

Can Parkinson's Disease be Predicted....and Ultimately Prevented?

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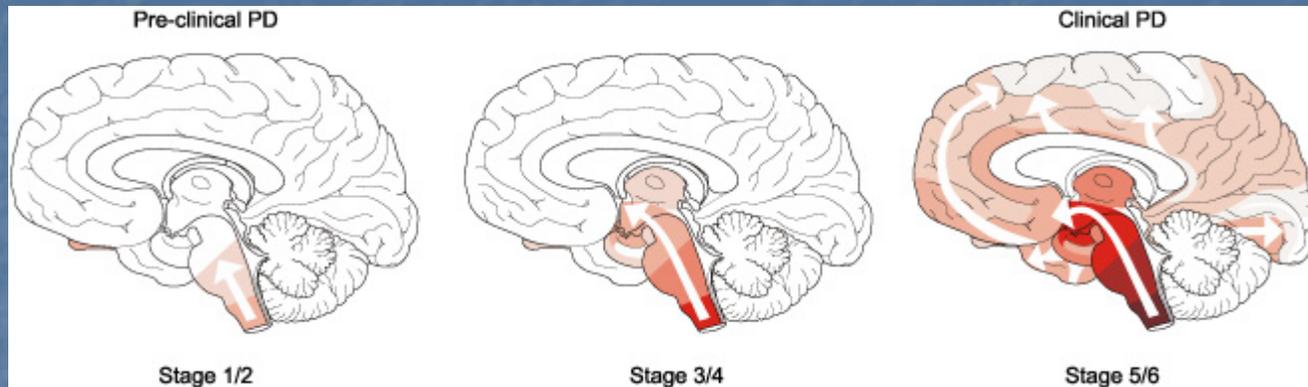
Premises

- PD has a “preclinical phase.”
- Markers of PD are detectable before symptoms.
- Interfering with the PD process earlier is better.
- Identifying PD before symptoms emerge offers hope for disease prevention

Is disease prevention possible for PD?

- Advances in genetics, epidemiology and our understanding of early non-motor PD features suggest that identification of at-risk populations is possible
- Available screening tests may be able to identify individuals among these groups at highest risk
- Biological (and newer clinical) studies suggest that therapies may be more effective if used earlier in PD
- Prevention of PD eliminates need for surrogate endpoints in trials

Natural History of PD



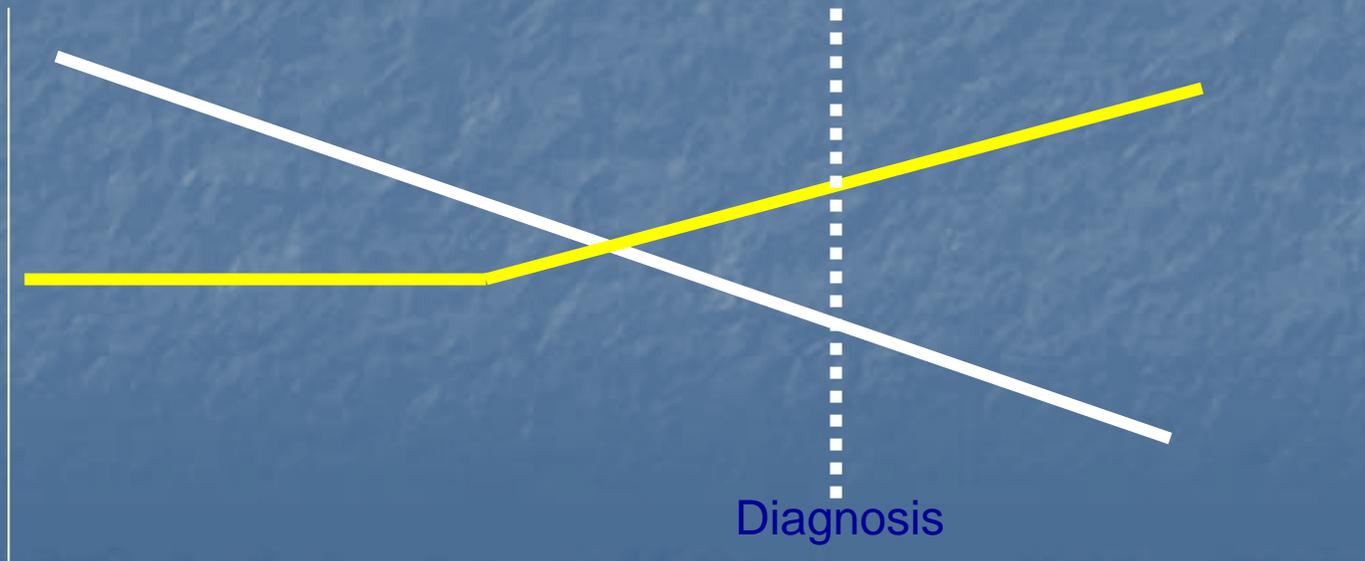
Preclinical Phase

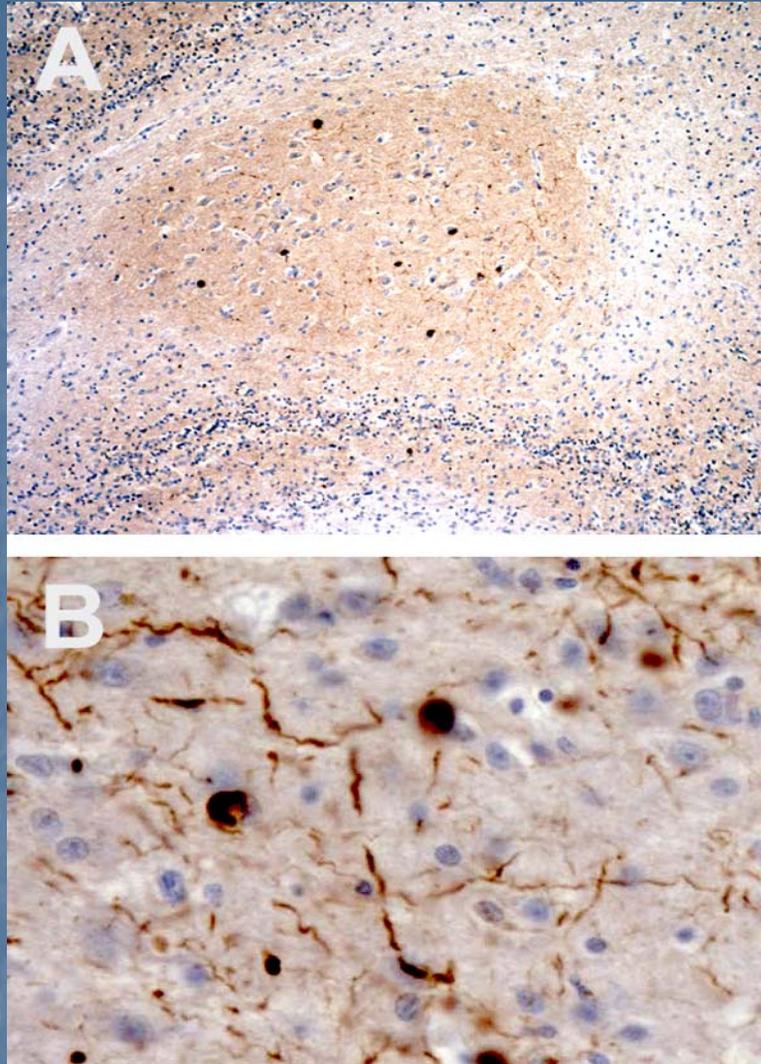
Clinical PD

Dopamine neurons

Symptom severity

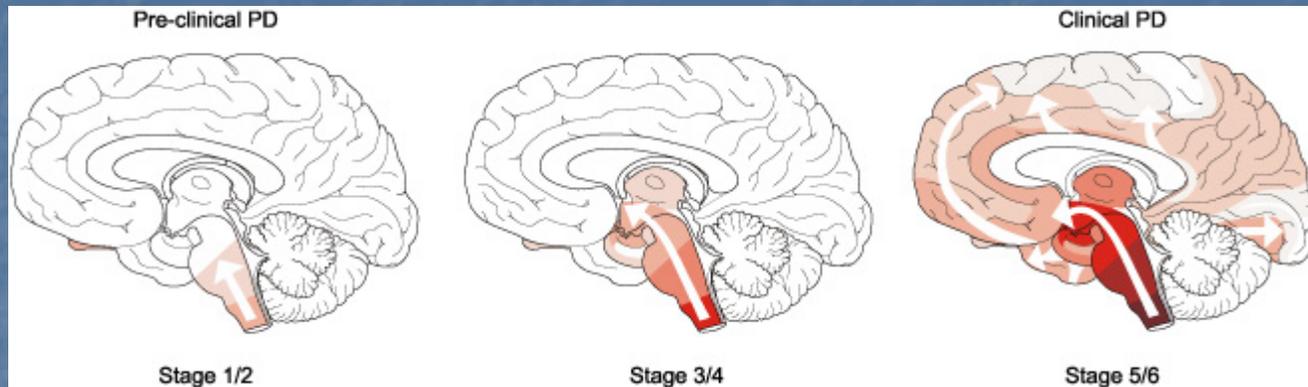
Diagnosis





Lewy Pathology in the Olfactory Bulb Alpha-synuclein immunostaining reveals Lewy pathology, including Lewy bodies and Lewy neurites in the olfactory bulb of patients with incidental Lewy body pathology. Low power magnification (Panel A) reveals Lewy pathology concentrating in the anterior olfactory nucleus and plexiform layers of the olfactory bulb while higher magnification (Panel B) of the anterior olfactory nucleus in a different individual reveals abundant Lewy bodies and Lewy neurites.
(Courtesy of John Duda, MD and J. Noorigian, MPH).

Natural History of PD



Preclinical Phase

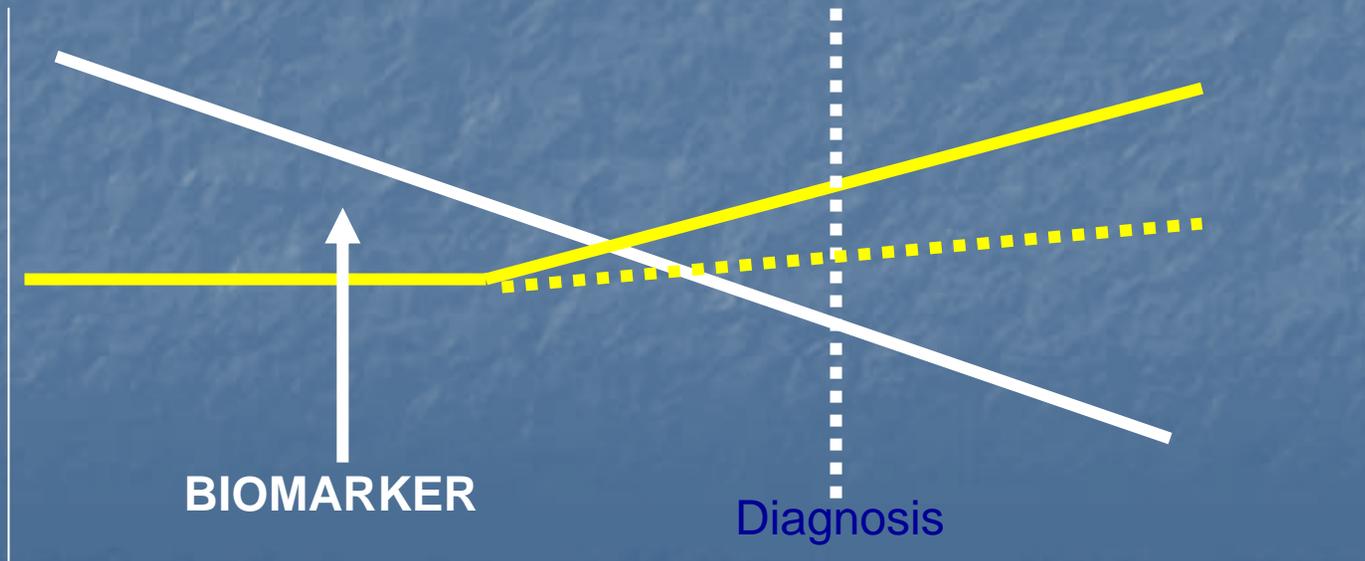
Clinical PD

Dopamine neurons

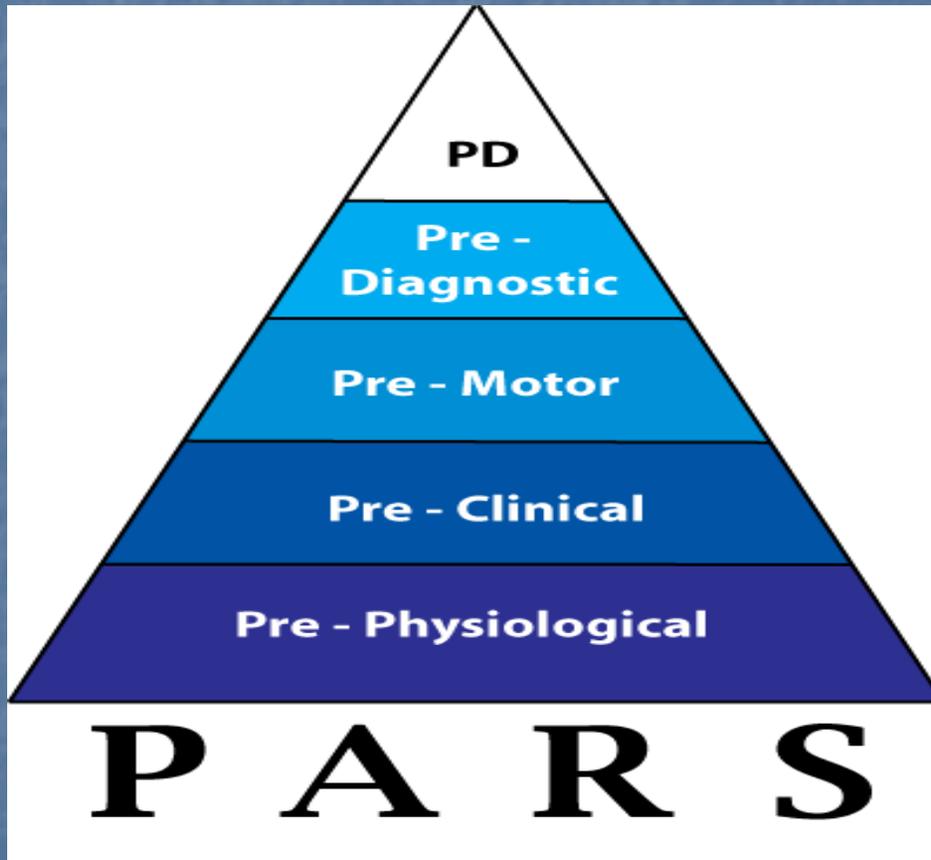
Symptom severity

BIOMARKER

Diagnosis



Parkinson's Disease Associated Risk Syndrome



- *Subtle motor features*
- *Non-motor features*
- *Neuroimaging changes*
- *Genetic predisposition*

PARS: Parkinson's Associated Risk Syndrome

- Genetic predisposition
- Olfactory loss
- Sensory and autonomic changes (Gut, heart, visual system)
- REM Behavior Disorder
- Cognitive or Affective markers
- Neuroimaging

PRE-PHYSIOLOGIC

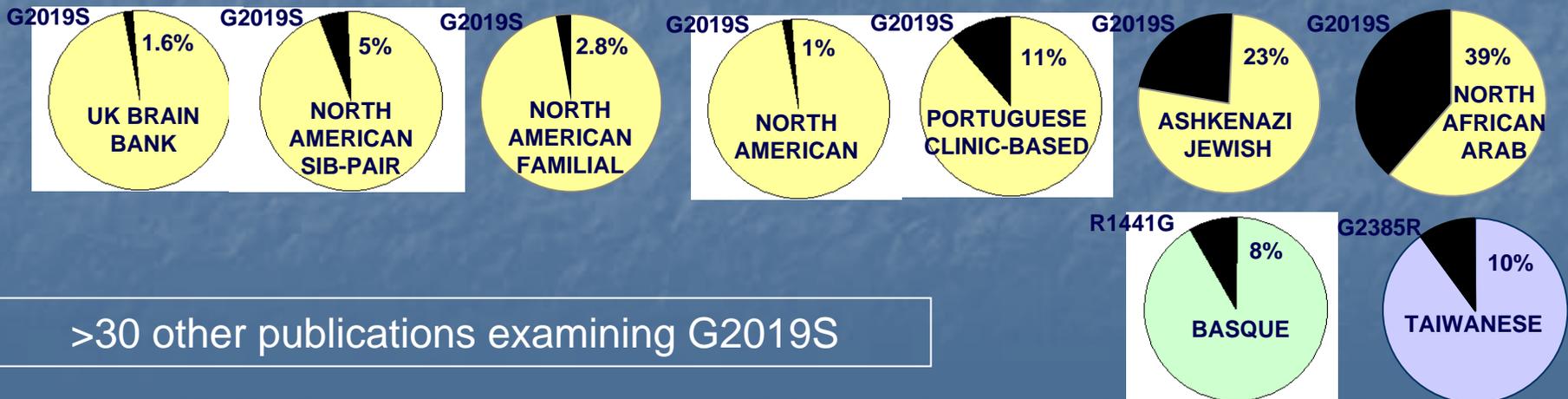
Advances in the Genetics of PD

- 1997: Identification of defect in alpha-synuclein in Greek-Italian kindred
- 2000: Association between early-onset PD and *parkin* gene mutations
- 2000: Familial aggregations of PD identified in Iceland
- 2004: 10 genes associated with PD have been identified
- 2005: 15 genes associated with PD

LRRK2 Mutations in PD

Assessing G2019S in other cohorts

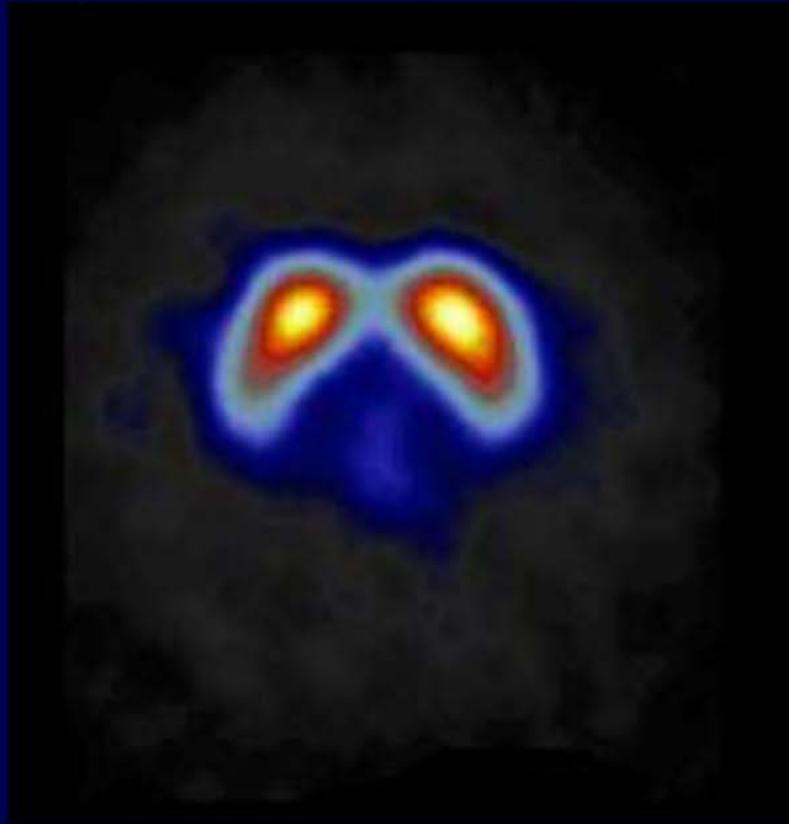
ISSUE: What is the penetrance of specific mutations?



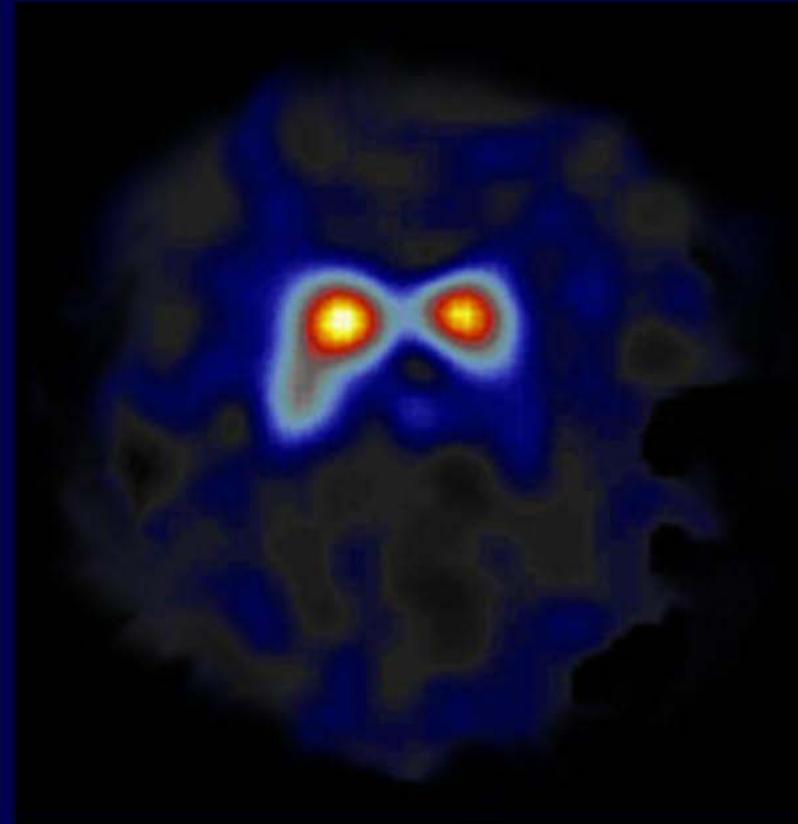
>30 other publications examining G2019S

PRECLINICAL

Functional Imaging: Healthy Controls vs Parkinson's Disease

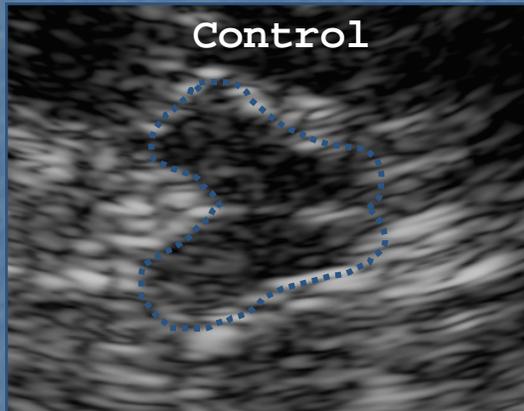


Healthy subject



Parkinson's disease patient –
Hoehn-Yahr Stage 1

Transcranial Sonography



- 92% of clinically probable PD cases show midbrain hyperechogenicity - but also 10% of normals (Berg, 2001)
- No correlation between disability and midbrain echogenicity in PD
- No significant TCS signal change over 5 years in PD despite UPDRS rise from 26 to 49 (Berg, 2005)
- *Is midbrain hyperechogenicity a trait rather than a state marker for PD?*
- *What is the pathologic correlate?*

Premotor

- Olfaction
- REM Behavior Disorder
- Cardiac Sympathetic Denervation
- Constipation
- Visual Changes (contrast sensitivity)
- Depression

Olfaction in PD

- Significant loss occurs early in the PD process
- Not characteristic of parkinsonian syndromes, MPTP parkinsonism, ET
- Olfactory bulb may be early pathologic target (Braak et al)
- May correlate with dopamine transporter imaging in early PD (Siderowf et al)

361 Relatives of PD Patients

Olfactory Tests

38 normosmic relatives

283 relatives

40 hyposmic relatives

NO patients developed clinical PD

4 with clinical PD at 2 years

SPECT RESULTS

Baseline: slight (but not significant) reduction in hyposmic group

2 years: rate of decline significantly greater in hyposmic group, even excluding 4 PD patients. 5 non-PD, hyposmic patients had annual loss of 15-23%

TWIN STUDY

62 pairs discordant for PD studied (UPSITS lower in PD patients)

After 7.3 years, 19 unaffected sibs had follow-up; 2 had developed PD.

The 2 new PD patients had normal UPSIT at baseline but a much greater decline than the 17 unaffected twins.

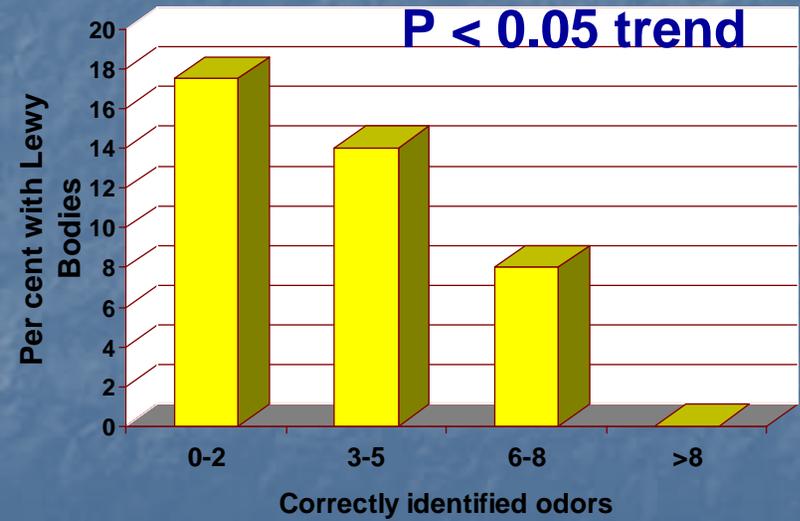
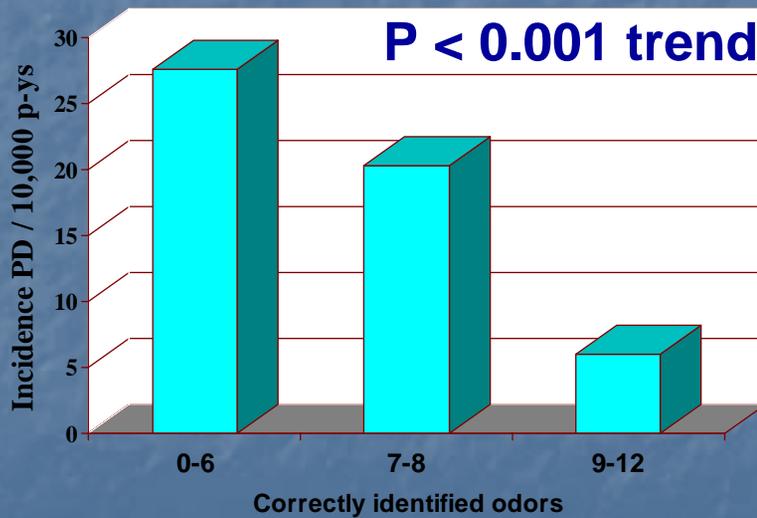
Does smell loss occur within 7 years of cardinal manifestations of PD?

Olfactory Dysfunction in the HAAS

Assessed using 12 odor cross cultural smell identification test – 1991 and 1994 exams

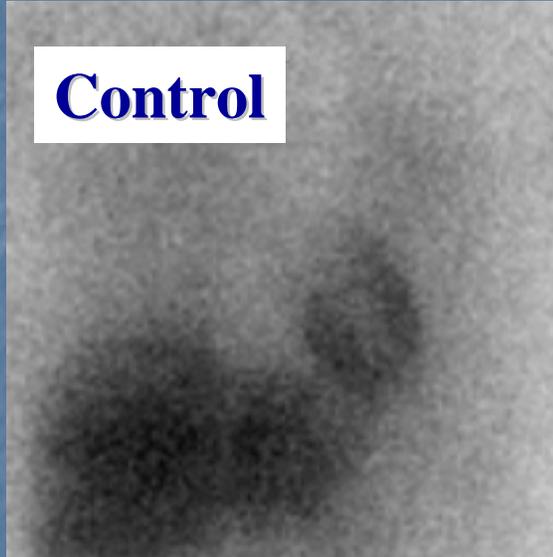
Age adjusted **PD incidence** / 10,000 p-ys by tertile of odor identification among 2263 men at risk

Per cent with **incidental LB** by quartile of odor identification among 185 descendants

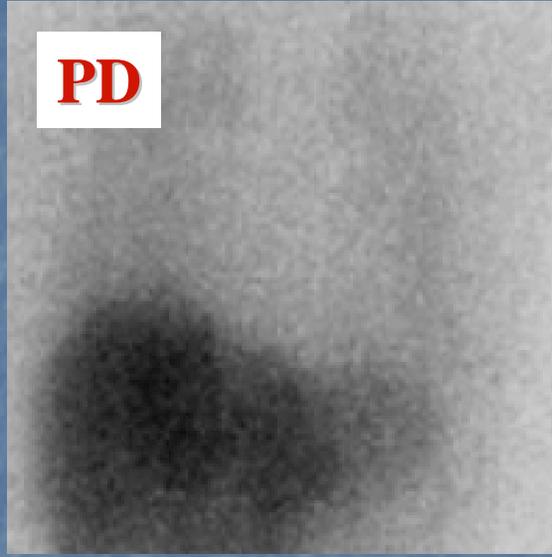


Cardiac MIBG Scintigram

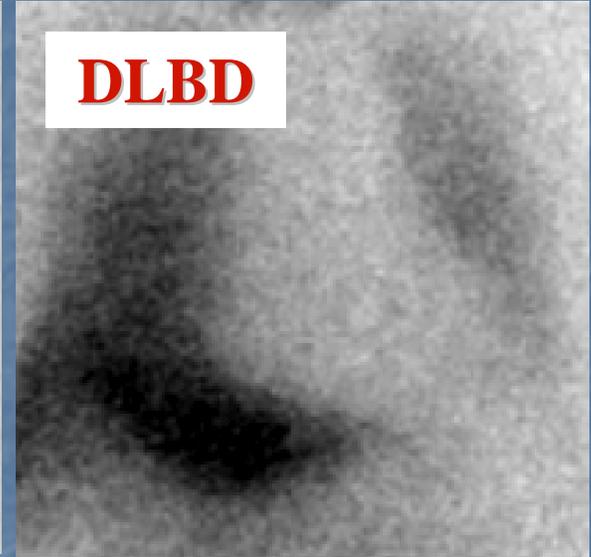
Control



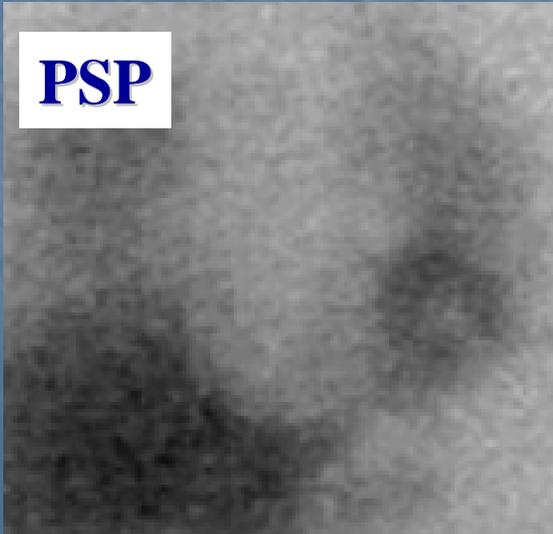
PD



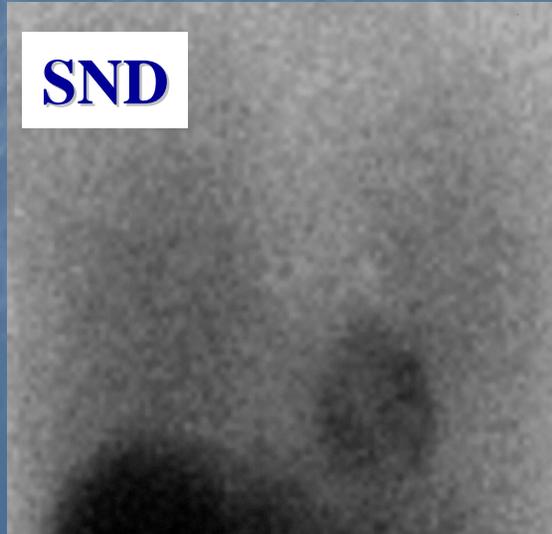
DLBD



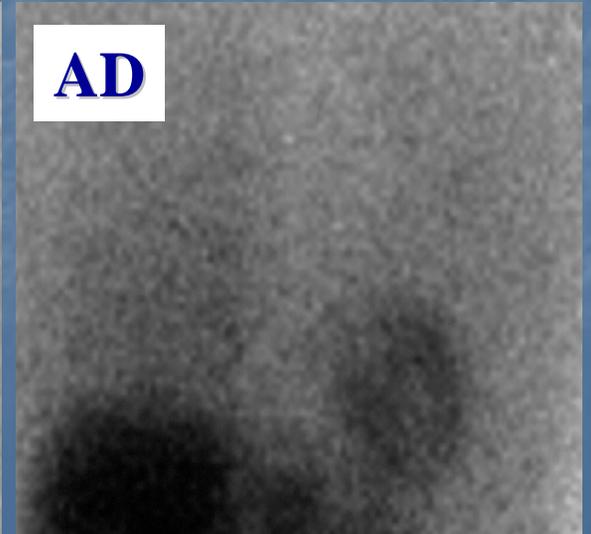
PSP



SND



AD



Potential Early Markers of Parkinson Disease in Idiopathic REM Sleep Behavior Disorder

Ronald B. Postuma, MD

Anthony E. Lang, MD

Jessica Massicotte-Marquez, BSc

Jacques Montplaisir, MD, PhD

CONCLUSIONS

Patients with RBD share risk factors for the development of PD

- ↓ Olfaction
- ↓ Color discrimination
- Subtle motor impairment

Parkinson's Associated Risk Syndrome Study

University of Pennsylvania
Institute of Neurodegeneration

Andrew Siderowf, M.D.
Matthew B. Stern, M.D.
Ken Marek, M.D.
Danna Jennings, M.D.



Hyposmotic first-degree relatives of PD patients share similar risk factors to PD patients:

- ↓ Smoking
- ↓ Caffeine intake
- ↓ B-CIT uptake

PARS Study Sample Size

3,000 PD patients (519)
provide letters to first-degree relatives (n=7,500)



(40% willing and eligible)

Eligible relatives sent UPSIT's (n=3,000) (936)



(72% return rate)
(50-60% return)

Valid UPSIT's (n=2,160) (573)



(≤12th percentile)

Olfactory loss (n=300) (52)

Advancing the Field Requires that PD be Diagnosed in its Pre- Neurologic Phase

**IS PD A NEUROLOGIC OR SYSTEMIC
DISEASE?**

**How early in the PD process do
olfactory, cardiac, GI and visual
changes occur?**

**CAN EXTRACEREBRAL MANIFESTATIONS
OF PD BE USED IN A SCREENING
PARADIGM??**