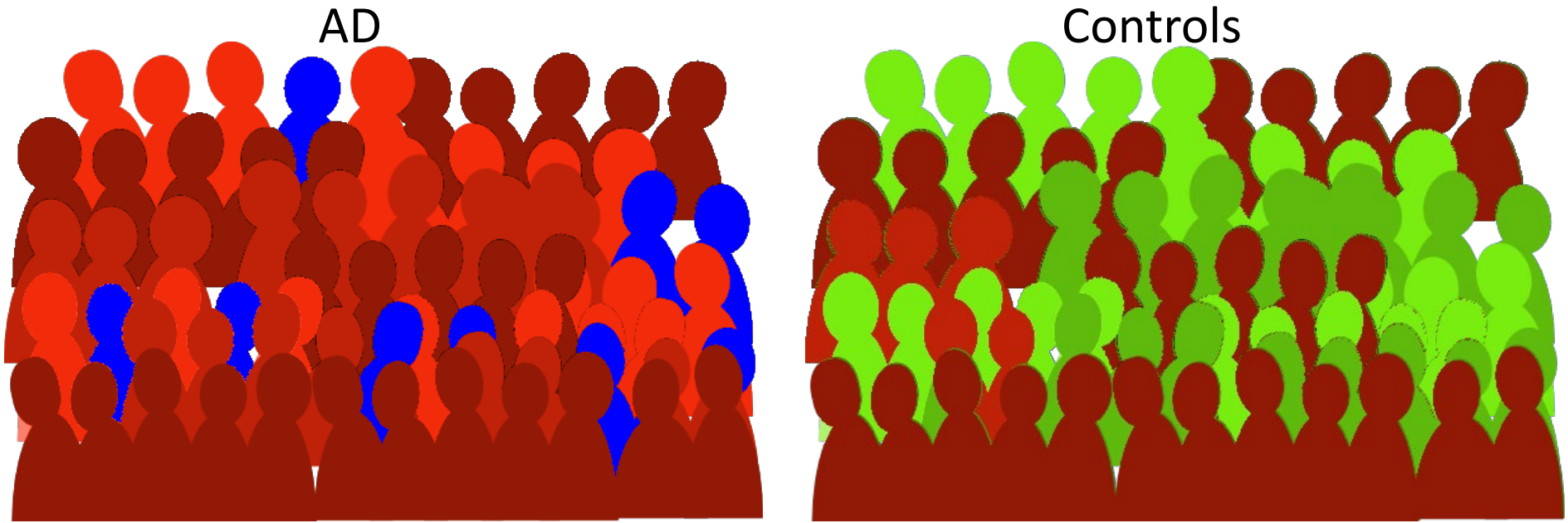
Controls

Potential Limitations of Case-Control GWAS



Clinical GWAS likely include many AD-mimics lacking AD pathology

Potential Limitations of Case-Control GWAS



Given the prevalence of AD and PART, many “controls” have “case” genetics.

Neuropathologically-Defined Association Studies

Autopsy-Confirmed AD

Autopsy-Confirmed PART

- Between group comparisons (e.g., AD vs. PART) allow you to isolate risk of amyloid.
- Within PART group comparisons allow you to isolate risk of tau, independent of amyloid

Limited Genetic Comparisons in PART To-Date

	Amyloid plaque density	Braak stage				
		0	I	II	III	IV
Number of subjects						
PART, definite	None	11	22	25	15	15
PART, possible	Low	4	16	27	16	31
–	Mod	2	11	15	32	50
–	High	3	7	10	39	83
Age at death (average)						
PART, definite	None	81.3	82.4	88.5	88.4*	92.0*,**
PART, possible	Low	88.4	80.4	84.7	89.7*	87.6*
–	Mod	89.0	80.2	87.4*	84.9	86.5
–	High	77.0	84.9	86.7	85.3	84.6
Final MMSE scores						
PART, definite	None	28.0	28.4	26.5	25.1***	24.3***
PART, possible	Low	28.5	25.8	24.4	24.6	21.9*
–	Mod	26.5	26.8	27.3	23.2*	19.8*
–	High	25.5*	24.5	27.9*	21.2*	18.8*,**
APOE ε4 positive (%)						
PART, definite	None	9.1	13.6	0.0	20.0	13.3
PART, possible	Low	25.0	12.5	14.8	37.5	35.5*
–	Mod	0.0	36.4	13.3	34.4*	50.0*
–	High	66.7*	28.6	50.0*	33.3*	56.6*,**

- No association of Definite PART with APOE ε4 reported by Crary et al., 2014
- …but, APOE ε4 is increased with higher Braak stages

Genotyping Approach

- Hypothesis-Driven strategy to evaluate 14 common variants previously associated with AD.
- PENN:
  - Genotyped for 95 SNPs using the Pan-Neurodegenerative Disease Risk Allele Panel (PANDoRA) on Fluidigm platform.
  - APOE ε4 obtained using TaqMan assay
  - Selected 14 hypothesized SNPs associated with AD + APOE ε4 (all MAF>0.1).
- NACC:
  - 14 hypothesized SNPs obtained from NACC cases via the ADGC and APOE ε4 obtained from NACC UDS.

Demographics of Study Cohorts

	PENN		NACC	
	PART	AD	PART	AD
N	65	312	311	878
Sex, % Female	53.85	55.77	50.80	43.73
Age at Death, Years	78.23 (10.11)	76.49 (10.86)	88.18 (8.14)	81.51 (9.83)
PART, % Definite	78.46	--	56.59	--

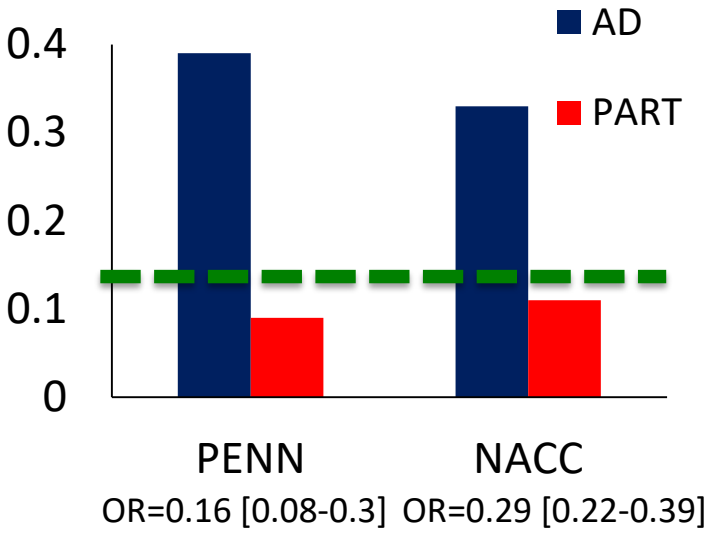
- More females with PART than AD in NACC; but overall matched for Sex.
- PART are older than AD in NACC (and combined cohort).
- Definite PART is more frequent in PENN compared to NACC cohort.

(McMillan et al, 2018)

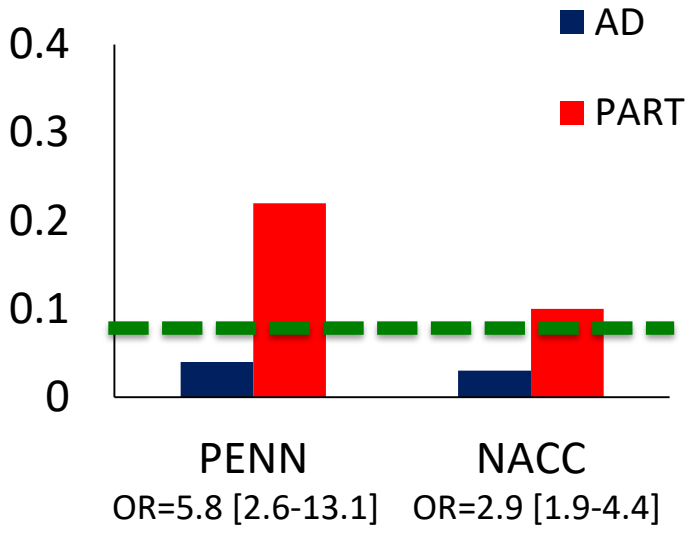
APOE Associations Between PART and AD

Population "Control" Frequency

APOE ε4



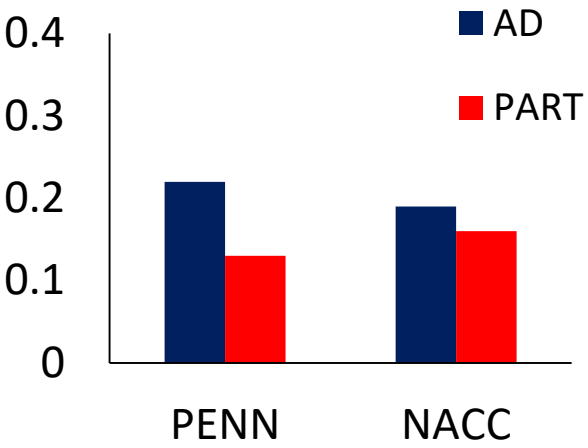
APOE ε2



(McMillan et al, 2018)

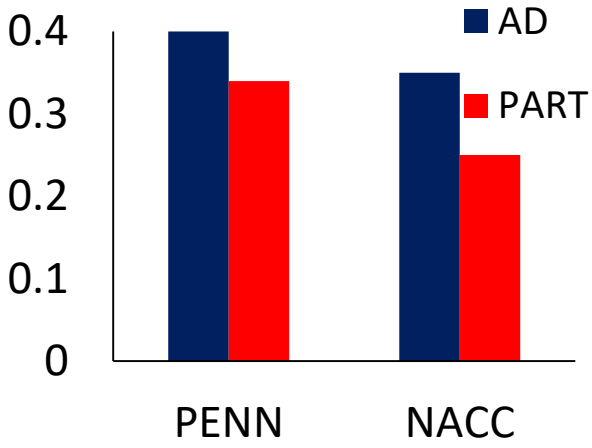
Additional AD Risk Associations Between AD and PART

rs6656401 (*CR1*)



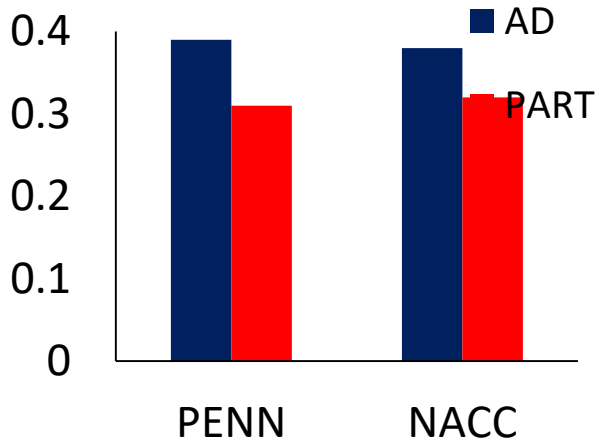
OR=0.54 [0.3-0.9] OR=0.74 [0.5-0.96]

rs744373 (*BIN1*)



OR=0.71 [0.48-1.03] OR=0.61 [0.5-0.8]

rs28834970 (*PTK2B*)

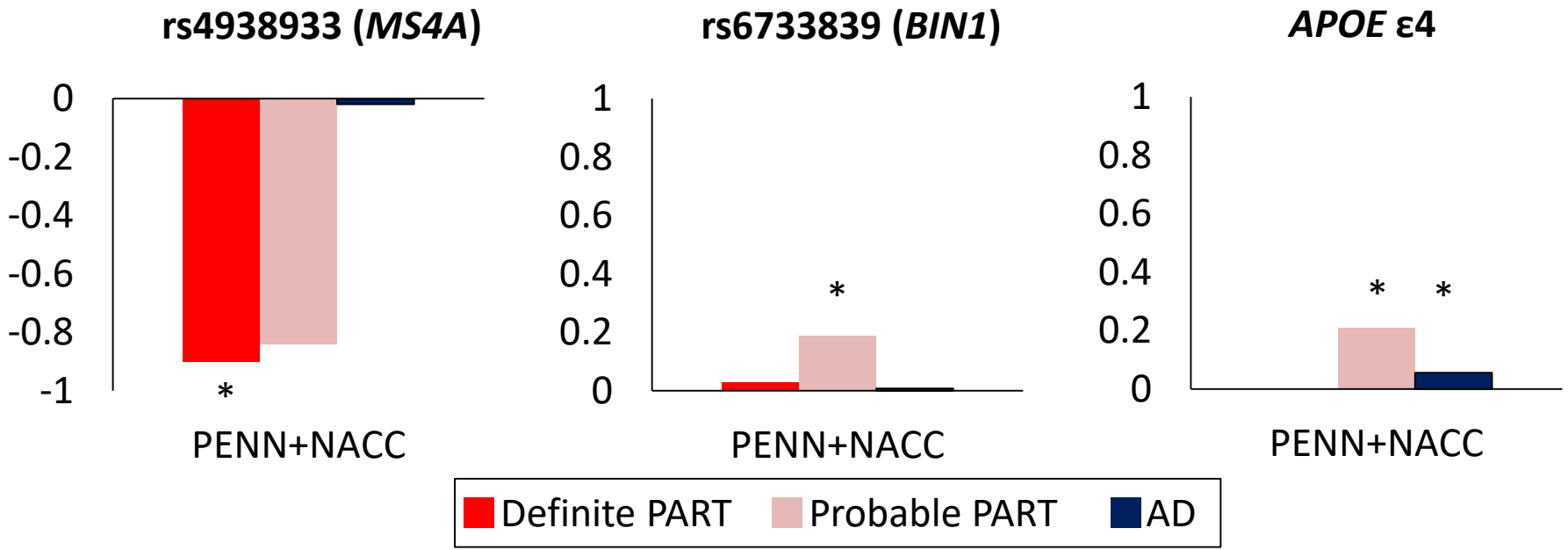


OR=0.71 [0.5-1.05] OR=0.77 [0.6-0.9]

Thus, there appear to be AD risk factors that are reduced in PART

(McMillan et al, 2018)

Associations with Tau Pathological Burden Across Definite PART, Probable PART, & AD



Associations of tau risk appear to differ in the context of amyloid

(McMillan et al, 2018)

Ongoing Genotyping Efforts

APOE Frequency in PART vs. AD Across Baltimore Studies

Genotype	PART(N = 37) Percentage	AD (N = 94) Percentage
APOE 2/2	0	0
APOE 2/3	21.6	10.6
APOE 3/3	70.3	58.5
APOE 2/4	2.7	0
APOE 3/4	5.4	26.6
APOE 4/4	0	4.3
Allele		
ε2	12.2†	5.3†
ε3	83.8	77.1
ε4	4‡	17.5‡

- **Recent converging evidence for APOE differences across PART and AD.**
- **PART Working Group has an ongoing GWAS with preliminary SNP associations.**

(Bell et al, 2019)

Conclusions

- There is clinical and genetic evidence that PART constitutes a distinct neuropathological entity from Alzheimer disease.

- **Clinical:**
  - Approximately half of PART cases have cognitive symptoms.
  - Severity and decline of cognitive impairment correlates with the degree of NFT distribution.
  - Cognitive impairment is present in Definite PART.

Conclusions

- **Genetic:** Several AD-associated risk loci have differing allele frequencies in PART relative to AD
  - *APOE*: interestingly associated with tau risk, but only in those with amyloid (e.g., Probable PART + AD) . Consistent with prior observations not separating out Definite PART. (Beecham et al, 2014)
  - *BIN1:* only associated with tau severity in cases with mild amyloid. Likely involved in tau propagation (Crotti et al, 2019)
  - *CR1* & *PTK2B*: previously associated with innate immunity (Kunkle et al, 2019)
  - *MS4A*: minor alleles associated with less NFTs. This gene cluster is involved in microglial response and immunity; regulator of TREM2.

Conclusions

- There are several practical reasons to study PART as a distinct entity
  - To compare relative to AD to better understand amyloid resistance (e.g., PART) or amyloid risk (e.g., AD).
  - Provides a retrospective *in vivo* model of tau risk.
  - Provides an opportunity to ”focus and reaffirm the amyloid cascade hypothesis”.

Conclusions

- There are also several caveats and challenges
  - Prospective *in vivo* approaches still require validation:
    - Does A- T+ N± capture ante-mortem PART?
    - Are the current generation of tau tracers sensitive to early Braak NFTs?
  - Power for *novel* genetic discovery in autopsy-confirmed cases is limited in comparison to case-control GWAS studies.

    → but, PART Working Group is making progress through large effort of pooling tissue.

  - What additional mechanisms support risk of tau and resistance to amyloid?

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We're Hiring Postdocs & Staff Scientists!!!

Appendix

Table 1
Median (IQR) and frequency summaries of demographics, baseline assessment of neuropsychological performance, and final assessment of neuropsychological performance for 226 individuals with neuropathological confirmation PART

	Visit	Definite PART I/II	Definite PART III/IV	Possible PART I/II	Possible PART III/IV	*P* value
Demographics						
N	—	79	49	39	59	—
Sex, % female	—	48.1%	61.2%	15.9%	64.4%‡	.021
Education, y	—	16.0 (12.5–18.0)	15.0 (14.0–18.0)	16.0 (13.0–18.0)	15.0 (12.0–16.5)	.518
Age at death, y	—	84.0 (78.0–90.0)	92.0* (88.0–94.0)	86.0 (82.0–91.0)	92.0† (86.0–96.0)	<.001
Frequency of visits, quantity	—	3.0 (2.0–5.5)	3.0 (2.0–5.0)	4.0 (3.0–5.0)	3.0 (2.0–5.0)	.733
Cognitively impaired, % total	—	37.7%	53.1%*	50.0%	69.0%†	
Age, y	Baseline	80.0 (73.0–86.0)	87.0* (84.0–90.0)	82.0 (77.5–85.0)	87.0† (81.0–91.5)	<.001
	Final	83.0 (77.0–88.5)	90.0* (87.0–93.0)	84.0 (80.5–89.5)	90.0† (85.0–94.5)	<.001
Global						
MMSE, total correct	Baseline	28.0 (27.0–30.0)	28.0 (26.0–29.0)	29.0 (27.0–29.5)	28.0 (26.5–29.0)	.328
	Final	28.0 (26.5–29.0)	28.0 (25.0–29.0)	28.0 (25.5–30.0)	27.0 (26.0–29.0)	.143
Executive						
Trails-B, completion time	Baseline	105.0 (78.0–150.5)	145.0* (90.0–190.0)	102.0 (82.5–132.0)	131.0 (105.5–184.5)	.003
	Final	123.0 (85.5–233.5)	164.0 (91.0–252.0)	112.0 (85.5–172.5)	199.0†,‡ (138.5–300.0)	.001
Memory						
Logical memory immediate, # words	Baseline	13.0 (9.5–16.0)	12.0 (7.0–16.0)	13.0 (8.0–15.0)	12.0 (10.0–15.0)	.518
	Final	14.0 (10.0–17.0)	12.0 (6.0–15.0)	12.0 (4.0–16.5)	11.0 (7.0–15.0)	.137
Logical memory delayed, # words	Baseline	12.0 (9.5–15.0)	11.0 (7.0–14.0)	11.0 (4.5–14.5)	11.0 (7.0–13.0)	.111
	Final	12.0 (8.0–16.0)	10.0 (1.0–15.0)	11.0 (2.0–16.0)	10.0 (5.0–13.5)	.092
Processing speed/attention						
WAIS Digit Symbol, correct pairs	Baseline	38.0 (29.8–46.0)	36.0 (28.0–43.0)	37.0 (31.8–45.0)	32.0† (24.8–38.3)	.015
	Final	33.0 (26.0–42.0)	31.0 (25.3–42.8)	32.0 (27.0–41.0)	25.0† (20.8–33.0)	.008
Trails-A, completion time	Baseline	41.0 (32.0–48.0)	45.0 (32.0–56.0)	42.0 (32.0–54.0)	45.0 (35.0–58.5)	.312
	Final	47.0 (33.5–61.0)	48.0 (35.0–74.0)	47.0 (35.3–56.8)	63.0† (42.0–78.0)	.043
Digit Span Forward, span length	Baseline	8.0 (7.0–10.5)	8.0 (7.0–9.0)	9.0 (7.0–10.0)	8.0 (7.0–10.0)	.34
	Final	8.00 (7.0–9.0)	8.00 (6.0–9.0)	8.00 (7.0–9.0)	8.00 (7.0–9.0)	.997
Digit Span Backward, span length	Baseline	7.0 (5.0–8.0)	6.0 (4.0–8.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)	.103
	Final	6.0 (5.0–8.0)	6.0 (4.0–7.0)	6.0 (5.0–7.0)	5.0 (4.0–7.0)	.161
Language and semantic memory						
Category fluency, # animal words	Baseline	17.0 (13.0–22.0)	17.0 (12.0–22.0)	17.0 (14.5–21.0)	16.0 (13.0–19.5)	.52
	Final	17.0 (11.0–21.0)	15.0 (10.0–20.0)	16.0 (11.5–19.0)	13.0 (10.0–17.0)	.065
Boston Naming Test, total correct	Baseline	28.0 (26.0–29.0)	27.0* (24.0–28.0)	27.0 (24.5–28.0)	25.0† (23.0–28.0)	.004
	Final	28.0 (25.0–29.0)	27.0* (24.0–28.0)	27.0 (22.5–29.0)	26.0 (23.50, 27.0)	.015

Table 2
Longitudinal linear mixed-effects regression models evaluating cognitive decline in 226 patients with PART

	Time		Braak stage		Neuritic plaques		Time × Braak definite PART		Time × Braak possible PART		Age at test		Education		Sex	
Model factor	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Global cognition																
MMSE (total correct)	−0.011	.914	−0.732	.124	−0.104	.815	0.105	.161	0.197	.003	−0.031	.267	0.170	.016	0.566	.158
Executive																
Trails-B (completion time)	−1.658	.558	33.414	.004	12.019	.267	−3.918	.060	−5.593	.002	2.133	.001	−2.751	.095	−1.090	.907
Memory																
Logical memory—immediate (# words)	−0.364	.014	−1.347	.089	−0.701	.341	0.243	.027	0.304	.002	−0.072	.128	0.415	.001	1.724	.012
Logical memory—delayed (# words)	−0.221	.178	−1.557	.075	−0.969	.233	0.145	.229	0.251	.018	−0.093	.075	0.469	.000	2.074	.006
Processing speed/attention																
WAIS Digit Symbol (correct pairs)	0.471	.160	−2.293	.181	−2.656	.098	0.527	.036	0.637	.004	−0.521	.000	0.489	.058	2.031	.168
Trails-A (completion time)	0.228	.823	6.432	.091	3.947	.266	−1.841	.014	−1.940	.003	0.799	.000	−0.019	.971	−1.119	.706
Digits—Forward (span length)	0.255	.002	−0.040	.896	−0.410	.158	−0.147	.015	−0.056	.296	−0.009	.602	0.103	.016	0.233	.339
Digits—Backward (span length)	0.045	.606	−0.874	.008	−0.577	.058	0.038	.550	0.107	.058	0.005	.758	0.139	.002	0.373	.143
Language and Semantic Memory																
Category Fluency (# animal words)	−0.072	.725	−1.063	.231	−1.653	.047	0.297	.051	0.425	.002	−0.125	.014	0.351	.006	0.304	.677
Boston Naming (total correct)	0.255	.006	−0.219	.739	−1.043	.089	−0.100	.148	−0.023	.700	−0.045	.270	0.215	.038	−0.662	.264

Abbreviations: MMSE, Mini-Mental State Examination; PART, primary age-related tauopathy.