RAPID OVERVIEW OF CLINICAL, BASIC, AND GENETIC FACTORS IN FRONTOTEMPORAL DEGENERATION

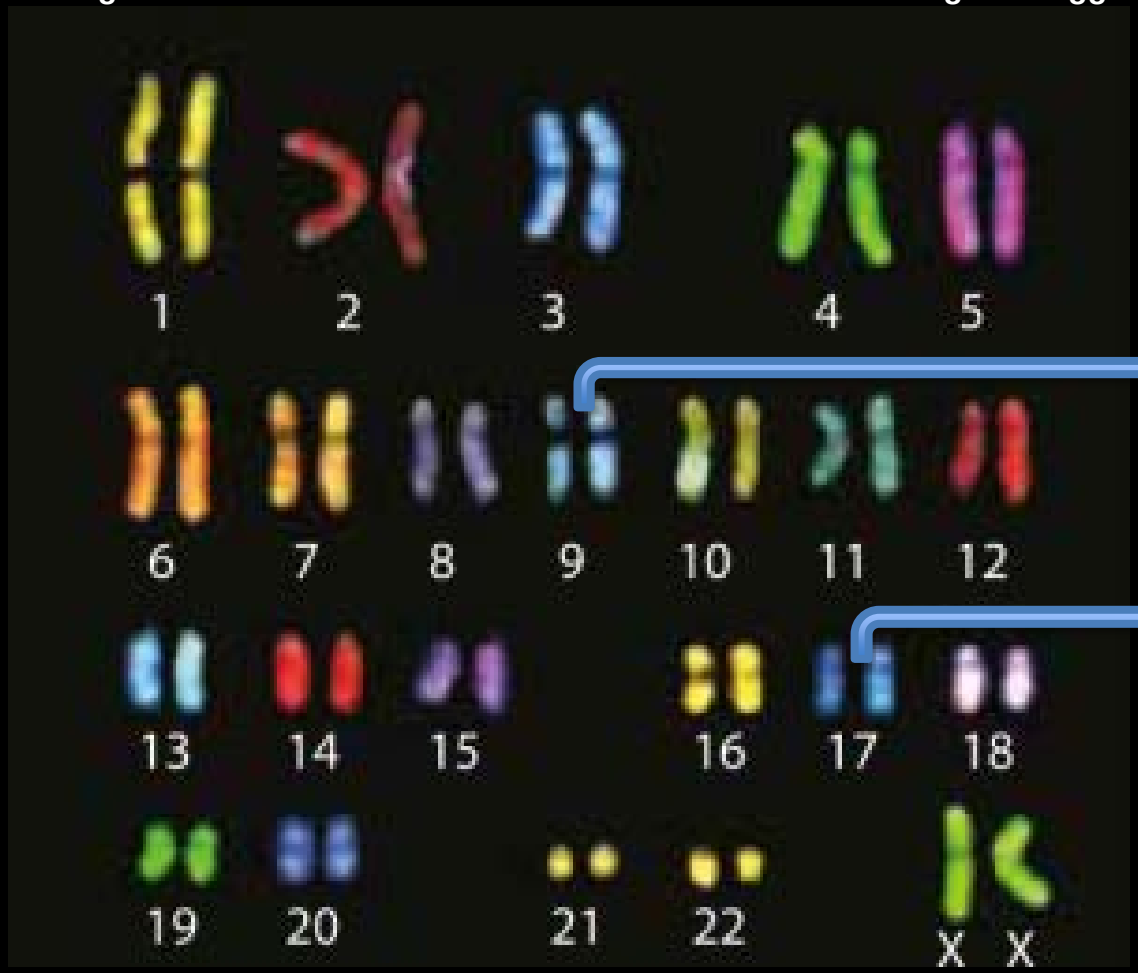
Marsel Mesulam, MD
Cognitive Neurology and Alzheimer's Disease Center
Northwestern University Feinberg School of Medicine
Chicago, IL USA

THE MAJOR PLAYERS

GENES → (identified through genotyping)	DISEASES → (identified by neuropathology)	SYNDROMES (identified by clinical evaluation)
MAPT	FTLD – TAU	PPA-G
GRN	FTLD - TDP	PPA-L
C9orf72		PPA-S
		bvFTD
		CBD-PSP
		ALS-FTD

THE 23 HUMAN CHROMOSOMES

Chromosomes are made up of long strings of DNA nucleotides (bases).
There are thousands of gene pairs per chromosome, one from each parent.
There are thousands of bases per gene.
Insertion of a single incorrect base or abnormal readout of the DNA string can trigger abnormal protein accumulations.

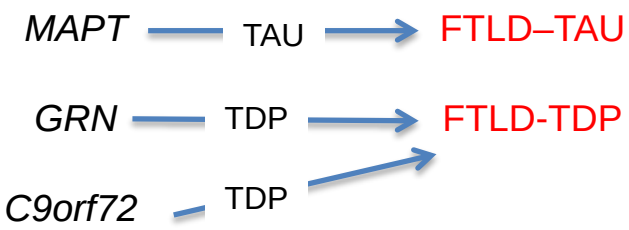


C9orf72 (TDP-43)

MAPT (tau), *GRN* (TDP-43)

THE MAJOR PLAYERS

GENES → DISEASES → SYNDROMES



PPA-G

PPA-L

PPA-S

bvFTD

CBD-PSP

ALS-FTD

NEUROPATHOLOGIC APPEARANCE OF FTLD SUBTYPES

FTLD-TAU

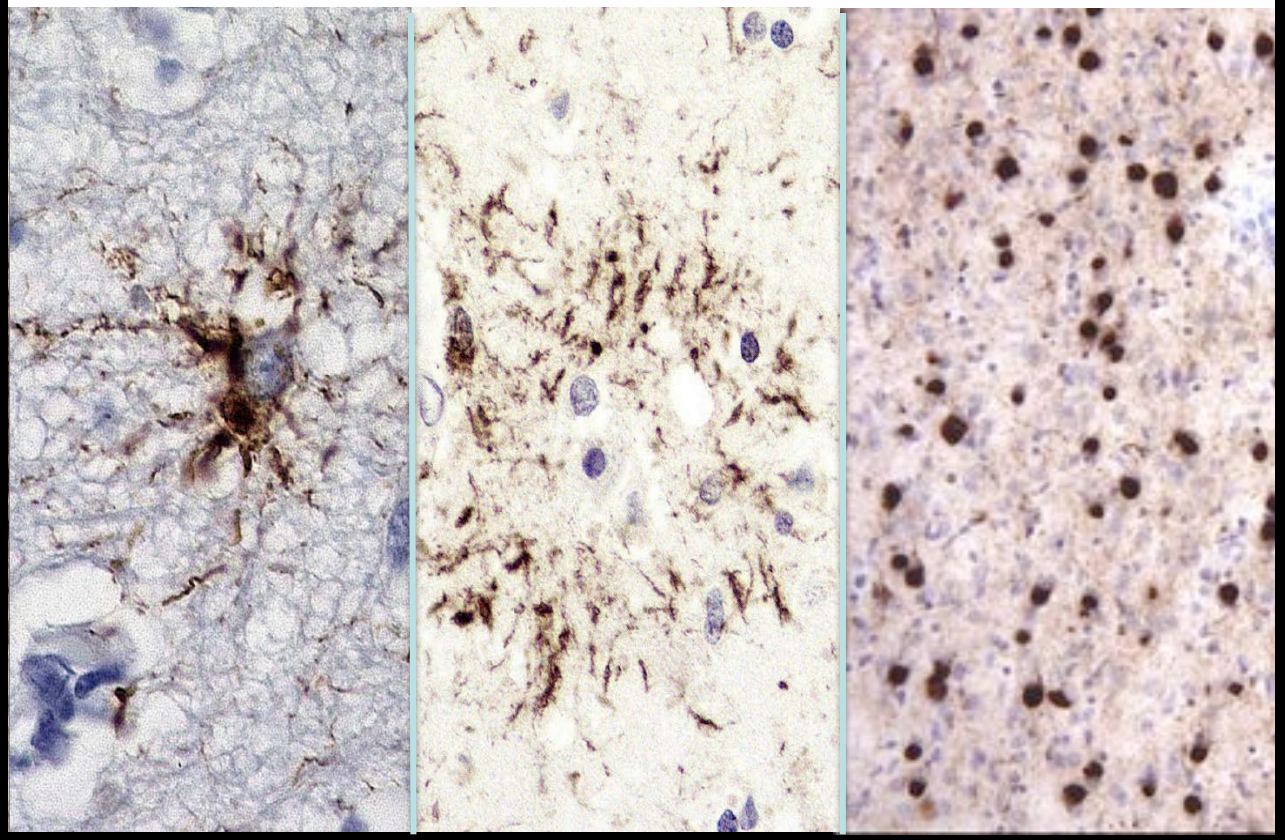
TUFTED ASTROCYTES

4 MICROTUBULE BINDING DOMAINS (4R)

ASTROCYTIC TANGLES

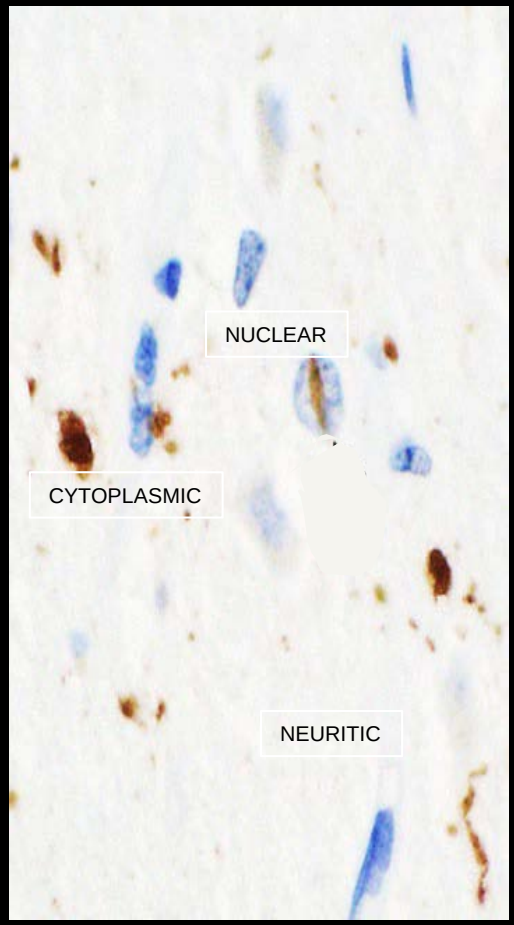
PICK BODIES

3 MICROTUBULE BINDING DOMAINS (3R)



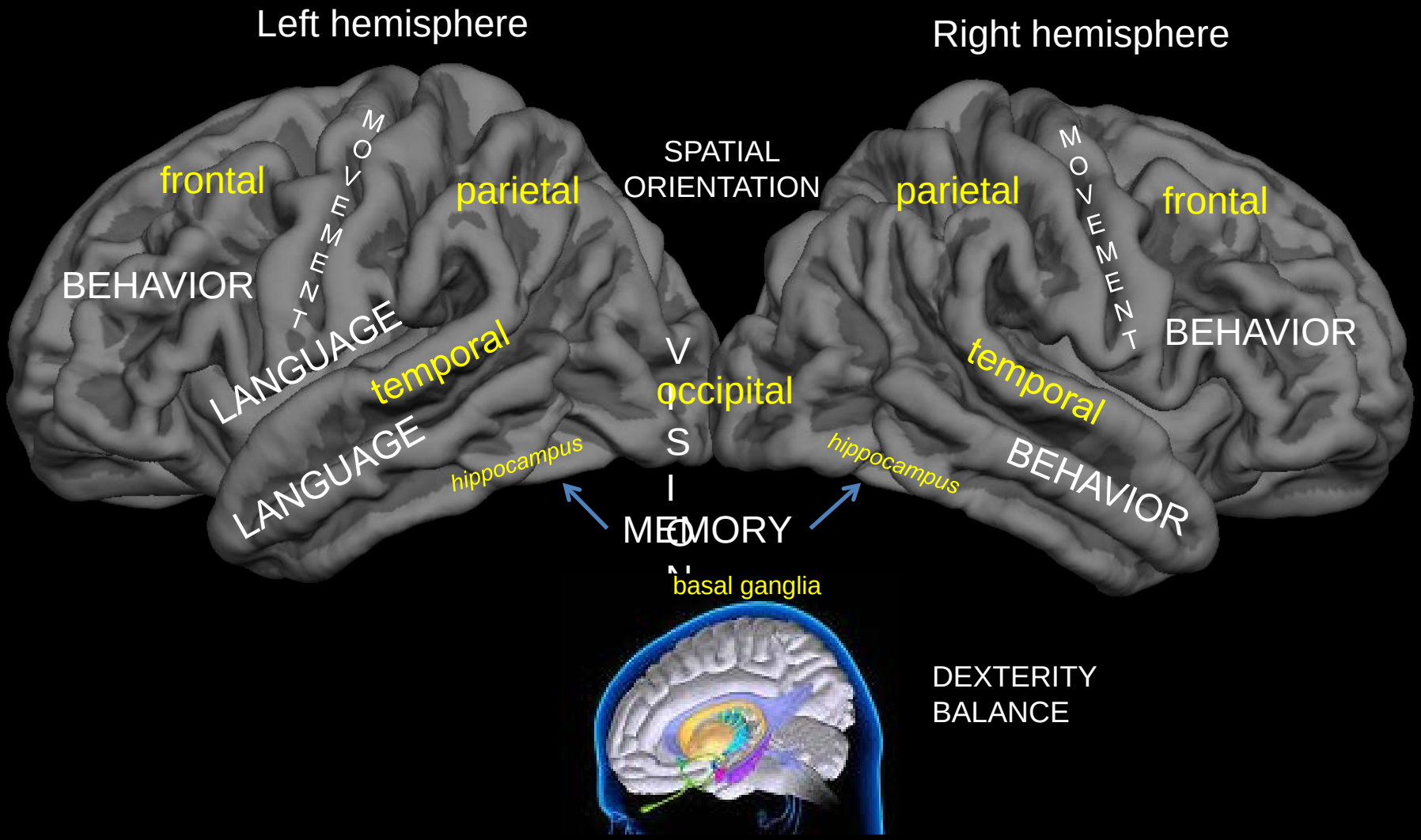
MAPT Mutations or Sporadic

FTLD-TDP (A, B, C, D)



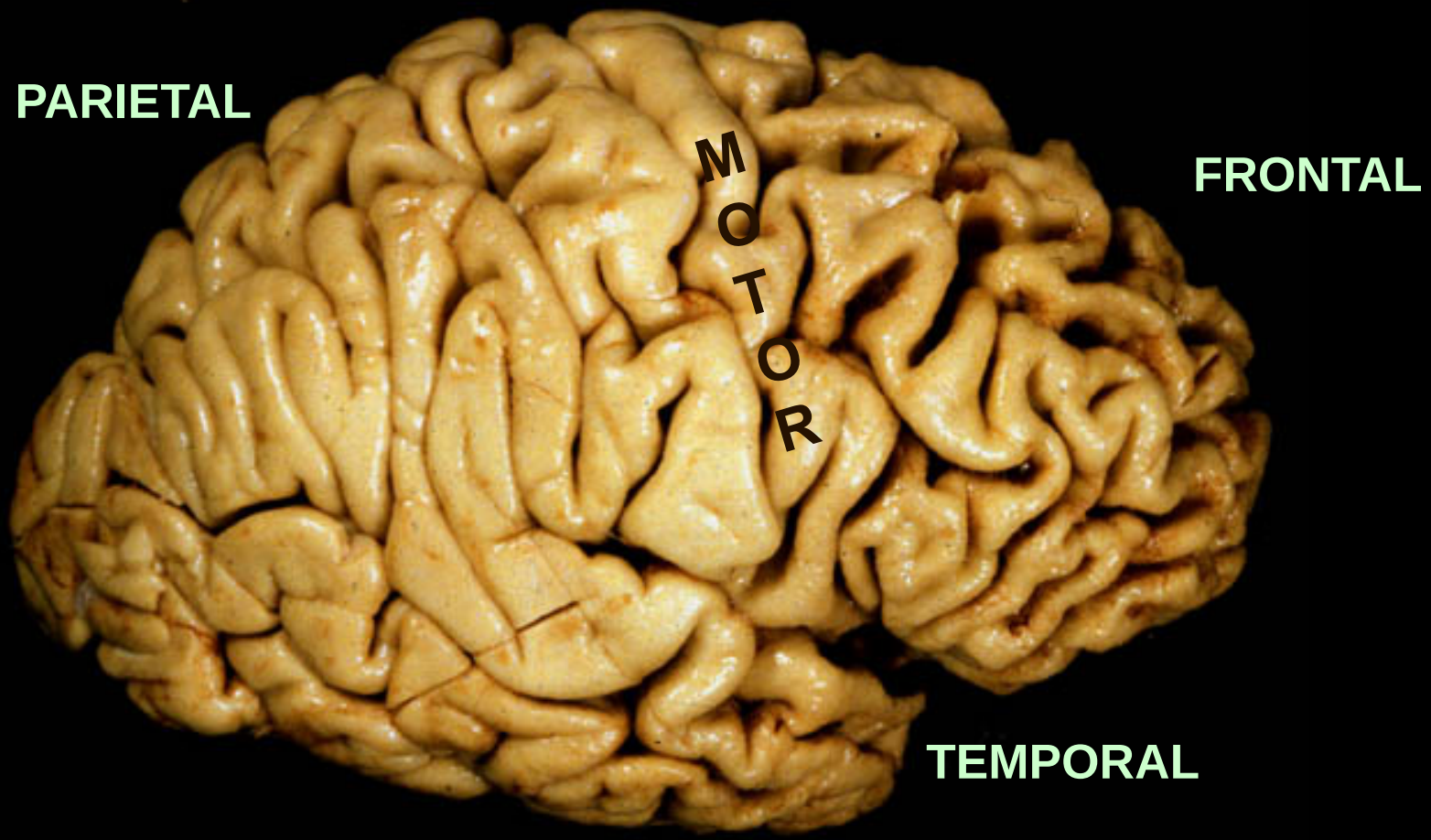
C9orf72 or GRN Mutations or Sporadic

JOB DESCRIPTIONS IN THE HUMAN BRAIN



FRONTAL-TYPE DEMENTIA (FTD, aka bvFTD)

- Personality, impulse control, executive functions, judgment, insight, social skills
- Apathetic/dysexecutive and disinhibited/behavioral subtypes
- Memory, language preserved



THE FTD SYNDROME: 40% FTLD-TAU, 40% FTLD-TDP, 20% AD

(MESSAGE 1- YOU CAN HAVE FTD WITHOUT FTLD)

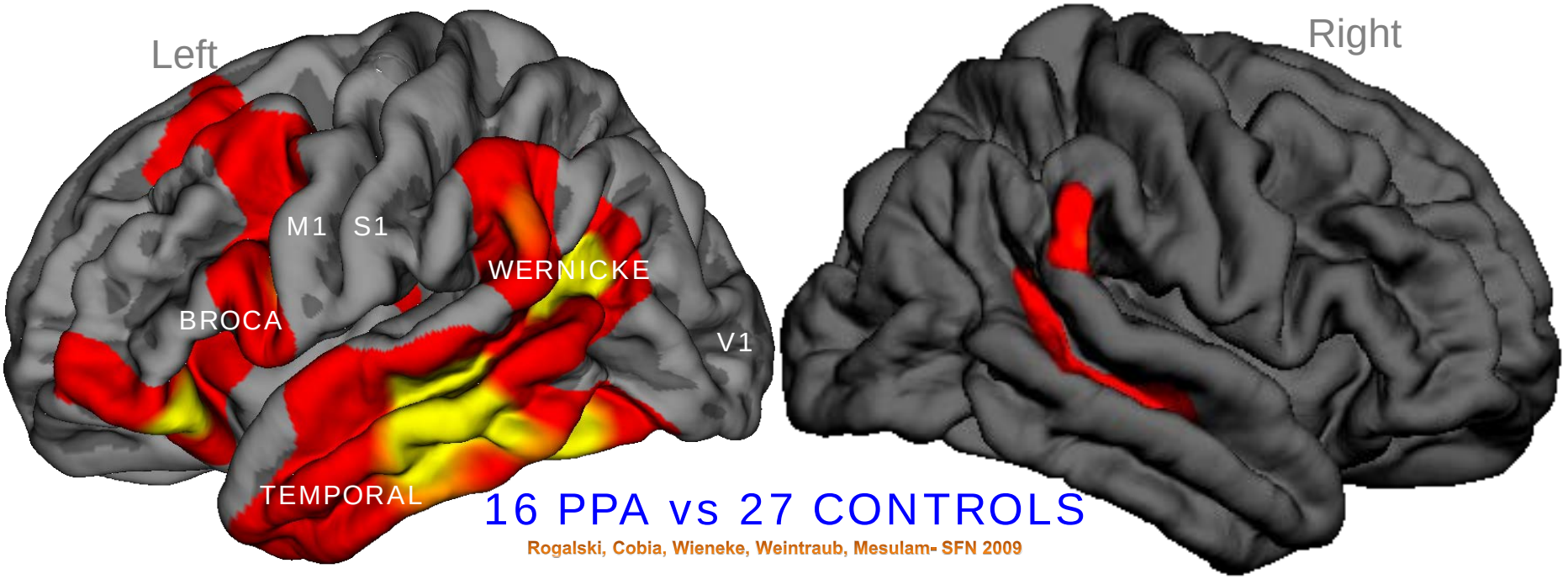
SYNDROME OF PRIMARY PROGRESSIVE APHASIA (PPA)

a) Acquired impairment of word-finding, word comprehension or sentence construction (i.e., aphasia)

b) The language disorder initially arises as *the principal deficit,* (i.e., primary)

c) The cause is a neurodegenerative disease (i.e., progressive)

(onset is most commonly between the ages of 55 to 65 and there is equal representation of males and females)



16 PPA vs 27 CONTROLS

Rogalski, Cobia, Wieneke, Weintraub, Mesulam- SFN 2009

PPA SUBTYPES

AGRAMMATIC
(PPA-G)
IMPAIRED GRAMMAR & FLUENCY

→ **MOSTLY FTLD-TAU**

LOGOPENIC
(PPA-L)
IMPAIRED WORD-FINDING

→ **MOSTLY AD**

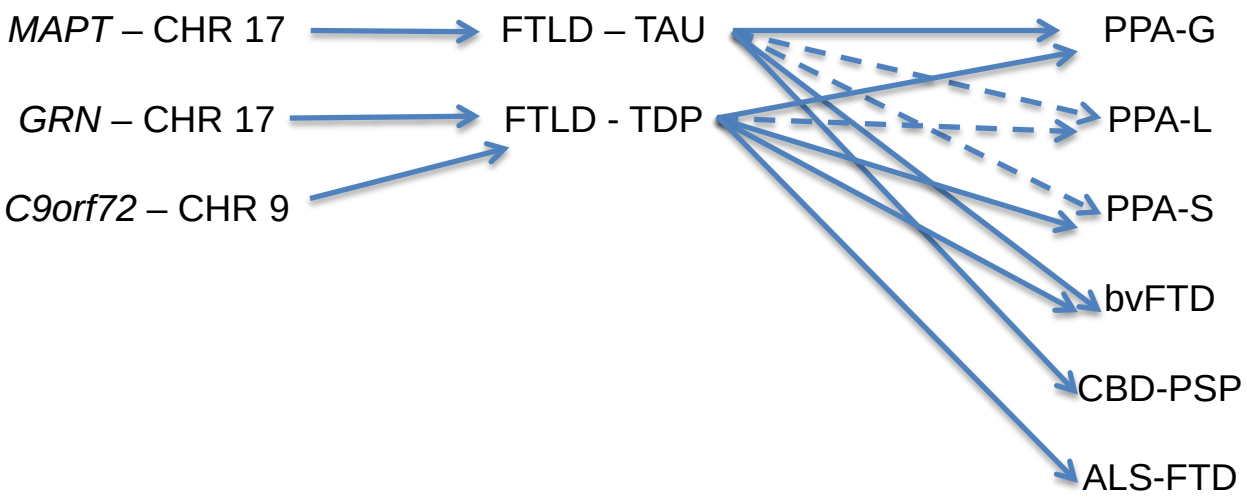
SEMANTIC
(PPA-S)
IMPAIRED WORD COMPREHENSION

→ **MOSTLY FTLD-TDP**

(MESSAGE 2- YOU CAN HAVE FTLD WITHOUT FTD)
(MESSAGE 3- YOU CAN HAVE BOTH PPA AND AD)

PERSONALIZED PRECISION MEDICINE IN FTD

GENES → DISEASES → SYNDROMES



GENOTYPING

COUNSELLING,
PREIMPLANTATION
IN VITRO DIAGNOSIS

BIOMARKERS

IS IT AD?

MEDICATION,
CLINICAL TRIALS

MULTIDISCIPLINARY TEAM APPROACH

SYMPTOMATIC
INTERVENTION