Motor symptoms in prodromal Parkinson’s disease

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Prodromal ≠ pre-motor

Pre-diagnosis
Gait disturbances play a major role in the motor manifestation of PD.

Gait changes frequently observed include decreased stride length and an increased stride time variability even early in the disease.

Increased stride time variability has been reported as one of the hallmarks of gait in PD

Stride time variability is especially sensitive to challenging conditions
Gait Changes in PD

Hausdorff et al 2006
Power spectral density (prs)

Stride time Variability

Coefficient of Variation = 100 x standard deviation/mean

Amplitude

Width
Gait variability in healthy subjects at risk

Non carriers = 25, carriers = 25

Are these changes related to disease or are they an endophenotype of LRRK2?
Gait in PD

PD Carriers N = 50, PD Non-Carriers N = 50

Mirelman et al. in press MDJ
PD Carriers N =50,  PD Non-Carriers N= 50

Mirelman et al in press MDJ
Stride time variability under challenging conditions

NMNC=61, NMC=62, PD-=50, PD+=50
Summary

- Differences in motor performance can be detected between carriers and non-carriers of G2019S LRRK2 mutation.
- Evidence exists to support subtle motor changes in the prodromal phase of PD, exposed in challenging conditions.
- Motor decline changes with course of disease progression.
- It is likely that there is a specific motor phenotype that can be related to G2019S LRRK2.
- Creating a motor index could help in diagnosing early motor markers.
# The team

<table>
<thead>
<tr>
<th>Tel Aviv Medical Center, Israel</th>
<th>Beth Israel Medical Center NY, NY</th>
<th>Columbia University, NY, NY</th>
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<tbody>
<tr>
<td>Nir Giladi</td>
<td>Susan Bressman</td>
<td>Karen Marder</td>
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<td>Avi Orr-Urtreger</td>
<td>Rachel Saunders-Pullman</td>
<td>Lorraine Clark</td>
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<td>Anat Mirelman</td>
<td>Deborah Raymond</td>
<td>Itsik Pe’er</td>
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<td>Maayan Zelis</td>
<td>Vicki Shanker</td>
<td>Helen Mejia</td>
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<td>Kira Yasinovsky</td>
<td>Mark Groves</td>
<td>Brian Rakitin</td>
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<td>Jeff Hausdorff</td>
<td>Christina Palmese</td>
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<td>Tanya Gurevich</td>
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<td>Roy Alcalay</td>
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<td>Hertzl Shabtai</td>
<td>Jeannie Soto-Valencia</td>
<td>Tsvyatko Dorovski</td>
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<td>Yaacov Balash</td>
<td>Akhila Iyer</td>
<td>Martha Orbe Reilly</td>
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<td>Avner Thaler</td>
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<td>Anat Bar Shira</td>
<td>Jose Cabassa</td>
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<td>Lucien Cote</td>
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<td>Mali Gana Weiss</td>
<td>Ann Hunt</td>
<td>Jose Cabassa</td>
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<td>Noa Bregman</td>
<td>Laurie Ozelius (Mount Sinai)</td>
<td>Andres Deik</td>
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<td>Meir Kestenbaum</td>
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<td>Anat Shkedy</td>
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<td>Inbal Maidan</td>
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<td>Arella Hillel</td>
<td>Gait Consortium</td>
<td>Jan Aasly-Trondheim, Norway</td>
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<td>Aner Weiss</td>
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<td>Daniela Berg- Tubingen, Germany</td>
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<td>Hagar Bernad</td>
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<td>Eduardo Tolosa- Barcelona, Spain</td>
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<td>Eran Gazit</td>
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<td>Bill Chen- Beijing, China</td>
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<td>AJ consortium</td>
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<td>Inbal Maidan</td>
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Thank you!
Natural History of Parkinson disease
Prodromal PPMI cohort

• Enroll subjects at risk for PD proximate to conversion to motor PD
• Sequential biomarker strategy to identify subjects with olfaction and/or RBD, plus DAT deficit
• Enrollment DAT deficit (80%) and no DAT deficit (20%) group
• Follow group with DAT deficit and normal DAT for approx 4-5 years (n=100)
  • Establish prodromal biomarker signature
  • Define phenoconversion
P-PPMI Outcome measures

• Change in biomarker signature – Clinical, Imaging, biologic
  • Exploratory comparison of P-PPMI to PD Healthy, SWEDD

• Phenoconversion to motor PD
  • BBB modified criteria
  • Data driven definition
Prodromal PPMI cohort

- Utilize existing PPMI infrastructure
  - Sites
  - Cores
  - Database
  - Website
- Establish olfactory and RBD core
- Develop processes to identify ‘at risk’ subjects and refer to PPMI sites for enrollment
Eligibility for P-PPMI

Hyposmic Subjects

80% Mild to moderate DAT
20% Min to No-DAT

RBD Subjects

Min to No-DAT

DAT imaging

Eligible for PPMI

Not eligible for PPMI

500-700 Subjects scanned

100 subjects
Olfaction
Prodromal Cohort: Olfaction Process

Danna Jennings, MD
PPMI Olfactory Core
Prodromal: Olfactory Process

No DAT deficit

DAT deficit consistent with prodromal PD
PARS
Sequential biomarker assessment

**PHASE 1**
First degree relatives, non-relatives

- Eligible subjects sent UPSITs \( n = 9,379 \)
  - Valid UPSITs \( n = 4,871 \)
    - \(< 15\% \) percentile
  - Olfactory loss \( n = 650 \)
  - Hyposmic participants \( n = 203 \)
  - DAT deficit \( n = 23 \)

**PHASE 2**
Clinic and Imaging visits \( n = 303 \)
1. UPDRS
2. Diagnostic form
3. SCOPA-aut
4. Non-motor review
5. Neuropsych assess
6. DAT imaging
7. HRV
8. Blood, CSF sampling
Hyposmia recruitment...it’s all about numbers

- 10,000 eligible surveys
  - 5,000 completed UPSITs
    - 500 hyposmics
    - 200 participants
    - 25 DAT deficit subjects

- 15,000 eligible surveys
  - 7,500 completed UPSITs
    - 750 hyposmics
    - 300 participants
    - 38 DAT deficit subjects

- 20,000 eligible surveys
  - 10,000 completed UPSITs
    - 1,000 hyposmics
    - 400 participants
    - 50 DAT deficit subjects
P-PPMI Olfaction Referral Sources

20,000 surveys completed

- Centrally initiated regional outreach: 35%
- Site recruitment: 40%
- Online resources: 25%
P-PPMI Olfaction Recruitment Sources

Site recruitment 40%
- Distribute surveys to patients, family friends
- Engage institutional resources to distribute surveys

Centrally initiated local outreach 35%
- Mass emails to people within site vicinity
- MJFF to engage local media

Internet resources 25%
- Google ads, MJFF website link
- FTF - reach out to HC population
Site recruitment goals

• Sites to identify 40% of olfactory cohort (20,000 X 0.4 = 8,000)
• Recruitment period - 10 months
• 365 returned eligible surveys/site (22 sites)
• Approx 730 need to be distributed to get 365 returned
• Goal: distribute roughly 75/month
Olfaction: site outreach

- Packets of surveys in waiting rooms/clinic rooms for family to complete
- Packets of surveys for a PD patient to mail to family and friends–study coordinators and MDs to offer this to all patients
- Identify point person in your clinic to:
  - Remind neurologists/coordinators/nurses to approach all patients in clinic
  - Make sure clinic is stocked with surveys
- Reconnect with people interested in the original PPMI who were 1st degree relatives – ask them to take the survey
- Share info with other coordinators/departments within institution (i.e. geriatrics)
- Materials to share and present at local support groups and community outlets (slides, newsletter stories, etc)
- Engage a Parkinson advocate in your area
Olfaction Process: US Sites

1. Identify 20,000 people to complete the olfaction survey
2. Eligibility evaluated by Olfactory Core
3. Olfactory Core sends Olf ICF, UPSIT and SRQ to eligible subjects
4. If UPSIT <10th percentile, referred to site. Site contacts subject to sched visit
Olfaction Process: EU Sites

1. Identify people to complete the olfaction survey
2. Eligibility evaluated by EU Site
3. EU site sends Olf ICF, UPSIT and SRQ to eligible subjects
4. UPSIT returned to Olf Core
   - If UPSIT <10th percentile, referred back to site. Site contacts subject to sched visit
Olfactory data so far......

### Site generated surveys

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Total received - Sites and other sources</td>
<td>330</td>
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<tr>
<td>Eligible</td>
<td>442</td>
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<tr>
<td>Ineligible</td>
<td>62</td>
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<tr>
<td>PD dx</td>
<td>19</td>
</tr>
<tr>
<td>AD dx</td>
<td>5</td>
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<tr>
<td>Age &lt; 60</td>
<td>26</td>
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<tr>
<td>distance from site</td>
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<tr>
<td>other</td>
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### Online Surveys

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<td>Total received - Online sources</td>
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<tr>
<td>Eligible</td>
<td>217</td>
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<tr>
<td>Ineligible</td>
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### UPSITs

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<tbody>
<tr>
<td>UPSITs sent</td>
<td>442*</td>
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<tr>
<td>UPSITs received</td>
<td>154</td>
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<tr>
<td>Hyposmics identified</td>
<td>9</td>
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<tr>
<td>Hyposmics referred</td>
<td>5</td>
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<tr>
<td>Hyposmic enrolled</td>
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*176 sent in past week
Online Recruitment Sources
(n=217 eligible subjects)

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<tr>
<th>#</th>
<th>%</th>
<th>Source</th>
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<tbody>
<tr>
<td>86</td>
<td>40%</td>
<td>Friend or Family Member</td>
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<tr>
<td>42</td>
<td>19%</td>
<td>MJFF Newsletter, Email, or Event</td>
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<td>40</td>
<td>18%</td>
<td>MJFF Website</td>
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<tr>
<td>15</td>
<td>7%</td>
<td>Facebook or Social Media Outlet</td>
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<td>13</td>
<td>6%</td>
<td>Other</td>
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<td>11</td>
<td>5%</td>
<td>Site Referral</td>
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<td>6</td>
<td>3%</td>
<td>Fox Trial Finder</td>
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<tr>
<td>2</td>
<td>1%</td>
<td>Doctor or Medical Care Provider</td>
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<tr>
<td>1</td>
<td>0%</td>
<td>Support Group</td>
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RBD

PPMI Prodromal Cohort Training
January 28th and 30th, 2013
RBD Operations

• **RBD Sleep Core**
  - Core at Hephata Clinic in Schwalmstadt Germany
  - Lead Investigator for core is Geert Mayer

• **Responsibilities**
  - Provide standardized criteria for polysomnography (PSG)
  - Draft Technical Operations Manual for RBD sites
  - Receipt and tracking of polysomnography data for P-PPMI
  - QC and artifact discrimination of polysomnography data
  - Scoring of PSG as PPMI eligible or not eligible
  - Report to P-PPMI Referral Team
RBD Subject Flow
Site identifies subjects – PSG Review central

- Selected PPMI sites will conduct pre-screening activities for subjects with a diagnosis of RBD identified at Sleep centers

- Subjects with RBD identified by/referred to PPMI sites

- PPMI Investigators and Coordinators will contact patients
  - Provide more information about PPMI study
  - Get initial consent to obtain and centrally review their PSG to determine eligibility for PPMI

- PSG transferred and reviewed by RBD core

- P-PPMI Referral Team informs PPMI sites about subject eligibility.
RBD Screening

• Once site has received IRB or EC approval for Amendment-5

• For consented subjects PPMI site will send de-identified PSG to RBD Core for standardized evaluation

• Site will receive auto-reply confirmation of upload

• Site will receive confirmation that PSG is evaluable for PPMI (24-48 hrs post upload)

• RBD core will evaluate PSG for RBD and provide evaluation to P-PPMI referral team

• Referral team will send site RBD Eligibility report (2 business days)
RBD Screening
RBD Subject Eligibility Report

• PPMI RBD Eligibility Report will be sent from PPMI Referral Team to sites

• Include in the subjects binder

• PPMI site to contact subject to schedule visit to enroll in PPMI

• Subjects not eligible based on PSG should be contacted by site
Prodromal Subject Enrollment
Eligibility of Prodromal Subjects

**Inclusion Criteria (Prodromal Subjects)**

Subjects must meet the eligibility for at least one of the following

*Hyposmia:*

a) Male or female age 60 years or older

b) Confirmation from olfactory core that olfaction as determined by UPSIT is at or below the 10th percentile by age and gender *Part of pre-screening completed by Olfactory Core*

*REM Behavior Disorder (RBD):*

a) Male or female age 60 years or older

b) Confirmation from sleep core that subject’s Polysomnography (PSG) meets criteria for RBD *Part of pre-screening completed by select sites in collaboration with sleep center and RBD Core*
Eligibility of Prodromal Subjects

**Inclusion Criteria (Prodromal Subjects)**

**4.2.7.2.** Confirmation from imaging core that screening dopamine transporter SPECT scan is read as eligible (see below).

About 80 subjects will have a range of DAT deficit similar to subjects with early PD (mild to moderate DAT deficit). About 20 subjects will be selected with no DAT deficit or minimal DAT deficit similar in age, gender, and risk profile to those with mild to moderate DAT deficit.

**4.2.7.3.** Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations

**4.2.7.4.** Willing and able to comply with scheduled visits, required study procedures and laboratory tests.

**4.2.7.5.** Women may not be pregnant, lactating or planning pregnancy during the course of the study.
Includes a negative urine pregnancy test on day of screening scan prior to injection (DaTSCAN)
Eligibility of Prodromal Subjects

Exclusion Criteria (Prodromal Subjects)

4.2.8.1. Current or active clinically significant neurological disorder or psychiatric disorder (in the opinion of the Investigator).

4.2.8.2. GDS score greater than or equal to 10 (GDS score of 5 – 9 requires Investigator discretion to enter study).

4.2.8.3. STAI Form Y-1 greater than or equal to 54 requires Investigator discretion to enter study.

4.2.8.4. A clinical diagnosis of dementia as determined by the investigator (Appendix 1).

4.2.8.5. A clinical diagnosis of Parkinson disease at the Screening visit as determined by the Investigator.

Note: if subjects would qualify for PPMI de novo PD they are not prodromal
Eligibility of Prodromal Subjects

Exclusion Criteria (Prodromal Subjects)

4.2.8.6. Received any of the following drugs that might interfere with dopamine transporter SPECT imaging: Neuroleptics, metoclopramide, alpha methylldopa, methylphenidate, reserpine, or amphetamine derivative, within 6 months of Screening.

4.2.8.7. Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture.

4.2.8.8. Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.

4.2.8.9. Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.

4.2.8.10. Use of investigational drugs or devices within 60 days prior to Baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).

4.2.8.11. Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).
Eligibility of Prodromal Subjects

Subject Consenting:

Hyposmic, RBD (REM behavior disorder) who meet pre-screening criteria and are able and willing to enroll into PPMI all sign the same ICF.
Eligibility – soft motor signs
When does prodromal become motor PD?

- Mild motor signs vs early PD – judgement call

- If subject meets criteria for PPMI PD group then not eligible for P-PPMI
  - Single asymmetric motor sign + DAT deficit
DaTSCAN
Why DAT imaging?

• DAT imaging used to determine those proximate to Phenoconversion among those at risk

• Evidence that Olfaction, RBD and LRRK2 studies plus DAT deficit results in approx 30% phenoconversion in 2-3 years
DaTSCAN - What is abnormal?

- Percent age expected lowest Putamen - β-CIT
  - <65% mild to mod DAT deficit
  - 65%-80% minimal DAT deficit
  - >80% no DAT deficit

- Linear discriminant function – DaTSCAN
  - Use PPMI PD and healthy subjects to identify best imaging discriminators
  - Developed simple tool - using ipsilateral striatal, Lowest striatum, asymmetry index – correctly classified >95% of PD and HC

- Visual assessment
  - Readers will assess with same visual method as in PPMI

DAT deficit will require both quantitative and visual evidence
DaTSCAN - Why no DAT deficit

- Enroll 80% mild to mod DAT deficit
- Enroll 20% minimal to NO DAT deficit
  - Reduce bias regarding clinical assessments and phenoconversion
  - Note all subjects have PD risk

- Sites will be informed whether the subjects DaTSCAN is eligible or not eligible
Phenoconversion
P-PPMI Cohort - Outcomes

- Define the biomarker signature during the prodromal period
- Assess Phenoconversion
Defining Phenoconversion to PD in the P-PPMI cohort

• Critical outcome for P-PPMI cohort
• Established phenoconversion definition not available
• Approach: develop a standardized diagnosis with minimal inter-rater variability
• Data Driven diagnosis
Phenoconversion

- **Primary:**
  - Based on UK Brain Bank Criteria
  - Data mapped from the ‘Diagnostic Features Questionnaire’

- **Secondary:**
  - Prodromal Diagnostic Questionnaire
    - Current most likely clinical diagnosis (Q#1)
    - Confidence level regarding motor symptoms c/w a diagnosis of Parkinsonian syndrome (Q#2)
Phenoconversion - Exploratory Strategies

- Assess conversion to PPMI diagnosis

- Develop conversion to biomarker outcomes – DAT, CSF analytes, cognition
UK PD Society Brain Bank Diagnostic Criteria

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<thead>
<tr>
<th>Step 1: Diagnosis of Parkinsonism</th>
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<tbody>
<tr>
<td>Bradykinesia and at least one of the following:</td>
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<tr>
<td>• Muscular rigidity</td>
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<td>• 4–6 Hz resting tremor</td>
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<td>• postural instability not caused by primary visual, vestibular, cerebellar or Proprioceptive dysfunction</td>
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<tr>
<th>Step 2: Features tending to exclude Parkinson’s disease as the cause of Parkinsonism</th>
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<tr>
<td>• History of repeated strokes with stepwise progression of parkinsonian features</td>
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<tr>
<td>• History of repeated head injury</td>
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<tr>
<td>• History of definite encephalitis</td>
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<tr>
<td>• Neuroleptic treatment at onset of symptoms</td>
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<td>• &gt;1 affected relatives</td>
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<tr>
<td>• Sustained remission</td>
</tr>
<tr>
<td>• Strictly unilateral features after 3 years</td>
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<tr>
<td>• Supranuclear gaze palsy</td>
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<tr>
<td>• Cerebellar signs</td>
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<tr>
<td>• Early severe autonomic involvement</td>
</tr>
<tr>
<td>• Early severe dementia with disturbances of memory, language and praxis</td>
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<td>• Babinski's sign</td>
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<tr>
<td>• Presence of a cerebral tumour or communicating hydrocephalus on computed tomography scan</td>
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<tr>
<td>• Negative response to large doses of levodopa (if malabsorption excluded)</td>
</tr>
<tr>
<td>• MPTP exposure</td>
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- Vascular disease
- Family history
- Autonomic disorder
- Sleep Apnea
- Cognitive disorder
PPMI

PRODROMAL DIAGNOSTIC QUESTIONNAIRE

SUBJECT ID __________ VISIT NO __________
INITIALS __________ SITE NO __________ VISIT DATE __________

1. Indicate the current most likely clinical diagnosis from one of the categories listed below (choose one):

01 = Idiopathic PD
02 = Alzheimer’s disease
03 = Chromosome-17 frontotemporal dementia
04 = Corticobasal degeneration
05 = Dementia with Lewy bodies
06 = Dopa-responsive dystonia
07 = Essential tremor
08 = Hemiparkinson/hemiatrophy syndrome
09 = Juvenile autosomal recessive parkinsonism
10 = Motor neuron disease with parkinsonism
11 = Multiple system atrophy
12 = Neuroleptic-induced parkinsonism
13 = Normal pressure hydrocephalus
14 = Progressive supranuclear palsy
15 = Psychogenic illness
16 = Vascular parkinsonism
17 = No PD nor other neurological disorder
18 = Spinocerebellar Ataxia (SCA)
23 = Prodromal non-motor PD (at least one non-motor symptom and no motor symptoms)
24 = Prodromal motor PD (at least one motor symptom to meet eligibility for enrollment in PPMI as PD subject)
97 = Other neurological disorder(s) (specify) ________________________________
2. To what degree are you confident that this subject has motor signs consistent with a parkinsonian syndrome (PS) (any condition in which there is neurodegeneration of dopaminergic cells in the substantia nigra)?

1 = Motor abnormalities that are signs of PS (90 - 100%)
2 = Motor abnormalities that are likely signs of PS (70 - 89%)
3 = Motor abnormalities that may be signs of PS (50 - 69%)
4 = Non-specific motor abnormalities (25 - 49%)
5 = No evidence of parkinsonian motor signs (0 - 24%)
Prodromal discussion

- Best way for sites to dispense olfactory questionnaires
- Motor symptoms at screening?
- Clinical diagnosis at phenoconversion?
- Is DaTSCAN data provided?
PRODROMAL PPMI

G. Mayer
Schwalmstadt-Treysa
Philipps-Universität Marburg, Dpt. neurology
RBD EPISODE
84Y, LIVELY DREAMS ATTACKING AND EATING UP PEOPLE
HEAD TRAUMA, BYPASS SURGERY, HYPERTENSION, PLMD

MJFF NY 2013
ICSD2

A. Violent or injurious behavior in sleep
B. Limb- or body movements that relate to dream contents behavior (one of the following criteria):
   - Aggressive sleep behavior
   - Acting out dream contents
   - Fragmentation of sleep continuity
C. Polysomnography
   - Excessive increase of chin EMG
   - Excessive chin EMG or limb movement
   - Complex, aggressive behavior
D. Symptoms must not be caused by psychiatric disorders, association with neurological disorders (no epilepsies!)
E. Other sleep disorders may be present but are not the cause
Epidemiology

Studies

- Ohayon 1997, Ohayon & Schenck 2010: 0.5%
- Chiu 2000: Estimated prevalence in general population: 0.38%
- Boeve 2008 (PSG based, unpublished): 0.02%
- Molano 2009, Boot 2012: prevalence population >60y: 8.9%

- Men vs women: 9:1
Postuma 2012:

- Participation 13 centers worldwide: 347 iRB, 347 controls
- Questionnaire for lifestyle risk factors
- Risk factors: smoking, head injury, pesticide exposure, farming
conversion: $14.2 \pm 6.2$

Postuma et al. 2010
There should be at least two prior episodes of clinically reported or witnessed dream-enacting behavior supported by REM sleep without atonia recorded by PSG.

To allow for assessment of change, the minimum frequency of RBD episodes should preferably be >2 times weekly (with complex movements, apart from any sleeptalking), to the extent that reliable reporting is possible by a bedpartner (especially for iRBD).

iRBD patients with “soft” neurological dysfunction (olfactory dysfunction, mild cognitive impairment...)

video-polysomnography – REM-atonia, quantitative EMG-analysis
PSG EVALUATION
RBD STUDY GROUP RECOMMENDATIONS

- PSG montage for RBD evaluation: standard PSG montage according to the AASM (plus bilateral flexor digitorum superficialis muscles on the upper extremity) is encouraged.
- It is important to consider the same filter settings and impedance measures; amplification has to be stated and shown on the PSG machine. Sampling frequency should be indicated.
- EDF format should be used for data provision.
- RWA is supported by the polysomnographic findings of either: 1) Tonic chin EMG activity in > 30% of REM sleep; or 2) Phasic chin EMG activity in > 15% REM sleep, scored in 20 sec epochs
- Any (tonic/phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in > 32% of REM sleep, scored in 30 sec epochs
Motor Event Rating:
- **0** = no visible motor activity, RWA present
- Only definition criteria of RWA according to ICSD are fulfilled, no other phasic muscle activity in the limbs or face is visible or obvious on recording.

- **1** = small movements or jerks
- Isolated, single hand or foot movements or facial jerks visible, restricted to the distal extremities and/or face

- **2** = proximal movements including violent behavior
- Single movements or series of movements including proximal extremities, no change of position

- **3** = axial movements including bed falls
- Movements with axial involvement and/or change of body position, or falls

Vocalization rating:
- **0** = no vocalization
- Snoring with some sound may be present and should be differentiated from REM-associated vocalization.
WHERE WE ARE

- All participating centers have successfully sent test files
- Two centers have sent 2 final files each: 3 PSGs passed the requirements
Quantification of risk for neurodegenerative diseases in idiopathic RBD

Long-term follow-up of 113 patients with iRBD

Estimated risk for neurodegeneration:
- 5 years: 17.7%
- 10 years: 40.6%
- 12 years: 52.4%

Majority of patients developed PD and DLB

PD + RBD: 33–46% PD; Gagnon et al., 2002; Sixel-Döring et al., 2011)
DLB: 75% (Ferman et al., 2011)
MSA: almost 100% (MSA; Vetrugno et al., 2004).
PPMI
Recruitment and Retention

Update to the PPMI Annual Meeting
May 8, 2013

Danna Jennings, R&R Working Group Chair
Claire Meunier, MJFF
PPMI Recruitment & Retention Working Group

- Daniela Berg
- Carey Christensen
- Emily Flagg
- Hubert Fernandez
- Alexandra Gaenslen
- Katharina Gauss
- Christine Hunter
- Danna Jennings (Chair)
- Jim Leverenz

- Zoltan Mari
- Claire Meunier
- Tanya Simuni
- Carlie Tanner
- Cathi Thomas
- Karen Williams
Recap of R&R Goals

• **Recruit** 400 *de novo* and 200 control subjects
  – **Site Goal:** Enroll 1 PD per month and 1 control every two months

• **Retain** subjects by keeping them engaged to participate in study visits over time
  – **Site Goal:** Remain connected and continue to cultivate volunteers as key partners in the study
Recruitment is complete!

- 419 PD (11 pending enrollment)
- 191 Controls (5 pending enrollment)
- 59 SWEDDDs (3 pending enrollment)
<table>
<thead>
<tr>
<th>Site Name</th>
<th>Total PD consented</th>
<th>Total Controls consented</th>
<th>PD + SW/month</th>
<th>Controls/month</th>
<th>Subjects/month</th>
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<tr>
<td>IND</td>
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<td>2.0</td>
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<td>0.5</td>
<td>1.31</td>
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<tr>
<td>The PI</td>
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<td>13</td>
<td>0.9</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Banner Health/APDC</td>
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<td>0.4</td>
<td>0.1</td>
<td>0.51</td>
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<tr>
<td>Macquarie</td>
<td>6</td>
<td>1</td>
<td>0.4</td>
<td>0.1</td>
<td>0.50</td>
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</tbody>
</table>
Site Awards

Drumroll, please.....
## Sites that met the year 2 goal in less than 24 months

<table>
<thead>
<tr>
<th>Site</th>
<th>Years to recruit 20 PD</th>
<th>Years to recruit 10 Controls</th>
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</thead>
<tbody>
<tr>
<td>IND</td>
<td>1.12</td>
<td>1.08</td>
</tr>
<tr>
<td>OHSU</td>
<td>1.41</td>
<td>1.16</td>
</tr>
<tr>
<td>Tuebingen</td>
<td>1.41</td>
<td>0.87</td>
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<tr>
<td>U Wash/VA Puget Sound</td>
<td>1.47</td>
<td>0.97</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>1.51</td>
<td>1.28</td>
</tr>
<tr>
<td>University of Alabama</td>
<td>1.74</td>
<td>1.12</td>
</tr>
<tr>
<td>Paracelsus-Elena Klinik</td>
<td>1.78</td>
<td>0.74</td>
</tr>
<tr>
<td>The PI</td>
<td>1.99</td>
<td>1.26</td>
</tr>
<tr>
<td>Northwestern</td>
<td>2.00</td>
<td>1.04</td>
</tr>
</tbody>
</table>
Top Enrolling Sites: #1

- 58 PD, 14 controls and 6 SWEDDDs were enrolled at this site
- And the winner is....

![Certificate of Recognition](image)
Top Enrolling Sites: #2

- 25 PD, 11 controls and 6 SWEDDDs were enrolled at this site
- And the winner is....
Highest Average Number of Controls Consented per Month

• An Average of .6 controls per month were consented at this site

• And the winner is....

U Washington
Push for Controls at the End (Since Jan 2013)

• 5 new controls consented in the last four months
• And the winner is....

CERTIFICATE OF RECOGNITION

This certificate is awarded to

UCSD

In gratitude for your involvement:

Michael J. Fox

Todd Sherer

Todd Sherer, PhD
CEO, Michael J. Fox Foundation for Parkinson's Research
Push for PD at the End (Since Jan 2013)

- 6 new PD subjects consented in the last four months
- And the winner is....

[Certificate of Recognition]

This certificate is awarded to

U Cincinnati

In gratitude for your involvement:

Todd Sherer

Michael J. Fox

Todd Sherer, PhD
CEO, Michael J. Fox Foundation for Parkinson's Research
Retention Progress to Date

- Overall study retention is 97.6%

- Sites with 100% of consented subject retained:
  - OHSU
  - U Washington
  - Baylor
  - The PI
  - Boston U
  - U South Florida
  - Hopkins
  - UC, San Diego
  - U Cincinnati
  - Imperial College
  - U Salerno
  - PD Center of Boca Raton
  - Macquerie U
Ongoing Retention Strategies

- Giveaways
- Subject newsletters (2x per year)
- Retention events
- Subject Travel and Accommodation funding

What other ideas should we be considering?
Site Awards

Drumroll, please.....
100% completion of Study Visits

• This site that has had every subject complete all of their study visits; has done 83 PPMI visits to date

• And the winner is...

CERTIFICATE OF RECOGNITION

This certificate is awarded to

Northwestern

In gratitude for your involvement:

Todd Sherer

Michael J. Fox

Todd Sherer, PhD
CEO, Michael J. Fox Foundation for Parkinson’s Research
100% completion of LP’s

• This site that has had every subject complete all of the LPs at their study visits; has done 72 LPs to date

• And the winner is...

CERTIFICATE OF RECOGNITION

This certificate is awarded to

Emory

In gratitude for your involvement:

Michael J. Fox

Todd Sherer, PhD
CEO, Michael J. Fox Foundation for Parkinson’s Research
The Road Ahead: Retain Retain Retain!

- **Retention**: Maintaining the stamina and loyalty of enrolled subjects
  - How do we keep this up?
  - How can we step this up over time?
  - What do you need at the sites to remain engaged with the study?
Questions?
Genetic PPMI

Ken Marek

PPMI Investigators Meeting
May 7, 2013
New York, NY
Natural history of Parkinson’s disease

Neuron Function

Prodromal

Symptomatic

Diagnosis

Clinical Ratings

P-PPMI

Gen

PPMI

PPMI-Gen
PPMI-LRRK2

• Leverage existing PPMI infrastructure and add sites with existing expertise and experience with LRRK2 patients and families.

• Enroll 200 -250 LRRK + PD and 200-250 LRKK2 + unaffected family members with and intensive longitudinal clinical assessment protocol.

• Follow PD and unaffected family members for for four years
  – Establish pre-motor biomarker signature
  – Define phenoconversion

• Maintain PPMI database structure and commitment to rapid access to data
PPMI-Synuclein

• Leverage existing PPMI infrastructure and add sites with existing expertise and experience with LRRK2 patients and families.

• Enroll 50 synuclein + PD and 50 synuclein + unaffected family members (duplication, triplication, point mutation) in intensive longitudinal clinical assessment protocol.

• Follow PD and unaffected family members for four years
  – Establish pre-motor biomarker signature
  – Define phenoconversion

• Maintain PPMI database structure and commitment to rapid access to data
PPMI - Cohorts

1300-1400 Subjects Enrolled

- 400 Parkinson disease (PD)
- 200 Healthy controls (HC)
- 60 subjects without evidence of dopaminergic deficit
- 100 Prodromal
- 200-250 Parkinson disease with LRRK2 mutation
- 200-250 unaffected family members of LRRK2 Parkinson disease patients and/or unaffected LRRK2 mutation carriers
- 50 Parkinson disease (PD) with a-synuclein mutation
- 50 unaffected family members of a-synuclein Parkinson disease patients and/or unaffected a-synuclein mutation carriers
- 600 – Registry subjects – LRRK2 PD/LRRK2 non-PD, LRRK2 family members non carriers/Synuclein PD/Synuclein non-PD, Synuclein family members non carriers
Two Stage Enrollment – LRRK2

• Consent 1 – Genetic testing/counseling (MGH genetics lab)
  – For PD – LRRK2/Syn +/-eligible -
  – For non-PD - Results provided but not required - informed that PPMI intensive biased to mutation carrier and registry biased to non-mutation carrier

GENETIC COORDINATING CORE – Allocates subjects

• Consent 2 – PPMI - PPMI intensive vs registry
  – All LRRK2/Syn pos PD eligible - PPMI intensive

  – Unaffected family members
    • LRRK2/Syn pos- PPMI intensive >>> registry
    • LRRK2/Syn neg - PPMI intensive <<< registry
Eligibility -

Parkinson disease (PD) with LRRK2/Syn mutation:

• Inclusion:

• Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia.

• A diagnosis of Parkinson disease for 10 years or less at Screening.

• Hoehn and Yahr stage < 4 at Baseline.

• Confirmation from imaging core that screening dopamine transporter SPECT scan is consistent with dopamine transporter deficit (or for sites where DaTSCAN™ is not available, that VMAT-2 PET scan is consistent with VMAT deficit).

• Male or female age 18 years or older at time of PD diagnosis.

• Confirmation of genetic mutation in LRRK2
Eligibility -

Parkinson disease (PD) with LRRK2/Syn mutation:

Not Exclusion

Atypical PD syndromes degenerative diseases (e.g., MSA progressive supranuclear palsy).

Currently taking levodopa, dopamine agonists, MAO-B inhibitors (e.g., selegiline, rasagiline), amantadine or other PD medication.

Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of baseline. Has taken levodopa or dopamine agonists prior to Baseline for more than a total of 60 days.

Use of investigational drugs or devices within 60 days prior to Baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
Eligibility -

Unaffected family members of LRRK2/SYN Parkinson disease patients and/or unaffected LRRK2/Syn mutation carriers

• Inclusion:
• Male or female age 50 years or older at Screening.
• First degree relative of PD patients with LRRK2/Syn and/or unaffected documented LRRK2/Syn mutation carriers
• Willingness to undergo genetic testing for LRRK2/Syn
Eligibility -

Unaffected family members of LRRK2/Syn Parkinson disease patients and/or unaffected LRRK2/Syn mutation carriers

Not Exclusion:
MoCA score of 26 or less (i.e., eligible if score is 27 to 30).
Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
Eligibility - Registry

LRRK2/Syn PD/Unaffected family members of LRRK2/Syn Parkinson disease patients and/or unaffected LRRK2/Syn mutation carriers

Inclusion:

- Male or female age 18 years or older at Screening.
- First degree relative of PD patients with LRRK2 and/or unaffected documented LRRK2/Syn mutation carriers or LRRK2 PD subject (note PD based on clinical dx - Willingness to undergo genetic testing)
Assessments PD and non-PD - Intensive

Screening to assess PD/eligibility
All PD assessments
Fam History assessment
Prodromal – Phenoconversion
Prodromal - additional -
  Motor
  Synuclein
Timing of assessments
  q 6 months
Assessments PD and non-PD - Registry

Screening to assess PD/eligibility
Baseline – UPDRS, MOCA, blood –DNA
  Fam hx

Timing of assessments
  q 24 months

Assessment – Phenoconversion, ?? Other reportable events
Genetic Cohorts

All PPMI sites are recruiting sites

New sites – will be added to PPMI (also can participate in Prodromal

F2F meeting Fall 2013?
Special issues

Tracking enrollment categories

Tracking whether subjects informed regarding genetic status

Phenoconversion

Family tracking

Conversion from registry to intensive

Web site - confidentiality
Genetic Timeline

Draft Amendment 6 – May 10, 2013

Submission amendment 6 to central IRB – May 24, 2013

Site visits and Approvals – May/June 2013

Site Contract May/June 2013

Site submission to IRB/Ethical committee – June-August 2013

Subject enrollment August 2013
PPMI
LRRK2/SNCA Initiative

Tatiana Foroud, Ph.D.
Indiana University
School of Medicine
What makes a family study different from a typical study?

• Family study involves the engagement and recruitment of multiple individuals

• Knowledge of one individual’s genetic status has impact on other family members
  – Some family members don’t want to know their status

• Geographic distribution
Challenge: Tracking Families

• When tracking only an individual, subject ID will suffice
• When tracking a family (multiple members) need a way to keep them together in a group with a unique identifier
  – Family ID is the most common way to do this
• Works within a site and across sites
Challenge:
Family Structure

• We can keep families together using a family ID, also need to track how they are related to each other

• Why?
  – Important in many analyses when assumptions of independence are critical
  – Can condition on relationships (when known)
  – Allows genetic transmission to be explored
Family Structure

- Will collect family information using Family History CRF
- Sites will need to augment this to assist in recruiting other family members
- Will confirm relationships among individuals in PPMI using DNA marker information
  - Can be used to verify paternity, half vs. full siblings, etc.
Challenge: Distributing Genetic Information

• Genetic information often receives a higher scrutiny than other types of data
  – Concerns primarily about identification of the subject
• Many different models are used to distribute genetic data
  – Vary in the way to access the information
  – Vary in the type of information made available
Challenge: Distributing Genetic Information

• In PPMI, we are exploring models like those used in ADNI (AD), DIAN (AD), PREDICT (HD)
  – DIAN and PREDICT focus on Mendelian diseases with high penetrance
  – ADNI has shared deep genetic data, but not in a Mendelian disease context

• dbGaP (database of Genotypes and Phenotypes)
  – NIH solution to the sharing of genetic data
Genetic Coordinating Center*

- Located at Indiana University

- Help develop family recruitment strategies
  - Work with sites for ethics approval
  - Provide recruitment materials
  - Train coordinators to recruit families
  - Advise sites on family expansion
Genetic Coordinating Center

• Coordinate *LRRK2/SNCA* testing
  – Help identify who to test within a family
  – Identify appropriate *LRRK2/SNCA* testing sites
  – Review *LRRK2/SNCA* genetic results
  – Assign subjects to Intensive or Registry arm
Partnering to Succeed

PPMI Infrastructure

Genetic Coordinating Center

PPMI Site

PPMI Site

PPMI Site
THE ASHKENAZI JEWS
LRRK2 – G2019S MUTATION CONSORTIUM
RESULTS OF THE CROSS SECTIONAL STUDY

PIs: Susan Bressman, Karen Marder, Nir Giladi, Avi Orr-Urtreger
Frequency of mutations in the GBA and LRRK2 genes in the general AJ population

Schulte & Gasser, 2011

### Table 1 Summary of genes and loci underlying Parkinson’s disease

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Chromosomal location</th>
<th>Inheritance</th>
<th>Type of parkinsonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK1/PARK4</td>
<td>SNCA</td>
<td>4q21</td>
<td>AD + risk</td>
<td>LOPD/EOPD, dementia</td>
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<td>6q25-q27</td>
<td>AR</td>
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<td>AR</td>
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<td>PARK15</td>
<td>FBXO7</td>
<td>22q12-q13</td>
<td>AR</td>
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<td>1q32</td>
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<td>GAK</td>
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<tr>
<td>–</td>
<td>BST1</td>
<td>4p15</td>
<td>Risk</td>
<td>LOPD</td>
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</table>

2.1% in AJ

6.4% in AJ

**Abbreviations:** AD, autosomal dominant; AR, autosomal recessive; EOPD, early-onset Parkinson’s disease; LOPD, late-onset Parkinson’s disease.
The frequency of mutation associated PD

World wide

Among Ashkenazi Jews

14%

19%
“Cross-sectional”: 4 year study

- Characterize the G2019S phenotype in diagnosed PD subjects, comparing LRRK2+ to other (AJ) PD
  - Compare motor, non-motor (cognitive, autonomic, mood, olfactory, sleep) other medical (cancer) and imaging (USG, DAT)
  - Identify early, pre-diagnosis markers of LRRK2 G2019S expression /pathology
  - Compare mutation carriers without PD to non-carrier relatives and controls examining posited early alterations including DAT
- Determine G2019S penetrance of diagnosed PD by interview screens and also direct exams and genotyping
- Assess level of knowledge and attitudes toward genetic testing
- Use GWAS to identify variants associated with PD or interacting with LRRK2
- Examine LRRK2 expression by transcription profiling and pathway analyses
  - compare AJ PD with and without LRRK2 as well as LRRK2 first-degree relatives and unaffected controls
The study includes three stages:

1) Screening evaluation of PD probands
2) In-depth evaluation of carriers, and subset of non-carriers and all willing first-degree family members
3) Longitudinal follow up on those recruited to the in-depth evaluation

The analyses presented here include the screening evaluation.
2000+ AJ PD

Of these 225 are LRRK2 +

150 LRRK2+ 150 LRRK2-
In-depth exams

Expand families of LRRK2+ 2-2.5 per family

100 spouse controls
In-depth exams
300 1st degree relatives
1/2 are carriers (not diagnosed with PD)
AJ consortium Total Probands Enrolled

N=950

TASMC
51% (n=476)

BI
24% (n=233)

CU
25% (n=241)
AJ consortium asymptomatic healthy relatives

N=260

- TASMC: 59% (n=169)
- BI: 22% (n=64)
- CU: 19% (n=55)
# Methods

<table>
<thead>
<tr>
<th>Domain</th>
<th>Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>DNA sample from blood</td>
</tr>
<tr>
<td>Medical history</td>
<td>life habits and environmental questionnaires</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>UPDRS, H&amp;Y, S&amp;E</td>
</tr>
<tr>
<td>Autonomic function and sleep</td>
<td>SCOPA-AUT, HRV, RBDQ, Epsworth</td>
</tr>
<tr>
<td>Olfaction</td>
<td>UPSIT</td>
</tr>
<tr>
<td>Mood and affect</td>
<td>BDI, GDS, Spielberger trait and state anxiety</td>
</tr>
<tr>
<td>Neuropsychological evaluation</td>
<td>MoCA, VF, Digit span, Stroop test, TMT, computerized cognitive assessment</td>
</tr>
<tr>
<td>Motor features</td>
<td>BBS, TUG, gait, arm swing</td>
</tr>
<tr>
<td>Brain activation</td>
<td>fMRI- cognitive, motor and emotional tasks</td>
</tr>
<tr>
<td>Dopaminergic neuronal integrity</td>
<td>DaT scan and FDG PET</td>
</tr>
</tbody>
</table>
Lower cognitive performance in healthy G2019S LRRK2 mutation carriers

- Stroop: Noncarriers vs. Carriers, p=0.007
- Accuracy rate: Noncarriers vs. Carriers, p=0.42
- Response time (msec): Noncarriers vs. Carriers, p=0.05
Research report

Neural correlates of executive functions in healthy G2019S LRRK2 mutation carriers

Avner Thaler a,b,*, Anat Mirelman a,c, Rick C. Helmich d, Bart F.L. van Nuenen d, Keren Rosenberg-Katz b,e, Tanya Gurevich a,b, Avi Orr-Urtreger b,f, Karen Marder g, Susan Bressman h, Bastiaan R. Bloem d, Nir Giladi a,b and Talma Hendler b,e

the LRRK2 Ashkenazi Jewish consortium

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Activation map, stroop task
Asymptomatic +/- G2019S mutation carriers

The brain areas with different activation between mutation carriers and non-carriers during the response to the stroop test

Thaler, et al, Cortex 2013

(N=60)
Cerebral pathological and compensatory mechanisms in the premotor phase of leucine-rich repeat kinase 2 parkinsonism

Bart F. L. van Nuenen,1,2 Rick C. Helmich,1,2 Murielle Ferraye,2 Avner Thaler,3 Talma Hendler,3 Avi Orr-Urtreger,4 Anat Mirelman,3 Susan Bressman,5 Karen S. Marder,6 Nir Giladi,3 Bart P. C. van de Warrenburg,1 Bastiaan R. Bloem1 and Ivan Toni2 on behalf of the LRRK2 Ashkenazi Jewish Consortium1*

interval: 3 – 4 s.

Foot response (left / right big toe)
G2019S mutation carriers use the brain differently to solve motor imagery problems

Bart F.L. van Nuenen et al, Brain, 2012
Gait Alterations in Healthy Carriers of the LRRK2 G2019S Mutation

Future direction

5 years longitudinal study with 150 1st degree subjects is on its way
# The Ashkenazi Jewish Consortium

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- Anat Mirelman
- Tanya Gurevich
- Jeff Hausdorff
- Avner Thaler
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- Kira Yasinovsky
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- Aner Weiss
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- Stanley Fahn
- Oren Levy
- Ernest Roos

## Mount Sinai School of Medicine, NY, NY

- Laurie Ozelius

## Yale, New Haven, CT

- Yale
- Ken Marrek
Mutation in the alpha-synuclein gene identified in families with Parkinson's disease.


Laboratory of Genetic Disease Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892-1430, USA.

Abstract
Parkinson's disease (PD) is a common neurodegenerative disorder with a lifetime incidence of approximately 2 percent. A pattern of familial aggregation has been documented for the disorder, and it was recently reported that a PD susceptibility gene in a large Italian kindred is located on the long arm of human chromosome 4. A mutation was identified in the alpha-synuclein gene, which codes for a presynaptic protein thought to be involved in neuronal plasticity, in the Italian kindred and in three unrelated families of Greek origin with autosomal dominant inheritance for the PD phenotype. This finding of a specific molecular alteration associated with PD will facilitate the detailed understanding of the pathophysiology of the disorder.
Symptomatic carriers (A53T)

<table>
<thead>
<tr>
<th>N</th>
<th>M/F</th>
<th>Age of onset Mean± SD (Range)</th>
<th>Disease duration Mean± SD (Range)</th>
<th>H&amp;Y Mean± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>10/10</td>
<td>44.8±10.3 (30-65 years)</td>
<td>7.1± 4.3 (0.5-18 years)</td>
<td>2.4 ±1.2 (1-5)</td>
</tr>
</tbody>
</table>
Symptomatic carriers (A53T) disease duration < 7 years

<table>
<thead>
<tr>
<th>N</th>
<th>M/F</th>
<th>Age of onset Mean± SD (Range)</th>
<th>Disease duration Mean± SD (Range)</th>
<th>H&amp;Y (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>6/7</td>
<td>46.3±11.8 (30-65 years)</td>
<td>4.4± 1.7 (0.5-7 years)</td>
<td>1-3</td>
</tr>
</tbody>
</table>
• Phenotypic variability between families and members of the same family
## Asymptomatic carriers

<table>
<thead>
<tr>
<th>N</th>
<th>M/F</th>
<th>Age (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1/8</td>
<td>51.4 ± 18 (35-90 years)</td>
</tr>
</tbody>
</table>
Areas were most of the current families are located
PPMI Data Analyses

Christopher S. Coffey
The University of Iowa

Ken Marek
The Institute for Neurodegenerative Disorders

PPMI Investigators Meeting
May 8, 2012
New York, NY
Goals-

- High quality, rapid publication
- Consistent with the broad PPMI collaboration
  - SC, Cores, Sites, Working Groups
- Encourage non-PPMI community
Publication Policy

- Key Primary
- Primary
- Others
- Abstracts for meetings
- Role of DPC
Key Primary Publications - *Key Primary Publications* are defined as those reports, analyses and publications identified by the PPMI Steering Committee as fulfilling the primary objectives of the study. Examples of these reports include publications detailing the baseline or yearly data-cuts.

The SC will be primarily responsible for completion of all Key Primary Publications. Key Primary publications will be authored by the Steering Committee, Investigators, Study Cores and Working Groups reflecting the contribution of those authors.
For KEY primary publications

“And The Parkinson’s Progression Markers Initiative*” will be written on the author line of the manuscript with an asterisk referring to the list of names of individuals identified on the PPMI author list. The author list must be included as an appendix to ensure that all authors may be cited. The complete list of PPMI Study Investigators can be found at www.ppmi-info.org/Authorslist

Sent to both the PPMI Steering Committee and the PPMI Data & Publications Committee (DPC) for review prior to journal submission.
Primary Publications - Primary publications are defined as reports, analyses and publications that are initiated by PPMI study members that utilize PPMI data, but which do not address the primary objectives of the study. Examples of these studies include a focus on specific biomarkers of disease progression, study infrastructure or recruitment.

Publications developed by study investigators, cores, working groups and authorship will reflect the contribution of those authors. In addition to the authors, “And The Parkinson’s Progression Markers Initiative*” will be written on the author line of the manuscript with an asterisk referring to the list of names of individuals identified on the PPMI author list. The author list must be included as an appendix to ensure that all authors may be cited. The list of PPMI Study Investigators can be found at www.ppmi-info.org/Authorslist
Primary Publications - Sent to both the PPMI Steering Committee and the PPMI Data & Publications Committee (DPC) for review prior to journal submission
Other Publications - It is expected that investigators outside of the study will conduct research and seek to publish analyses using PPMI data and specimens. These individuals are encouraged to publish novel scientific findings that result from their research using PPMI. Authorship of such a publication will not include PPMI in the author line,
PPMI personnel and PPMI funding support will be acknowledged by including the following within the manuscript:

"Data used in the preparation of this article were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.”

“PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson’s Research and funding partners, including [list the full names of all of the PPMI funding partners found at www.ppmi-info.org/fundingpartners ].”

Make link to webpage
All other publications must be sent to the PPMI DPC for administrative review prior to journal submission. To submit to the DPC, please upload the publication for review via the PPMI website.
Authors should develop data analysis plan in collaboration with Stats

Authors should develop time-line for drafts and completion of report

Goal is to identify authors for primary publications.
Source and Cut of Data

- Source should be LONI data so need to submit all data
- Timing of Data cuts - Data cuts to be published by SC
  - Baseline, 6 months, 1 year, then yearly
- Definition of full data set
Publication and Analysis plans
Baseline data

- Primary baseline
- Subsets
- Cognitive – domains, compare UPDRS
- Imaging - DAT, AV133, DTI, Resting state
- Biologics - CSF analytes, Urate, Genetics
- Process - Recruitment, Imaging, CSF
- Ancillary - Tap
- SWEDD
## Baseline data Papers

<table>
<thead>
<tr>
<th>Paper #</th>
<th>Description</th>
<th>Contact</th>
<th>Status</th>
<th>Date of Most Recent Change to List</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Overall Baseline Paper</td>
<td>Ken Marek</td>
<td>Preliminary Tables Reviewed</td>
<td>24 Apr 2013</td>
</tr>
<tr>
<td>2</td>
<td>Cognitive Paper</td>
<td>Dan Weintraub</td>
<td>Building Tables with Data</td>
<td>18 Apr 2013</td>
</tr>
<tr>
<td>3</td>
<td>DATSCAN Paper</td>
<td>John Seibyl / Ken Marek</td>
<td>Tables Sent to John and Ken / Feedback Pending</td>
<td>18 Apr 2013</td>
</tr>
<tr>
<td>4</td>
<td>DTI Paper</td>
<td>Norbert Schuff</td>
<td>-</td>
<td>24 Apr 2013</td>
</tr>
<tr>
<td>5</td>
<td>Biologics Paper</td>
<td>Les Shaw / John Trojanowski</td>
<td>-</td>
<td>18 Apr 2013</td>
</tr>
<tr>
<td>6</td>
<td>Urate Paper</td>
<td>Constantinescu Radu</td>
<td>Tables for an abstract sent to Radu / Feedback Pending</td>
<td>18 Apr 2013</td>
</tr>
</tbody>
</table>
Planned Analysis #1: Comparison of Baseline Characteristics Among Health Subjects and PD Subjects.

- Continuous variables assessed using t-test
- Dichotomous variables assessed using chi-square test
- Appropriate assumptions will be assessed for each comparison and any necessary adjustments (i.e., transformations) will be made prior to analysis
12 month data

- Primary baseline
- Subsets
- Cognitive – domains, compare UPDRS
- Imaging - DAT, AV133, DTI, Resting state
- Biologics - CSF analytes
- Process – Retention, CSF
- Ancillary - Tap
- SWEDD
Baseline

Tabulate and compare for all subjects Demographics by diagnostic category (PD, HC, SWEDD; Compare PD vs HC; PD vs SWEDD)

- Age
- Gender
- Education
- Ethnicity
- Race
- Family history of PD

(From tables 3 and 4 – monthly)
Baseline

Tabulate and compare for all subjects Summary clinical scores by diagnostic category (PD, HC, SWEDD; Compare PD vs HC; PD vs SWEDD)

- UPDRS Total and subscore
- Hoehn and Yahr
- Schwab and England
- Dur of Dis
- MOCA total
- GDS Total
- SCOPA AUT total
- State Anxiety
- QUIP
- UPSIT
- Epworth

(From tables 4 and 5)
Baseline

Tabulate and compare for all subjects DAT imaging SBR by diagnostic category (PD, HC, SWEDD; Compare PD vs HC; PD vs SWEDD)

- Mean striatal
- Mean putamen
- Mean caudate
- Ipsilateral Caudate
- Contralateral Caudate
- Ipsilateral Putamen
- Contralateral Putamen
Baseline

Tabulate and compare for all subjects CSF synuclein, amyloid, Tau by diagnostic category (PD, HC, SWEDD; Compare PD vs HC; PD vs SWEDD)

- $A\beta_{1-42}$ (pg/mL)
- t-tau (pg/mL)
- $p$-tau$_{181}$ (pg/mL)
- t-tau/$A\beta_{1-42}$ ratio
- $p$-tau$_{181}$/A$\beta_{1-42}$ ratio
- $p$-tau$_{181}$/t-tau ratio
- A-syn (pg/mL)

Should we include hemoglobin data?
PLANNED ANALYSES

Baseline

UPDRS as an anchor: relationship between baseline UPDRS with non-motor, imaging, biologic at baseline (PD, HC, SWEDD; Focus on PD) – See Ravina et al. *Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson’s Disease*

Adjusted for age, gender, duration of disease

To be compared

- MOCA total
- GDS Total
- SCOPA AUT total
- State Anxiety
- QUIP
- UPSIT
- Epworth
- DAT
- Aβ_{1-42} (pg/mL)
- t-tau (pg/mL)
- p-tau_{181} (pg/mL)
- t-tau/Aβ_{1-42} ratio
- p-tau_{181}/Aβ_{1-42} ratio
- p-tau_{181}/t-tau ratio
- A-syn (pg/mL)
Baseline

DAT scan as anchor: relationship between baseline DAT with motor, non-motor biologics at baseline (PD, HC, SWEDD; Focus on PD) See Ravina et al. *Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson’s Disease*

Adjusted for age, gender, duration of disease
To be compared

- UPDRS
- MOCA total
- GDS Total
- SCOPA AUT total
- State Anxiety
- QUIP
- UPSIT
- Epworth
- $A\beta_{1-42}$ (pg/mL)
- t-tau (pg/mL)
- $p$-tau$_{181}$ (pg/mL)
- t-tau/$A\beta_{1-42}$ ratio
- $p$-tau$_{181}$/A$\beta_{1-42}$ ratio
- $p$-tau$_{181}$/t-tau ratio
- A-syn (pg/mL)
- Urate
Planned Analysis #2: Comparison of Short-Term Change in Progression Endpoints.

- Examine short-term change during first six months for each progression endpoint using mixed model (continuous endpoints) or logistic regression (dichotomous endpoints).
- Initial model will include all baseline characteristics, indicator for whether healthy control of PD patient, and all possible two-way interactions.
- Will utilize backwards selection to build a model for each progression endpoint.
Planned Analysis #3: Examination of Whether Short-Term Change in Progression Endpoints is Predictive of Change in Long-Term Endpoints

- Consider only progression endpoints that show differences between healthy subjects and PD patients
- Primary focus on long-term change in UPDRS score – additional long-term endpoints may be considered as well
- Ten-fold cross-validation procedure will be used to test predictive validity of each model
- If successful, final model will provide subset of short-term progression endpoints predictive of change in long-term endpoints – suggest biomarkers for future studies of interventions in PD patient populations
Planned Analysis #4: Examination of PD Subsets

- Each of first three sets of analyses will be repeated comparing subsets of PD patients
- If successful, final model will determine whether some short-term progression endpoints are more predictive of long-term endpoints for some subsets of PD patients and less predictive for other subsets
Planned Analysis #5: Proportion of SWEDD subjects that have a change in diagnosis over 24 month evaluation period

- Percentage and 95% confidence interval will be reported
- Other possible diagnoses will be further divided into 2 categories:
  - Other parkinsonian syndrome with a dopamine transporter deficit
  - Other condition with a dopamine transporter deficit
Planned Analysis #6: Exploratory analysis of SWEDD subjects

- Important changes over time found in planned analyses 1-3 will be assessed in the SWEDD subjects
- Will help to assess whether changes over time in SWEDD subjects are similar or dissimilar to PD subjects
- TD vs PIGD
- Meds vs no Meds
- Comparison cognitive with imaging/CSF
- Sleep assessments
- Enrollment/recruitment
- Comparison of DAT and DTI
- UPDRS vs cognitive measures