Genes and Environmental Factors: How do they Act and Interact in Parkinson’s Disease

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Neurology, SOM
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Parkinson’s Disease (PD)

Patients – Clinical Picture
Motor symptoms  Tremor, Rigidity, Akinesia, Postural reflex impairment

**Plus:** Non-motor symptoms: sleep disorders, peripheral nervous system autonomic dysfunction, depression, dementia, etc.

Patients – Pathology
Loss of dopaminergic cells in the substantia nigra of the brain
Lewy-body disease of neurons

Populations – Epidemiology:
- PD affects 5-10 adults per 1,000 over age of 60 in the US
- 2nd most common neurodegenerative disease after Alzheimer
From Nature vs. Nurture to Nature and Nurture...

**Geneticists**
- Discover **novel genes** and disease pathways
- Discover why some gene carriers do and others do not develop disease (high/low penetrance subgroups)

**Clinicians**
- Build better **prognostic models** and inform **treatment** (e.g. predictors of PD or side effects from treatment such as dyskinesia)

**Population / Environmental Scientists**
- Identify those more or less sensitive to certain **exposures** causing disease and eliminate them to **prevent disease or progression**
Genes and Parkinson's

Progress in understanding the role of genetics in PD is recent (~20 years)

Mutation in the alpha-synuclein gene identified in families with Parkinson's disease.
Polymeropoulos et al. Science 1997

- Mutations in SNCA, LRRK2, VPS35, Parkin, PINK1, and DJ-1 produce rare, monogenic forms of the disease
- Common mutations in LRRK2 and GBA are risk factors for PD in special populations (>20 common variants)
- However, why or how these genes increase risk is unknown
- No treatment methodologies have been developed for these patients
- PD mutations and risk variants explain only a small percentage of disease -- 5-10%.
Environment and Parkinson’s Disease: Self-Reported Exposures?

?? Causation or Reporting Bias?

Age, Male

pesticides

solvents, metals

Head trauma

Fam History

Vit D

?? Protection or Reverse Causation?

GOUT

solvents, metals

pesticides

caffeine

smoking

NSAIDs

diet

physical activity

Vit D

Age, Male
Pesticides, why we should care..?

Widely used in agriculture and many are known for their acute neurotoxicity (organophosphates)

Importantly: the 1999-2000 NHANES (US population survey, participants aged 6-59) found urine pesticide metabolites

- Chlorpyrifos (TCPY) > 96% of samples
- Diazinon (IMPY) 29% samples

Both among top 20 toxic air contaminants in CA

Chlorpyrifos banned for **indoor use** by EPA in 2000, but still used outdoors and reconsidered for indoor use

Accidental Discoveries:
MPTP - designer heroin contaminant – caused acute Parkinsonism in young drug users in California in the early 1980s
Enrolled >800 newly diagnosed PD cases & ~1,000 population controls from 2001-2016 in three rural California counties:

- Clinical exam by movement specialists
- Blood samples for genetics etc.
- Interviews collect
  - Medical co-factors
  - Address histories
  - Work and lifestyle factors
- ~500 PD patients are now also being assessed for progression

Parkinson's, Environment and Gene Study (PEG) funded by NIH/ National Institute of Environmental Health Sciences
RO1ES10544, P01ES016732
17,000 addresses of PEG participants were geocoded (located on maps)

Residential and Occupational (GoogleEarth)
California is the ideal place to study pesticide health effects: California Agricultural Pesticide Use Reporting (PUR) records exist since 1974.

Data provided per 1 square mile land section includes (example):

- County: Kern
- Location: 15M28S27E19
- Application date: 2/23/1989
- Commodity: 2503 (Grapes)
- Method: Ground
- Treated: 424 acres
- Product applied: 155 gallons
- Chemical: 00459 (Parathion)
- Percentage: 80%
- Active Ingredient Pounds: 1,241
1970-1990 land use maps were digitized to make them computer readable
California Agricultural Pesticide Use Reporting (PUR) starting 1974 overlaid on land use maps

Pesticide data provided per 1 square mile land section

• County: Kern
• Location: 15M28S27E19

Pesticides mapped as being applied to specific crops (e.g. almonds, citrus etc.)
Identify and calculate amounts of pesticides applied around residences and work places (located on maps) as pounds per acres per year
Downwind Herbicide Deposition
Varying Droplet Size and Wind Speed

- extremely coarse-very coarse spray, 3 mph wind
- medium spray, 3 mph wind
- extremely coarse-very coarse spray, 10 mph wind
- medium spray, 10 mph wind

Effect level for 50% of young plants

Deposition (fraction of application rate)

Downwind distance (ft)
Diazinon detected in 32% of all air samples (468) in 2006 applied 1,565 kg, # applications: 222
Pesticides and Parkinson’s: Translating paraquat & maneb animal models to exposed humans

Toxicity Testing in Animals: The ‘paraquat and maneb’ model

Next Step: Combine Genes and the Environment to understand PD
Study Genetic Variation in Pathways and Enzymes relevant to PD

Cell membrane transporter function differs between individuals (genetically programmed)

Cell Membrane Transporter (ABCB1) – located at the blood brain barrier
**DAT1** gene variants increase PD susceptibility with paraquat/maneb pesticide exposures

**Kelada et al., HMG 2006**

"5' and 3' region variability in the dopamine transporter gene (**SLC6A3**), pesticide exposure and Parkinson's disease risk: a hypothesis-generating study"


**Ritz et al. EHP 2009**

Dopamine Transporter Genetic Variants and Pesticides in Parkinson’s Disease

Beate R. Ritz, Angelika D. Manthripragada, Sadie Costello, Sarah J. Lincoln, Matthew J. Farrer, Myles Cockburn, and Jeff Bronstein
P-glycoprotein transporter (ABCB1) at the blood brain barrier increases PD susceptibility with work place exposure to organochlorine pesticides

Interaction Between ABCB1 and Professional Exposure to Organochlorine Insecticides in Parkinson Disease

Genetic variability in ABCB1, occupational pesticide exposure, and Parkinson's disease

Shilpa Narayan¹, Janet S. Sinsheimer², Kimberly C. Paul³, Zeyan Liew³, Myles Cockburn⁴, Jeff M. Bronstein⁵, Beate Ritz⁶,⁷

Environmental Research 143 (2015) 98–106
Genetic Variants that Determine Metabolism Rates of Enzymes

- Para-oxonase (PON1)
- Aldehyde dehydrogenase (ALDH2)

In DA neurons:

Dopamine $\rightarrow$ DOPAL $\rightarrow$ DOPAC

$\text{MAO}$

$\text{ALDH2}$

Toxic OP-Pesticide metabolite

OP- Pesticide

Non/less toxic metabolite
PON1 and organophosphate metabolism

In humans, there are 10 to 40-fold inherited differences in serum PON1 activity attributed to 2 common polymorphisms in the PON1 gene

PON1 activities towards diazoxon (50 mM) as defined by polymorphisms at position 55 and 192 [O’Leary et al. 2006]

<table>
<thead>
<tr>
<th>PON1</th>
<th>55-LL</th>
<th>55-LM</th>
<th>55-MM</th>
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<tbody>
<tr>
<td>192-QQ</td>
<td>15.6 ± 6.0</td>
<td>11.2 ± 5.0</td>
<td>6.35 ± 1.50</td>
</tr>
<tr>
<td>192-QR</td>
<td>18.1 ± 7.7</td>
<td>14.3 ± 2.8</td>
<td>-</td>
</tr>
<tr>
<td>192-RR</td>
<td>22.0 ± 9.4</td>
<td>16.4 ± 0.0</td>
<td>-</td>
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</table>
PD Risk changes with PON1 enzyme OP-Metabolizing Ability & Ambient OP-Pesticide Exposure
(genetic variants PON1L55M & PON1Q192R)

Functional paraoxonase 1 variants modify the risk of Parkinson's disease due to organophosphate exposure

Pei-Chen Lee	extsuperscript{a,b}, Shannon L. Rhodes	extsuperscript{a}, Janet S. Sinsheimer	extsuperscript{c}, Jeff Bronstein	extsuperscript{d}, Beate Ritz	extsuperscript{a,d,*}
PD Risk by araoxonase (PON1) Metabolizer Status and Household Pesticide Use

- Low metabolizer
- High metabolizer

Odds Ratio

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<thead>
<tr>
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<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td><strong>Never Use/Rare Use</strong></td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>ANY household pesticides</td>
<td>1.09 (0.72-1.65)</td>
</tr>
<tr>
<td>Frequent Use of any OP pesticides</td>
<td>1.03 (0.58-1.82)</td>
</tr>
<tr>
<td><strong>PON1 192RR + 192RQ</strong></td>
<td>2.62 (1.42-4.83)</td>
</tr>
<tr>
<td><strong>PON1 192QQ</strong></td>
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Household organophosphorus pesticide use and Parkinson's disease

Shilpa Narayan, Zeyan Liew, Kimberly Paul, Pei-Chen Lee, Janet S Sinsheimer, Jeff M Bronstein and Beate Ritz
Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease

**PD risk**

ALDH2 inhibiting pesticide exposures
Overview paper: GxE studies assessing Pesticides in PD

Of Pesticides and Men: a California Story of Genes and Environment in Parkinson’s Disease

Beate R. Ritz, Kimberly C. Paul, Jeff M. Bronstein
Environment (ExE) and Disease
Head trauma and paraquat pesticide exposure act together to increase PD risk

Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease

Graph showing the risk of PD in different scenarios:
- No TBI/paraquat
- No TBI/paraquat +
- TBI/paraquat -
- TBI/paraquat +

Pei-Chen Lee, PhD
Yvette Bordelon, MD, PhD
Jeff Bronstein, MD, PhD
Beate Ritz, MD, PhD

Neurology 79 November 13, 2012
Parkinson’s Disease Progression
Genes and the Environment
PEG – PD Progression Follow-up Study: Exams at Enrolment 2001-07
Exams for Progression 2007-12

2001-2007

PEG Cases Eligible for Follow-up
N=373

Not enrolled for follow-up
N=108; 29%

Enrolled for Neuro Exam / Interviews
N=265; 71%

2007-2012

Deceased
N=64 (17%)

Too Ill - withdrew
N=21 (6%)

Unable to Re-contact
N=21 (6%)

Re-Dx No iPD
N=13 (3%)

Enrolled and Followed
N=252 (68%)
α-Synuclein Genetic Variants Predict Faster Motor Symptom Progression in Idiopathic Parkinson Disease

Beate Ritz¹,², Shannon L. Rhodes¹, Yvette Bordelon², Jeff Bronstein²

¹ Department of Epidemiology, University of California Los Angeles, Los Angeles, California, United States of America, ² Department of Neurology, University of California Los Angeles, Los Angeles, California, United States of America

Faster motor progression in synuclein gene risk variant carriers

α-synuclein gene variants increase PD risk and motor progression
Genetic Predictors of Dementia in PD

APOE, MAPT, and COMT and Parkinson’s Disease Susceptibility and Cognitive Symptom Progression

Kimberly C. Paul\textsuperscript{a}, Rebecca Rausch\textsuperscript{b}, Michelle M. Creek\textsuperscript{c}, Janet S. Sinsheimer\textsuperscript{c,d}, Jeff M. Bronstein\textsuperscript{b}, Yvette Bordelon\textsuperscript{b} and Beate Ritz\textsuperscript{a,b,4}

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\textsuperscript{d}Department of Human Genetics, David Geffen School of Medicine, Los Angeles, CA, USA

Results from linear mixed model, using repeated measures, modeling age as random effect and adjusted for age, sex, race, education
Genetic Predictors of Progression in PD
The Role of PD GWAS Genetic Variants

**PEG Study Results:**
Faster progression (motor and cognitive deficits) with increasing number of genetic risk factors for PD previously identified in GWAS studies.
Long-term Ambient Organophosphate Exposure Contributes to Cognitive Decline In PD patients
Vitamin D and Parkinson’s: Genetic Variants in Vit D Receptor *(FokI A)* Predict Cognition Decline in PD patients

Journal of the Neurological Sciences
Available online 11 September 2016
In Press, Accepted Manuscript — Note to users

Vitamin D receptor gene polymorphisms and cognitive decline in Parkinson’s disease

Nicole M. Gatto, MPH, PhD
Kimberly C. Paul, Janet S. Sinsheimer, PhD
Jeff M. Bronstein, MD, PhD
Yvette Bordelon, MD, PhD
Rebecca Rausch, PhD
Beate Ritz, MD, PhD

![Graph showing predicted MMSE scores over follow-up time for different genotypes (GG, AG, AA).]
PEG Progression Study

Caffeine and Progression

Caffeinated Coffee and Tea are Protective

Caffeine and Cognitive Decline

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<thead>
<tr>
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<th>Coffee</th>
<th>Caffeinated Tea</th>
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<tr>
<td>Never Drinker</td>
<td>3.24</td>
<td>2.04</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent/Heavy</td>
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Caffeine and Mortality

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Lifestyle Factors and Progression in PD

- More years of education protect against cognitive decline
- Very long hours of sleep (10+ hours) are associated with faster cognitive decline
- Wine drinking protects against early mortality
Physical Activity Protects against Motor and Cognitive Decline in PD patients:

- Exercising as adult/senior
- History of competitive sports in youth are both protective

![PEG Progression Study - Physical Activity and Symptom Progression](image)

![Physical Activity and H&Y Motor Score Decline and Physical Activity and Cognitive Decline](chart)

- **MET-h/wk**
  - Low/Never: 0.57
  - High: 0.47
- **Competitive Sports**
  - Low/Never: 0.96
  - High: 0.47
Those with consistently high levels of physical activity are at lowest risk of Parkinson’s disease (PD).

But being active in your youth or taking up physical activity later in life also protects. …
A strong scientific story is important to justify and stimulate interventions, treatment trials, and public policies aimed at disease prevention.
Parkinson’s Disease
Research Resources
Funding for a registry pilot project was provided by NIEHS, MJFox and DoD between 2006-2010

However, to date PD registry has remained an unfunded state mandate…
UCLA Movement Disorder Specialists:
Jeff Bronstein & Yvette Bordelon

UCLA Undergraduate and Graduate Students, Staff and Postdocs