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>
</tr>
<tr>
<td>PARK2</td>
<td>Parkin</td>
<td>6q25-q27</td>
<td>AR</td>
<td>EOPD</td>
</tr>
<tr>
<td>PARK3</td>
<td>Unknown</td>
<td>2p13</td>
<td>AD</td>
<td>LOPD</td>
</tr>
<tr>
<td>PARK5</td>
<td>UCHL1</td>
<td>4p14</td>
<td>AD</td>
<td>LOPD</td>
</tr>
<tr>
<td>PARK6</td>
<td>PINK1</td>
<td>1p36</td>
<td>AR</td>
<td>EOPD</td>
</tr>
<tr>
<td>PARK7</td>
<td>DJ1</td>
<td>1p36</td>
<td>AR</td>
<td>EOPD</td>
</tr>
<tr>
<td>PARK8</td>
<td>LRRK2</td>
<td>12q12</td>
<td>AD + risk</td>
<td>LOPD</td>
</tr>
<tr>
<td>PARK9</td>
<td>ATP13 A2</td>
<td>1p36</td>
<td>AR</td>
<td>EOPD, Kufor-Rakeb syndrome</td>
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<tr>
<td>PARK10</td>
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<td>1p32</td>
<td>Unknown</td>
<td>LOPD</td>
</tr>
<tr>
<td>PARK11</td>
<td>GIGYF2</td>
<td>2q37</td>
<td>AD</td>
<td>LOPD</td>
</tr>
<tr>
<td>PARK12</td>
<td>Unknown</td>
<td>Xq21-25</td>
<td>X-linked</td>
<td>LOPD</td>
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<tr>
<td>PARK13</td>
<td>HTRA2</td>
<td>2p12</td>
<td>AD</td>
<td>LOPD</td>
</tr>
<tr>
<td>PARK14</td>
<td>PLA2G6</td>
<td>22q13</td>
<td>AR</td>
<td>EOPD, dystonia-parkinsonism</td>
</tr>
<tr>
<td>PARK15</td>
<td>FBXO7</td>
<td>22q12-q13</td>
<td>AR</td>
<td>EOPD, pallido-pyramidal syndrome</td>
</tr>
<tr>
<td>PARK16</td>
<td>Unknown</td>
<td>1q32</td>
<td>Risk</td>
<td>LOPD</td>
</tr>
<tr>
<td>PARK17</td>
<td>GAK</td>
<td>4p16</td>
<td>Risk</td>
<td>LOPD</td>
</tr>
<tr>
<td>PARK18</td>
<td>HLA</td>
<td>6p21</td>
<td>Risk</td>
<td>LOPD</td>
</tr>
<tr>
<td>–</td>
<td>EIF4G1</td>
<td>3q27</td>
<td>AD</td>
<td>LOPD</td>
</tr>
<tr>
<td>–</td>
<td>GBA</td>
<td>1q21</td>
<td>Risk</td>
<td>LOPD</td>
</tr>
<tr>
<td>–</td>
<td>MAPT</td>
<td>17q21</td>
<td>Risk</td>
<td>LOPD</td>
</tr>
<tr>
<td>–</td>
<td>BST1</td>
<td>4p15</td>
<td>Risk</td>
<td>LOPD</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EOPD, early-onset Parkinson’s disease; LOPD, late-onset Parkinson’s disease.

2.1% in AJ

6.4% in AJ
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)

BI and CU contribute to the total probands enrolled, with TASMC accounting for the majority.
AJ consortium asymptomatic healthy relatives

N=260

- TASMC 59% (n=169)
- BI 22% (n=64)
- CU 19% (n=55)
<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: 100 ± 10
  - Carriers: 100 ± 10
  - p = 0.007

- **Accuracy rate**:
  - Noncarriers: 100 ± 10
  - Carriers: 100 ± 10
  - p = 0.42

- **Response time (msec)**
  - Noncarriers: 500 ± 50
  - Carriers: 550 ± 50
  - 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

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h Beth Israel Medical Center, New York, NY, USA
Activation map, stroop task
Asymptomatic +/- G2019S mutation carriers

(N=60)

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

Thaler, et al, Cortex 2013
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


- Usual walk
- Dual task walk
- Fast walk

Stride time variability (CV %)

Non-carriers vs. carriers:
- Usual walk: p=0.06
- Dual task walk: p=0.02
- Fast walk: p=0.03

Non carrier – Fast walk
Carrier – Fast walk
Future direction

5 years longitudinal study with 150 1st degree subjects is on its way
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Blair Ford
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Ernest Roos