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

UCLA FIELDING SCHOOL OF PUBLIC HEALTH

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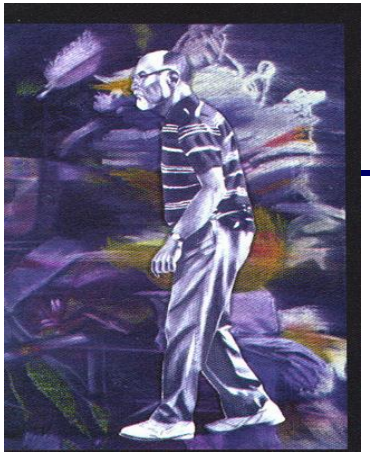
COEH Center for Occupational & Environmental Health

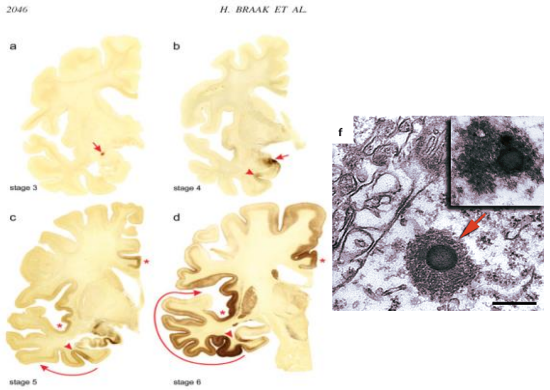


Parkinson‘s Disease (PD)

Patients – Clinical Picture

Motor symptoms Tremor, Rigidity, Akinesia, Postural reflex impairment

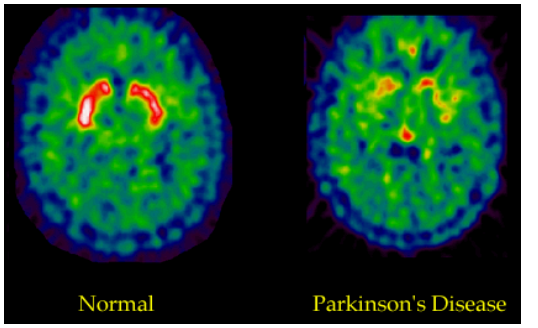
Plus: Non-motor symptoms: sleep disorders, peripheral nervous system autonomic dysfunction, depression, dementia, etc.

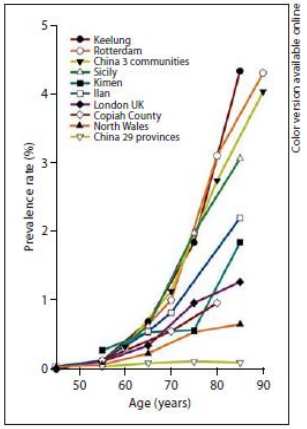


Patients – Pathology

Loss of dopaminerigic cells in the substantia nigra of the brain

Lewy-body disease of neurons

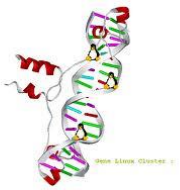




Populations – Epidemiology:

- 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

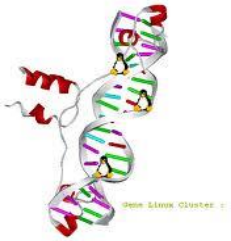
- Discover **novel genes** and disease pathways
- Discover why some gene carriers do and others do not develop disease (**high/low penetrance** subgroups)

Clinicians

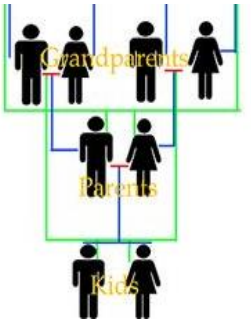
- Build better **prognostic models** and inform **treatment** (e.g. predictors of PD or side effects form treatment such as dyskinesia)

Population / Environmental Scientists

- Identify those more or less sensitive to certain **exposures** causing disease and eliminate them to **prevent disease or progression**



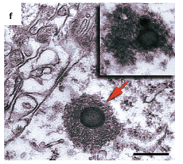
Genes and Parkinson's

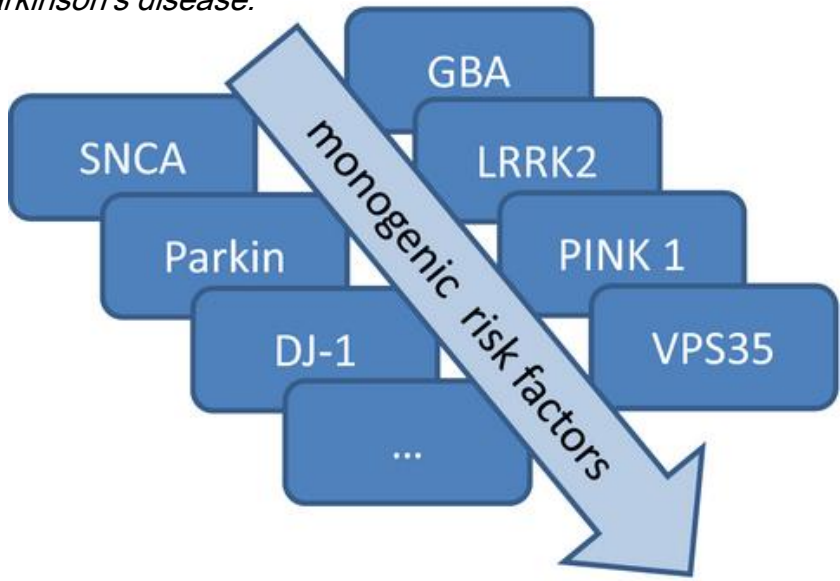


Progress in understanding the role of genetics in PD is recent (~20 years)

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%.



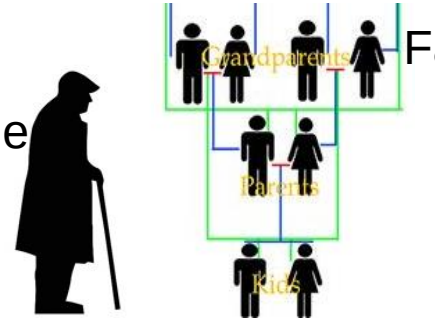


Mendelian inheritance of Parkinson disease

Environment and Parkinson's Disease: Self-Reported Exposures?

?? Causation or Reporting Bias?

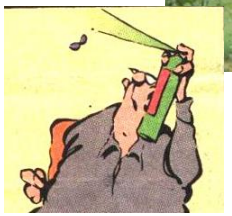
?? Protection or Reverse Causation?



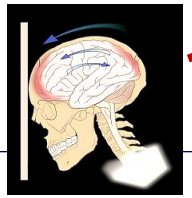
Fam History

Age, Male

pesticides



solvents, metals



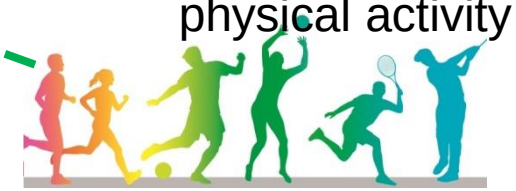
Head trauma

caffeine

smoking

NSAIDs

physical activity



diet

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

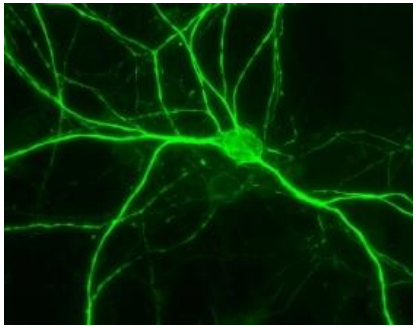
- Chlorpyrifos (TCPY) > **96%** of samples
- Diazinon (IMPY) 29% samples

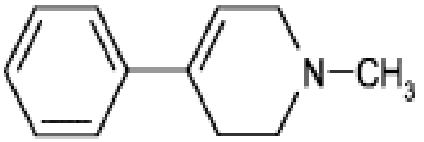
Both among top 20 toxic air contaminants in CA

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

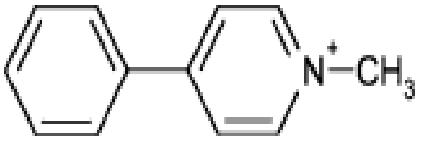
Barr et al. Concentrations of selective metabolites of organophosphorus pesticides in the United States population. Environ Res. 2005 Nov;99(3):314-26.

Finding Bad Players
Toxicity Testing in Animals and Cells



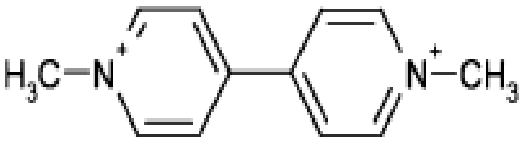


MPTP



MPP+

Accidental Discoveries:
MPTP - designer heroin contaminant – caused acute Parkinsonism in young drug users in California in the early 1980s



Paraquat



Parkinson's, Environment and Gene Study (PEG)

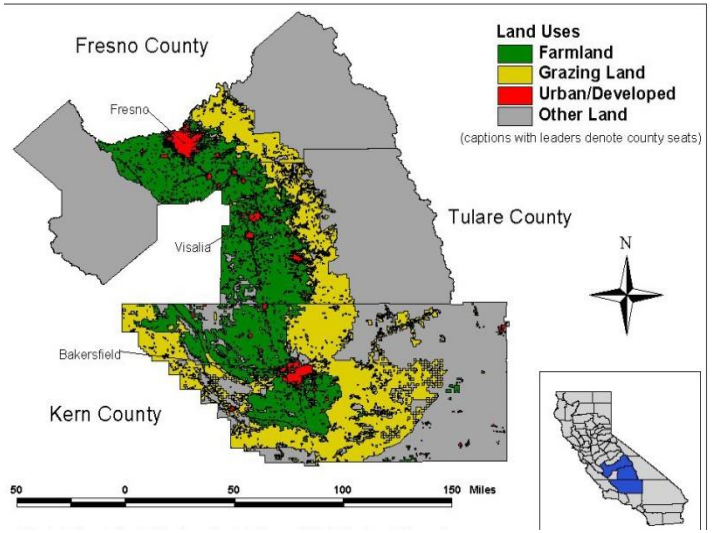
funded by

NIH/ National Institute of Environmental Health Sciences

RO1ES10544, P01ES016732

Enrolled >800 newly diagnosed PD cases & ~1,000 population controls from 2001- 2016 in three rural California counties:

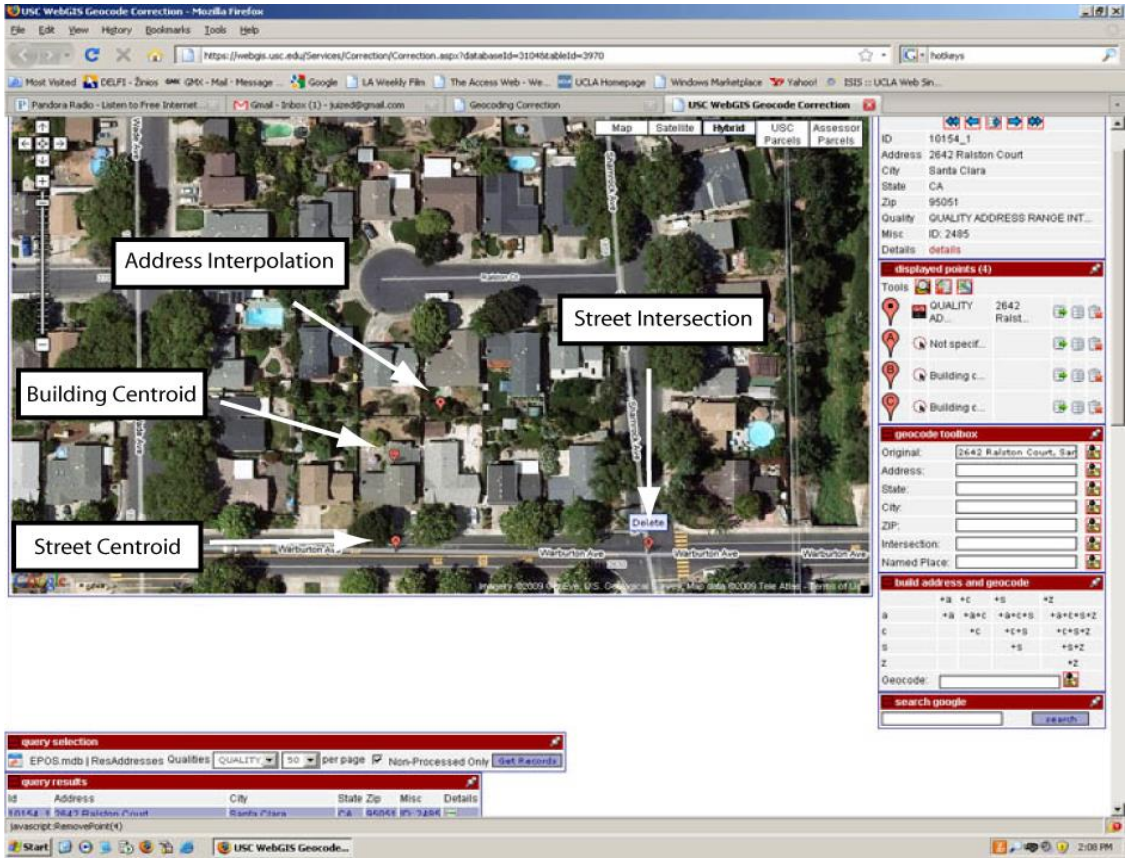
- Clinical exam by movement specialists
- Blood samples for genetics etc.
- Interviews collect
  - Medical co-factors
  - Address histories
  - Work and lifestyle factors



- ~ 500 PD patients are now also being assessed for progression

17,000 addresses of PEG participants were geocoded (located on maps)

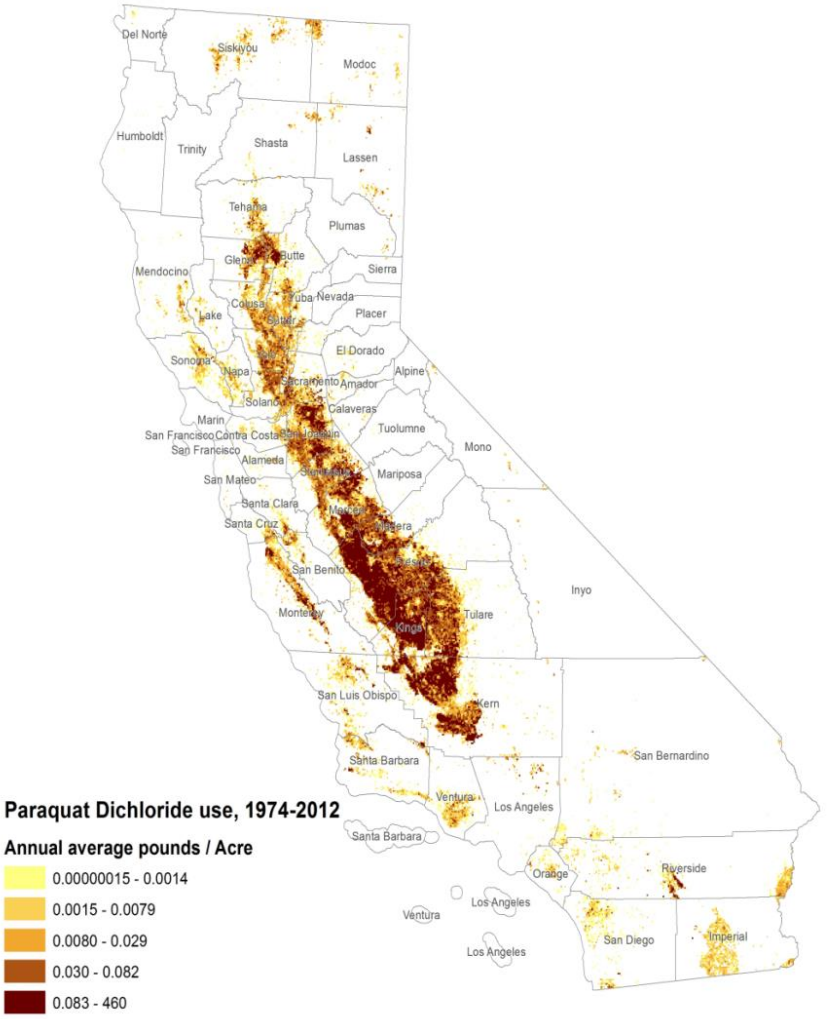
Residential and Occupational (GoogleEarth)



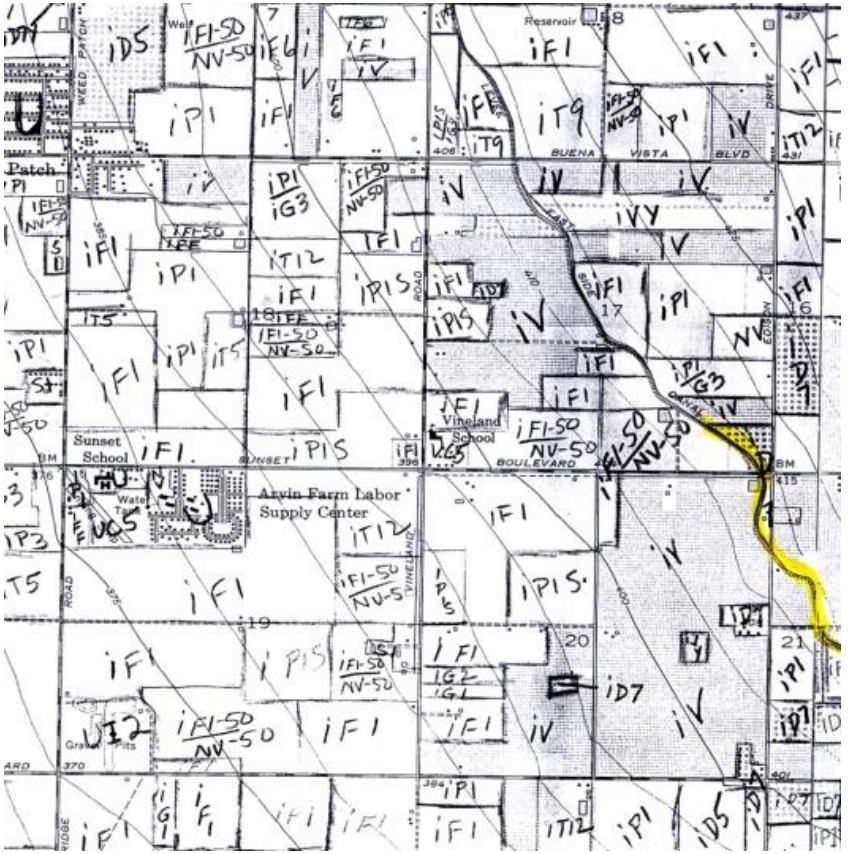
California is the ideal place to study pesticide health effects : California Agricultural Pesticide Use Reporting (PUR) records exist since 1974

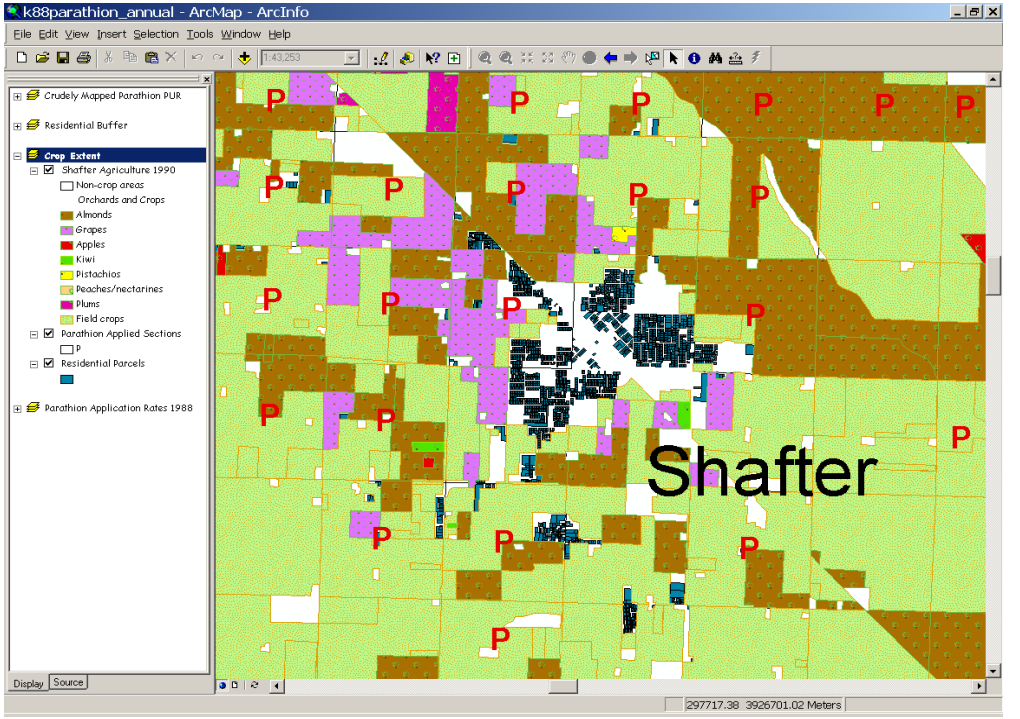
Data provided per 1 square mile land section includes (example):

- 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

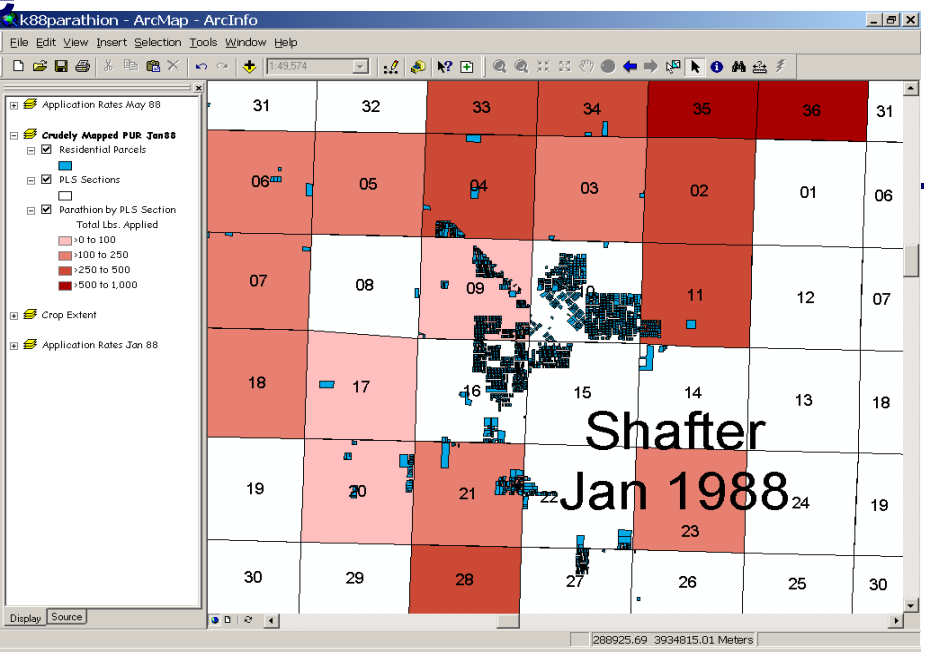




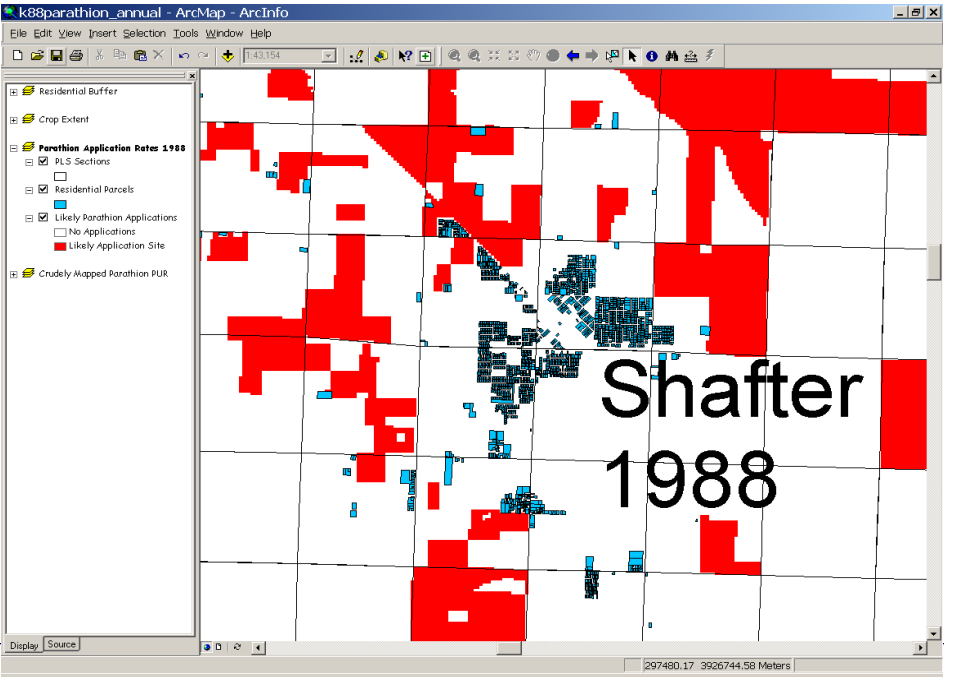
California Agricultural Pesticide Use Reporting (PUR) starting 1974 overlayed on land use maps

Pesticide data provided per 1 square mile land section

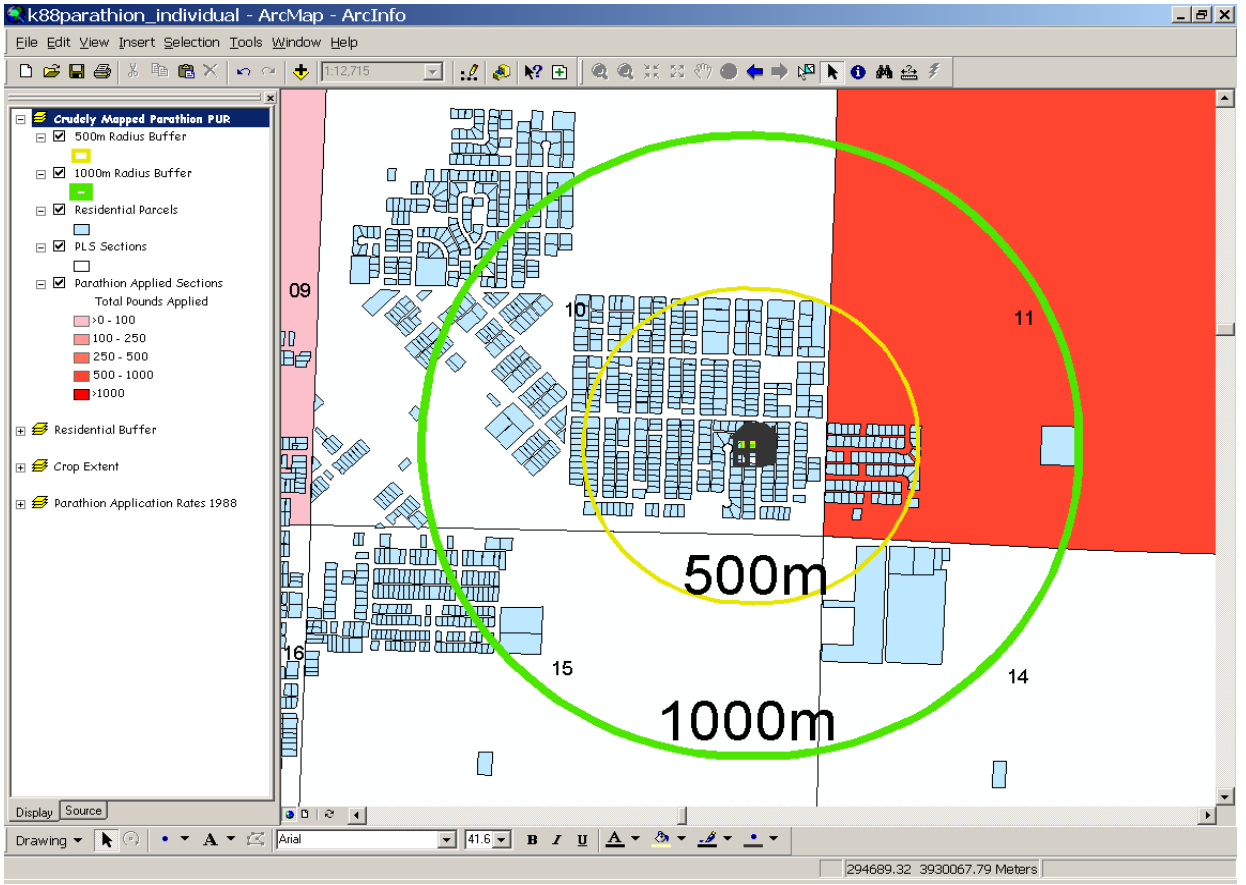
- County: Kern
- Location: 15M28S27E19

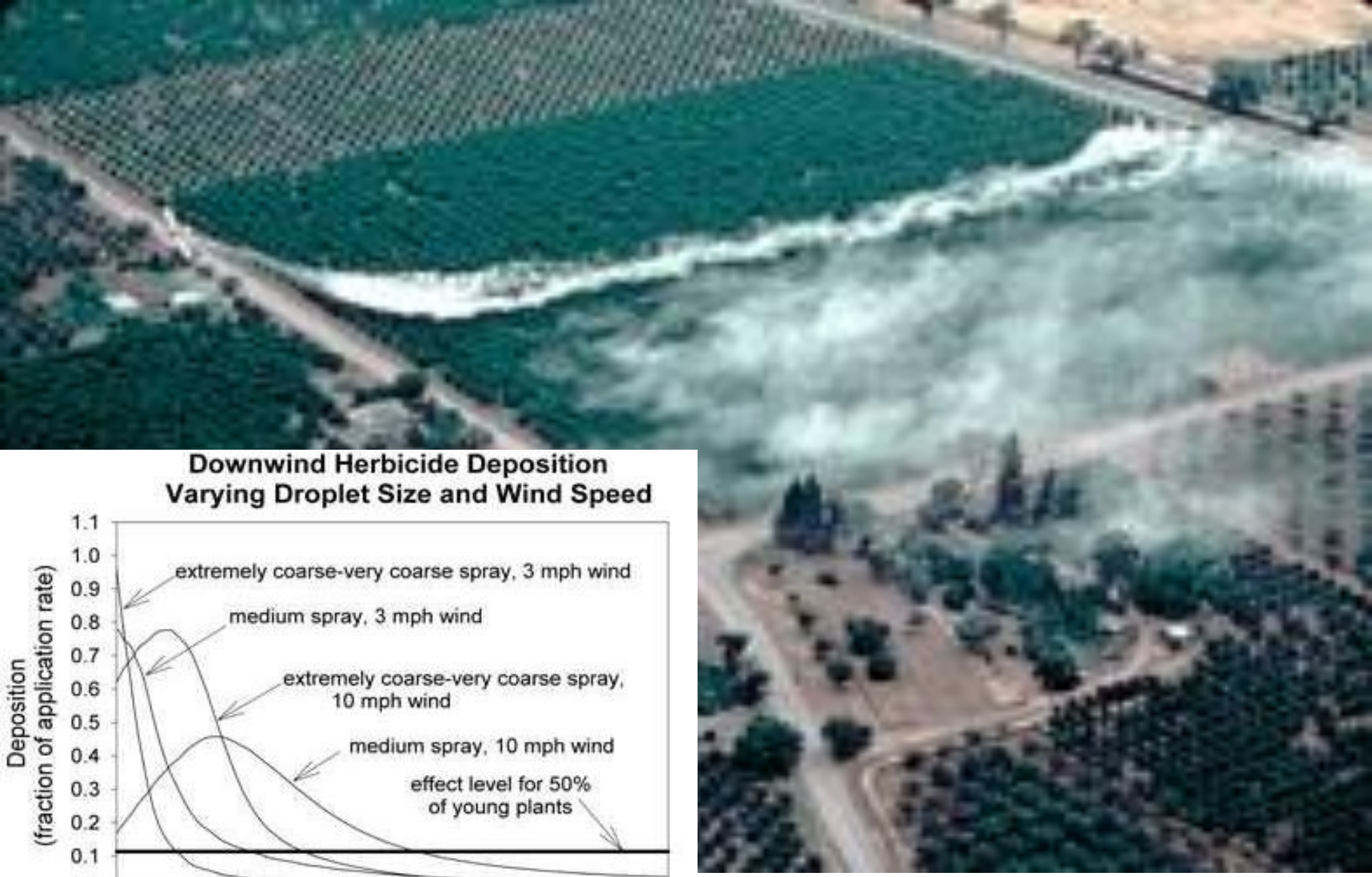


Pesticides mapped as being applied to specific crops (e.g. almonds, citrus etc.)



Identify and calculate amounts of pesticides applied around residences and work places (located on maps) as pounds per acres per year





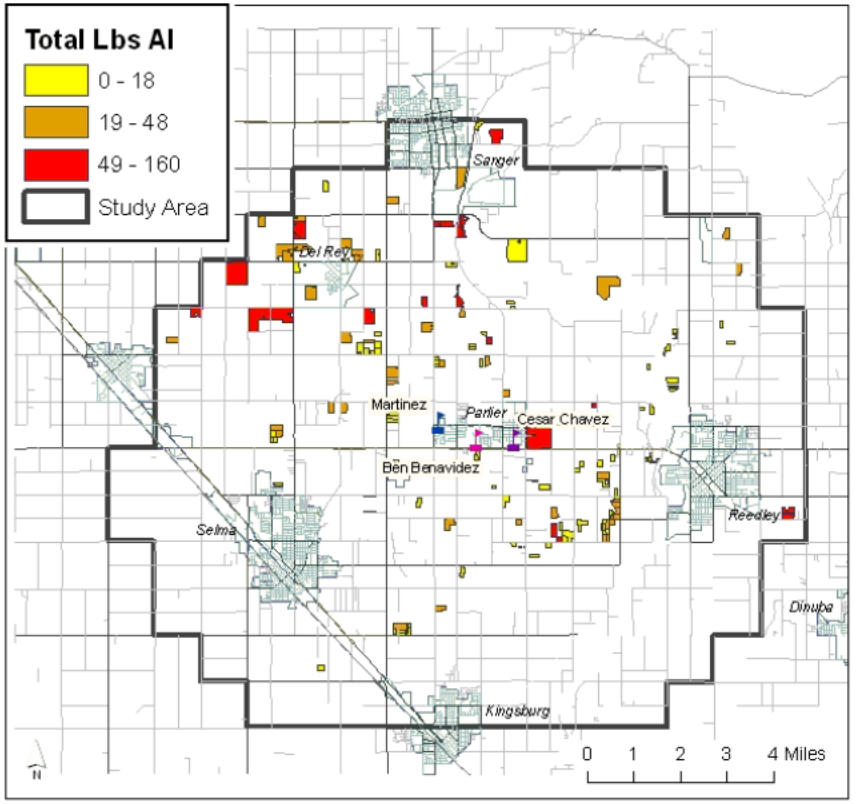
Downwind Herbicide Deposition
Varying Droplet Size and Wind Speed
Deposition
(fraction of application rate)
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
extremely coarse-very coarse spray, 3 mph wind
medium spray, 3 mph wind
extremely coarse-very coarse spray,
10 mph wind
medium spray, 10 mph wind
effect level for 50%
of young plants
0
200
400
600
800
1000
Downwind distance (ft)

Environ Monit Assess (2014) 186:1355–1370
DOI 10.1007/s10661-013-3394-x

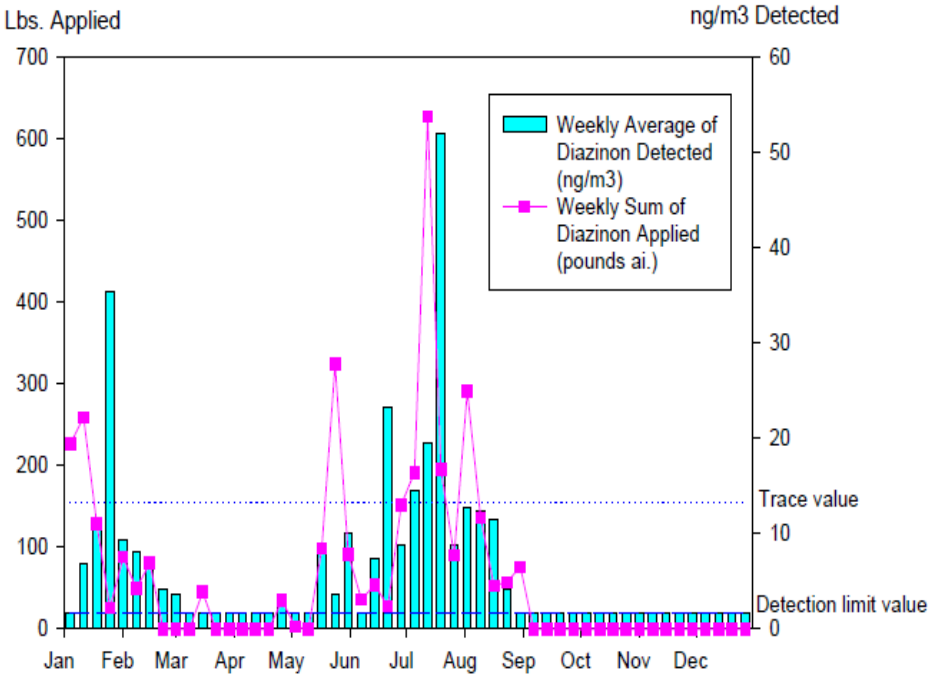
Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year

Pamela Wofford · Randy Segawa · Jay Schreider · Veda Federighi · Rosemary Neal · Madeline Brattesani

Figure 22. Diazinon: locations of all reported applications in 2006.



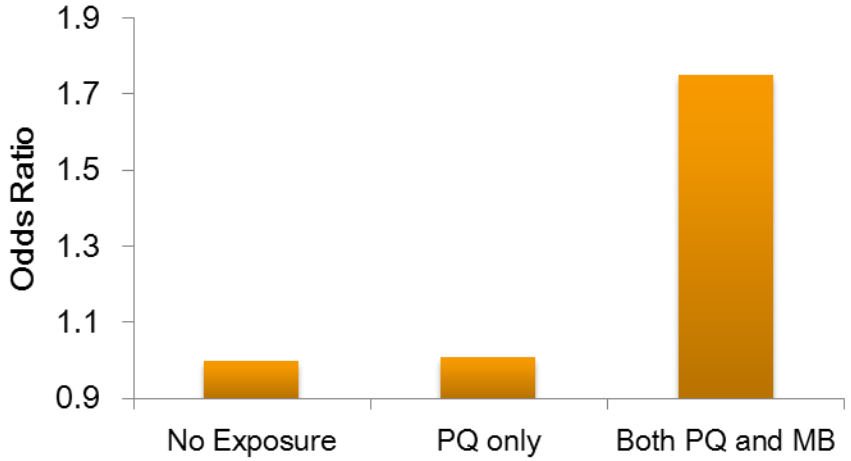
Diazinon detected in 32% of all air samples (468) in 2006 applied 1,565 kg , # applications: 222





Pesticides and Parkinson's: Translating paraquat & maneb animal models to exposed humans

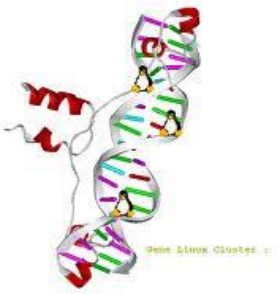
Toxicity Testing in Animals:



The 'paraquat and maneb' model

Costello S, Wahner A, Bronstein J, Cockburn M., Zhang X, Ritz B. Paraquat and Maneb exposure and Parkinson's disease in the California Central Valley. Am J Epidemiol. **2009 Apr** 15;169(8):919-26.

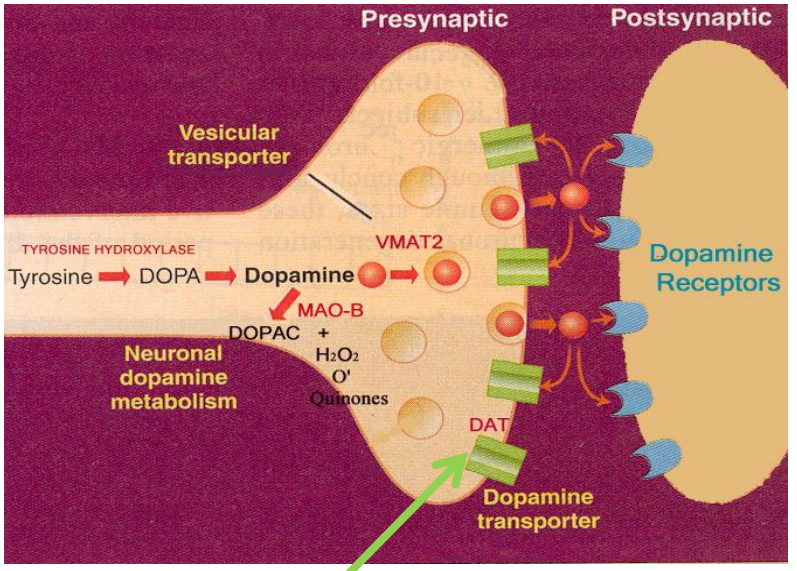
Next Step: Combine Genes and the Environment to understand PD



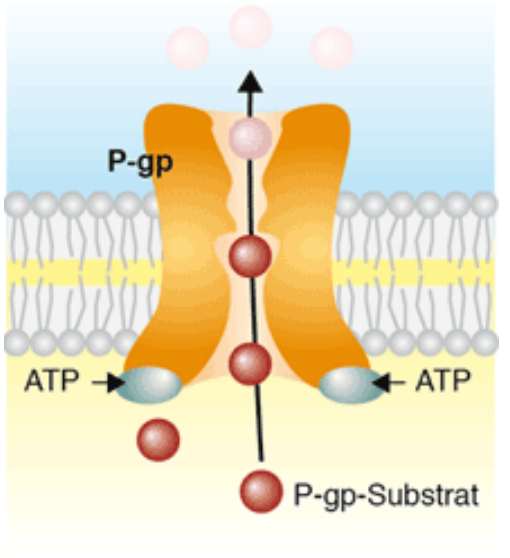
GxE

Study Genetic Variation in Pathways and Enzymes relevant to PD

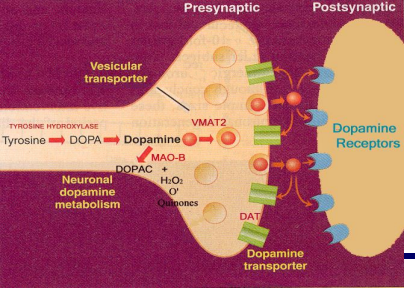
Cell membrane transporter function differs between individuals (genetically programmed)



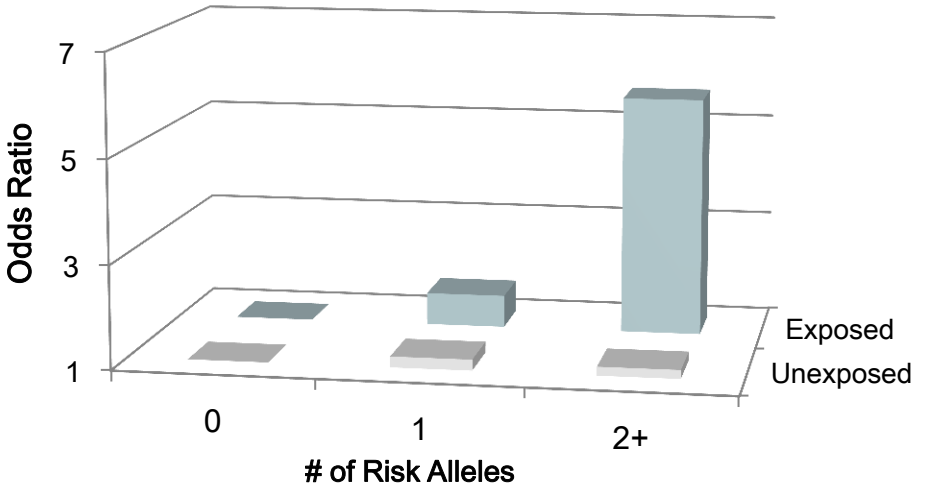
Dopamine transporter (DAT)



Cell Membrane Transporter (ABCB1) – located at the blood brain barrier



DAT1 gene variants increase PD susceptibility with paraquat/maneb pesticide exposures

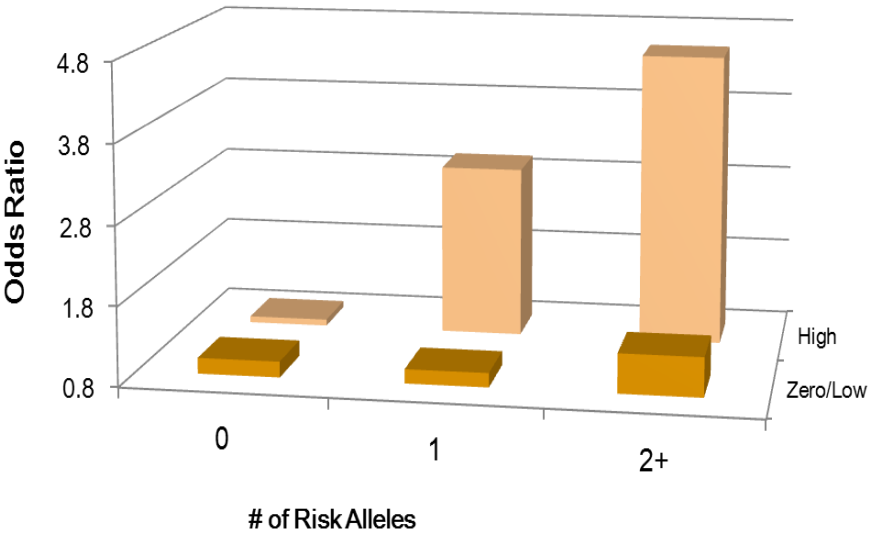


Kelada et al. HMG 2006

Human Molecular Genetics, 2006, Vol. 15, No. 20 **3055–3062**
doi:10.1093/hmg/ddl247
Advance Access published on September 8, 2006

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

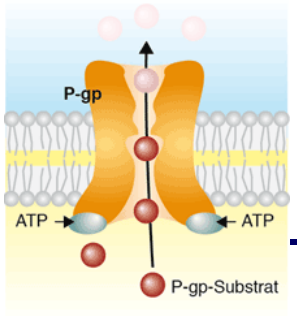
Samir N.P. Kelada[1,*], Harvey Checkoway[1,2], Sharon L.R. Kardia[4], Christopher S. Carlson[5], Paola Costa-Mallen[1], David L. Eaton[1], Jordan Firestone[1,3], Karen M. Powers[1], Phillip D. Swanson[3], Gary M. Franklin[1,3], W.T. Longstreth Jr[2,3], Terri-Smith Weller[1], Zahra Afsharinejad[1] and Lucio G. Costa[1,6]



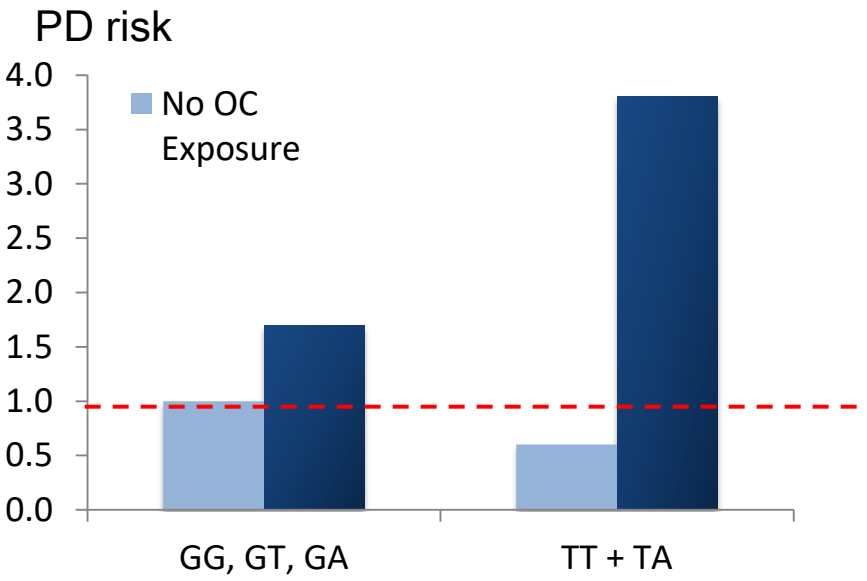
Ritz et al. EHP 2009

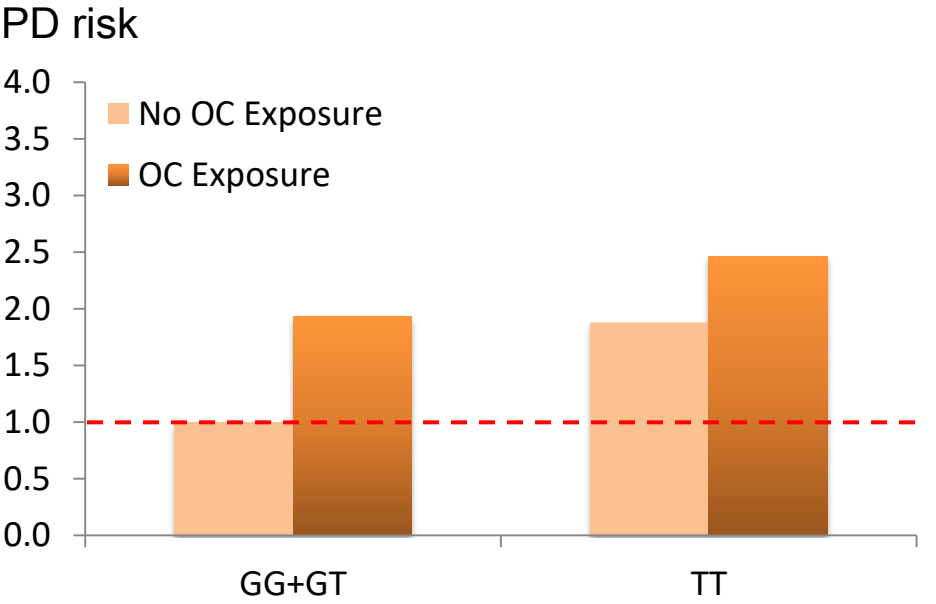
Dopamine Transporter Genetic Variants and Pesticides in Parkinson's Disease

Beate R. Ritz,[1,2,3] Angelika D. Manthripragada,[1] Sadie Costello,[1,4] Sarah J. Lincoln,[5] Matthew J. Farrer,[5] Myles Cockburn,[6] and Jeff Bronstein[3]



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

Fabien Dutheil, PhD; Philippe Beaune, Pharm, PhD; Christophe Tzourio, MD, PhD; Marie-Anne Loriot, Pharm, PhD; Alexis Elbaz, MD, PhD

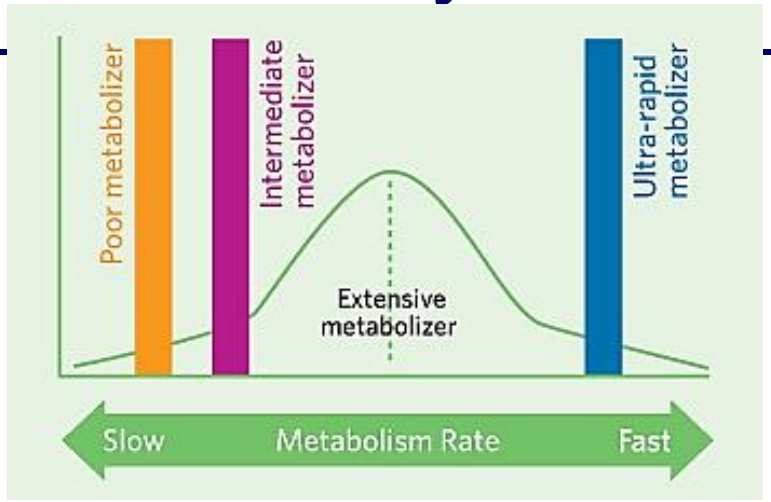
ARCH NEUROL/VOL 67 (NO. 6), JUNE 2010

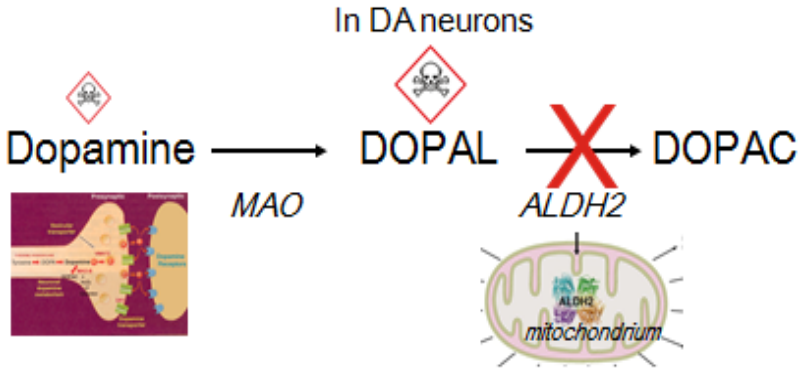
Genetic variability in *ABCB1*, occupational pesticide exposure, and Parkinson's disease

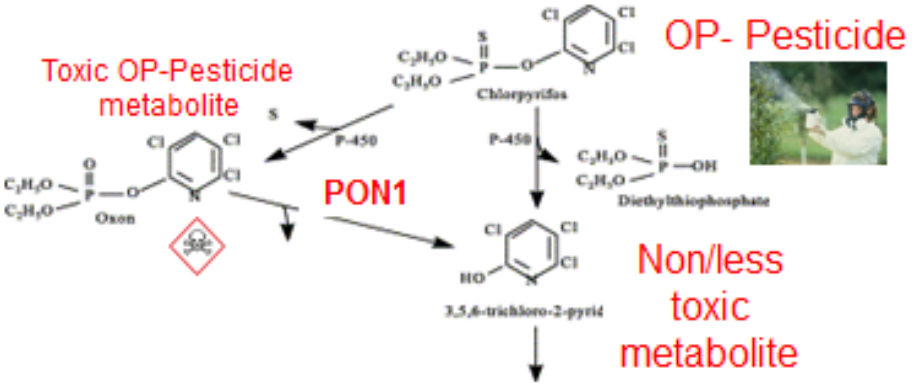
Shilpa Narayan [a], Janet S. Sinsheimer [b], Kimberly C. Paul [a], Zeyan Liew [a], Myles Cockburn [c], Jeff M. Bronstein [d], Beate Ritz [a,d,*]

Environmental Research 143 (2015) 98–106

Genetic Variants that Determine Metabolism Rates of Enzymes







Aldehyde dehydrogenase (ALDH2)

Para-oxonase (PON1)

PON1 and organophosphate metabolism

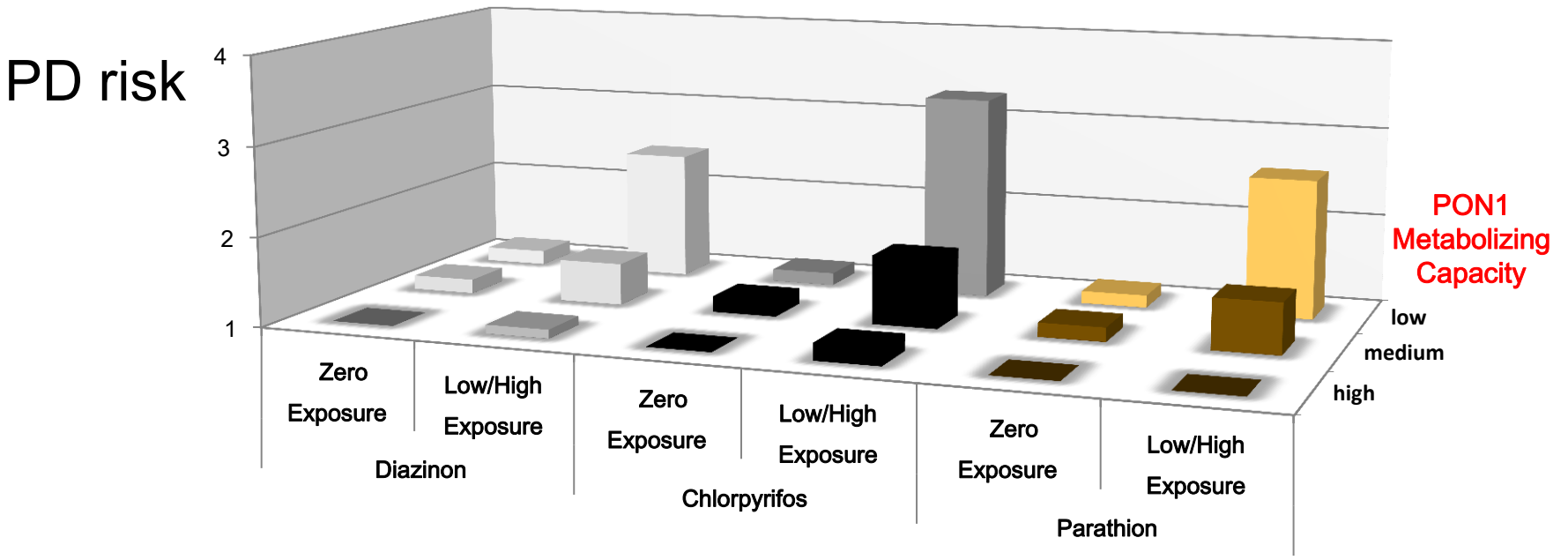
In humans, there are 10 to 40-fold inherited differences in serum PON1 activity attributed to 2 common polymorphisms in the *PON1* gene

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

PON1	55-LL	55-LM	55-MM
192-QQ	15.6 ± 6.0	11.2 ± 5.0	6.35 ± 1.50
192-QR	18.1 ± 7.7	14.3 ± 2.8	-
192-RR	22.0 ± 9.4	16.4 ± 0.0	-

PD Risk changes with PON1 enzyme OP-Metabolizing Ability & Ambient OP-Pesticide Exposure

(genetic variants *PON1L55M & PON1Q192R*)

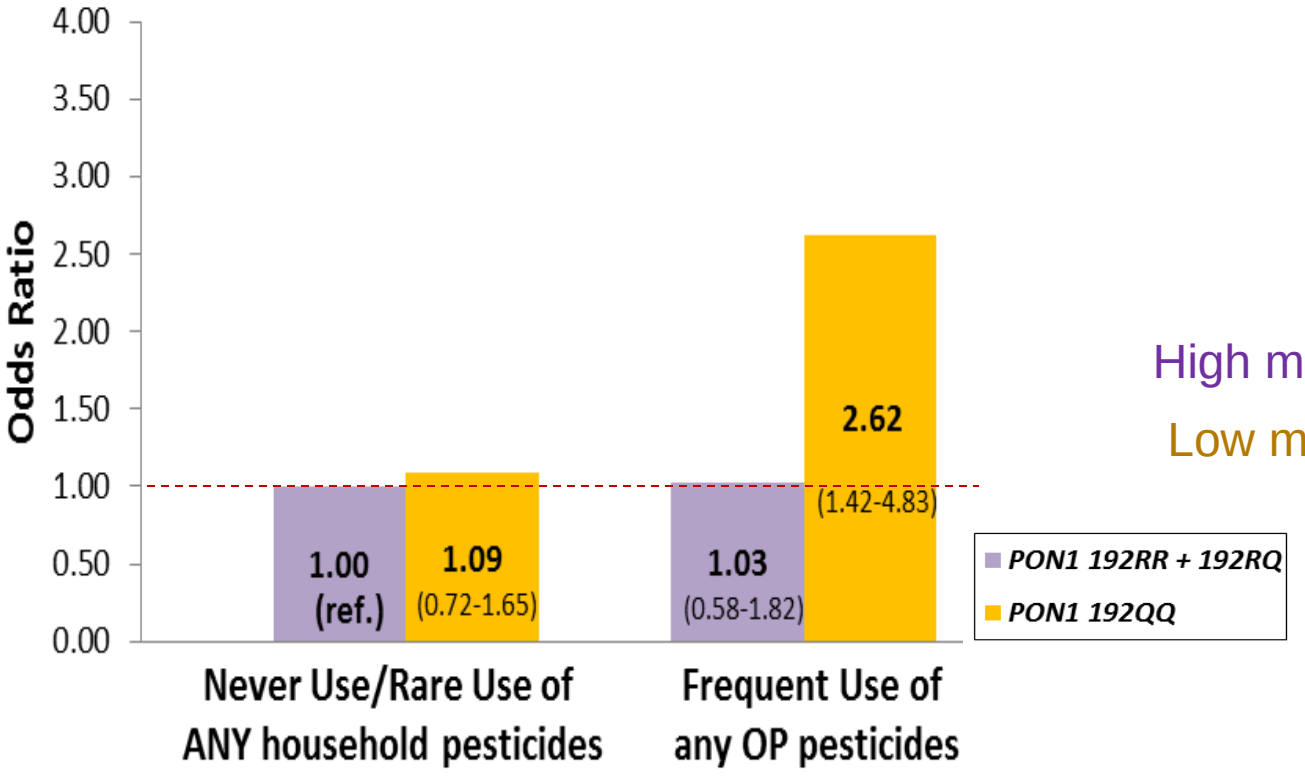


Functional paraoxonase 1 variants modify the risk of Parkinson's disease due to organophosphate exposure

Pei-Chen Lee [a,b], Shannon L. Rhodes [a], Janet S. Sinsheimer [c], Jeff Bronstein [d], Beate Ritz [a,d,*]

Environment International 56 (2013) 42–47

PD Risk by araoxonase (PON1) Metabolizer Status and Household Pesticide Use



High metabolizer

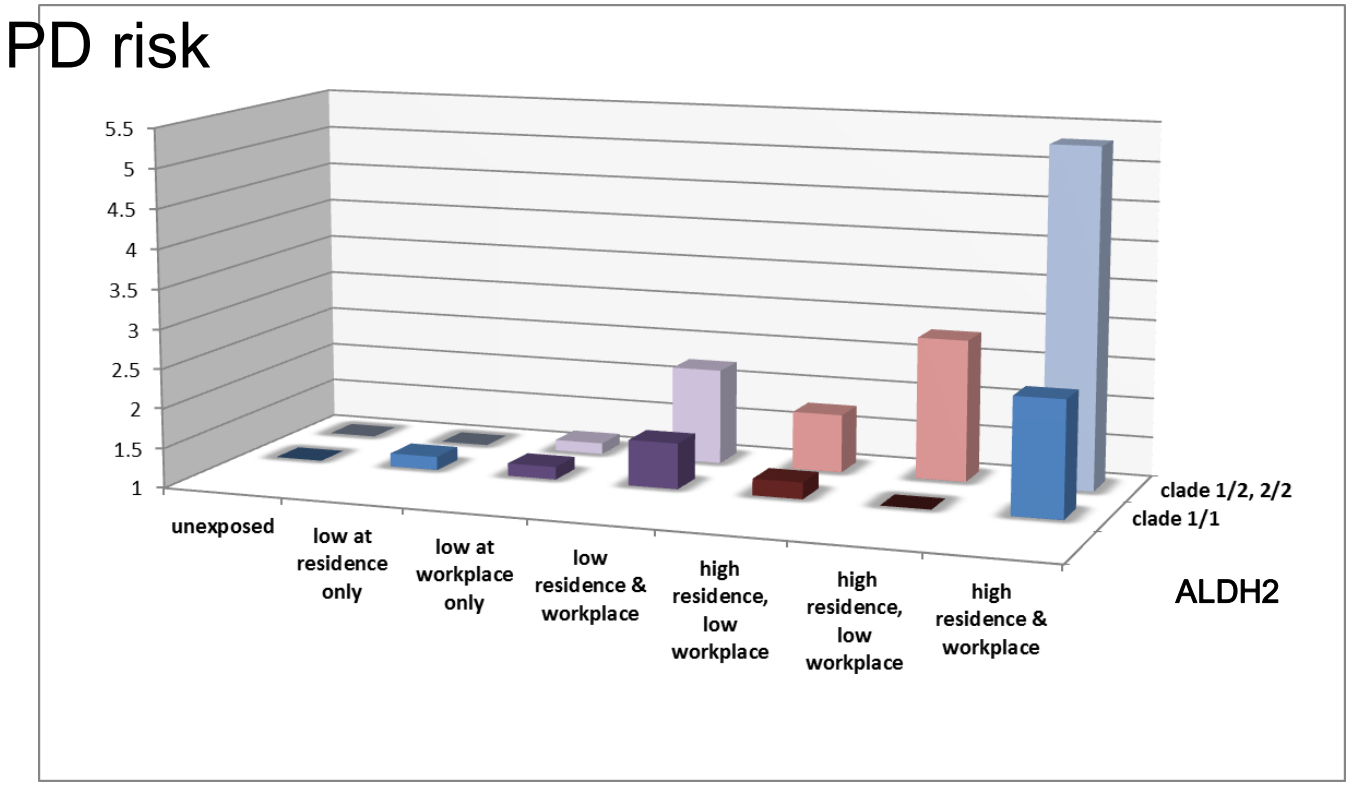
Low metabolizer

Household organophosphorus pesticide use and Parkinson's disease

Shilpa Narayan,[1] Zeyan Liew,[1] Kimberly Paul,[1] Pei-Chen Lee,[1] Janet S Sinsheimer,[2] Jeff M Bronstein[3] and Beate Ritz[1,3]*

Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease

Neurology® 2014;82:419-426



ALDH2 inhibiting pesticide exposures

Curr Envir Health Rpt
DOI 10.1007/s40572-016-0083-2

SUSCEPTIBILITY FACTORS IN ENVIRONMENTAL HEALTH (B RITZ, SECTION EDITOR)

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[1,2,3] · Kimberly C. Paul[1] · Jeff M. Bronstein[3]

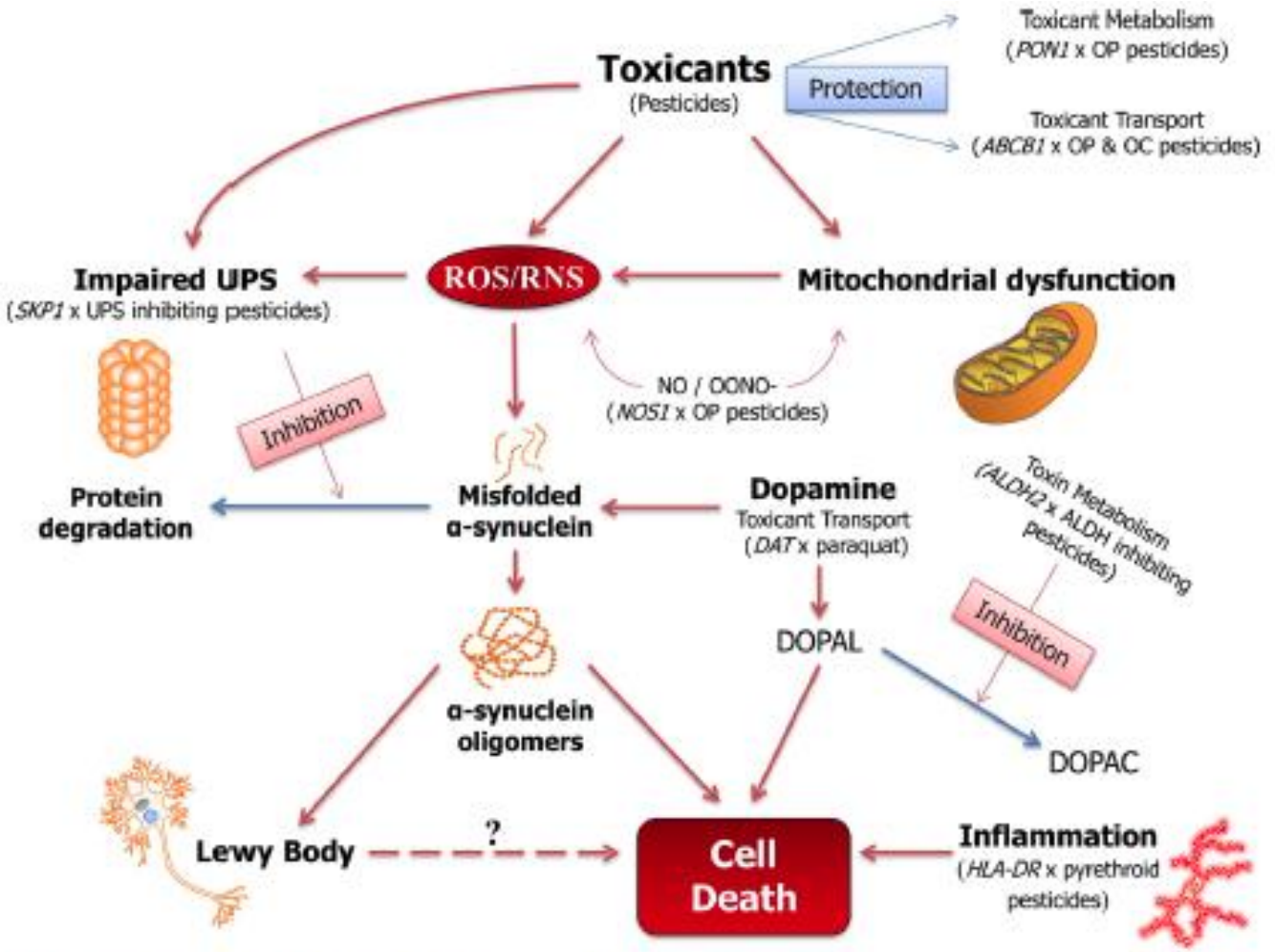
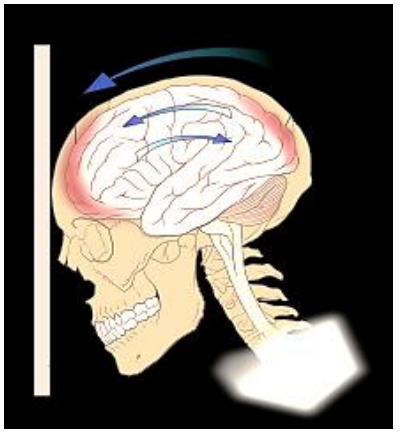


Fig. 1 Proposed Parkinson's disease pathological mechanisms involving discussed GxE reports

Environment (ExE) and Disease

ExE

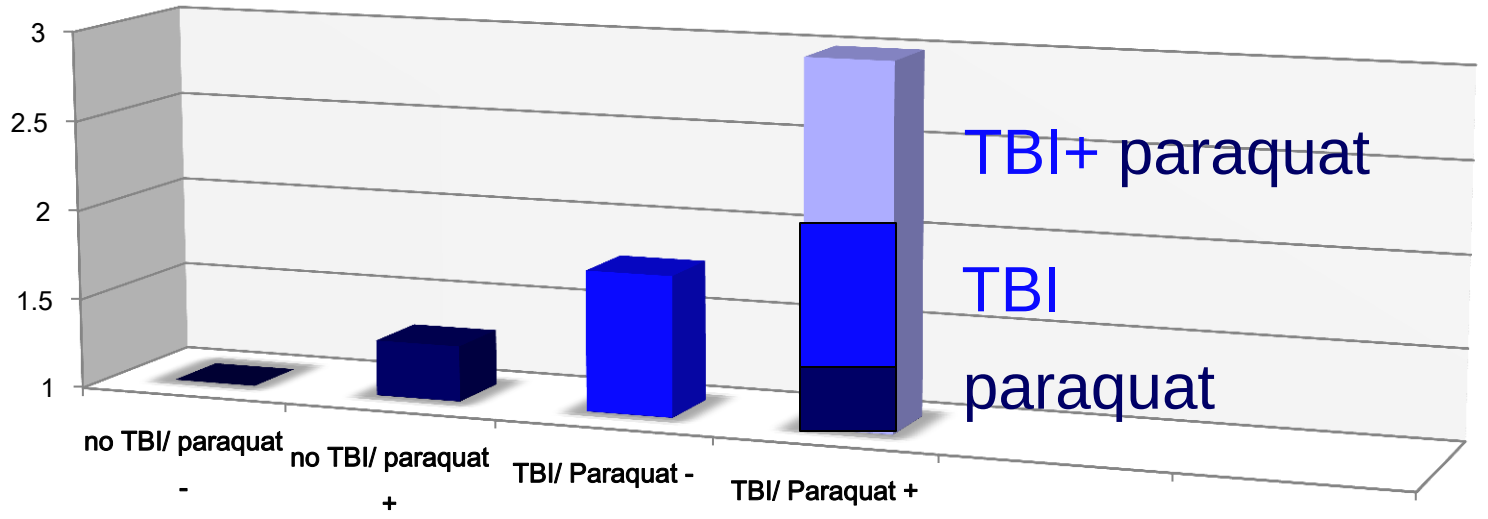


Head trauma and paraquat pesticide exposure act together to increase PD risk

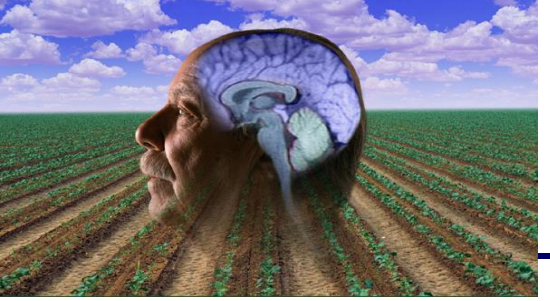
Pei-Chen Lee, PhD
Yvette Bordelon, MD, PhD
Jeff Bronstein, MD, PhD
Beate Ritz, MD, PhD

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

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

2007-2012

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

- Deceased N=64 (17%)
- Too Ill - withdrew N=21 (6%)
- Unable to Re-contact N=21 (6%)

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

- Re-Dx No iPD N=13 (3%)
- Enrolled and Followed N=252 (68%)

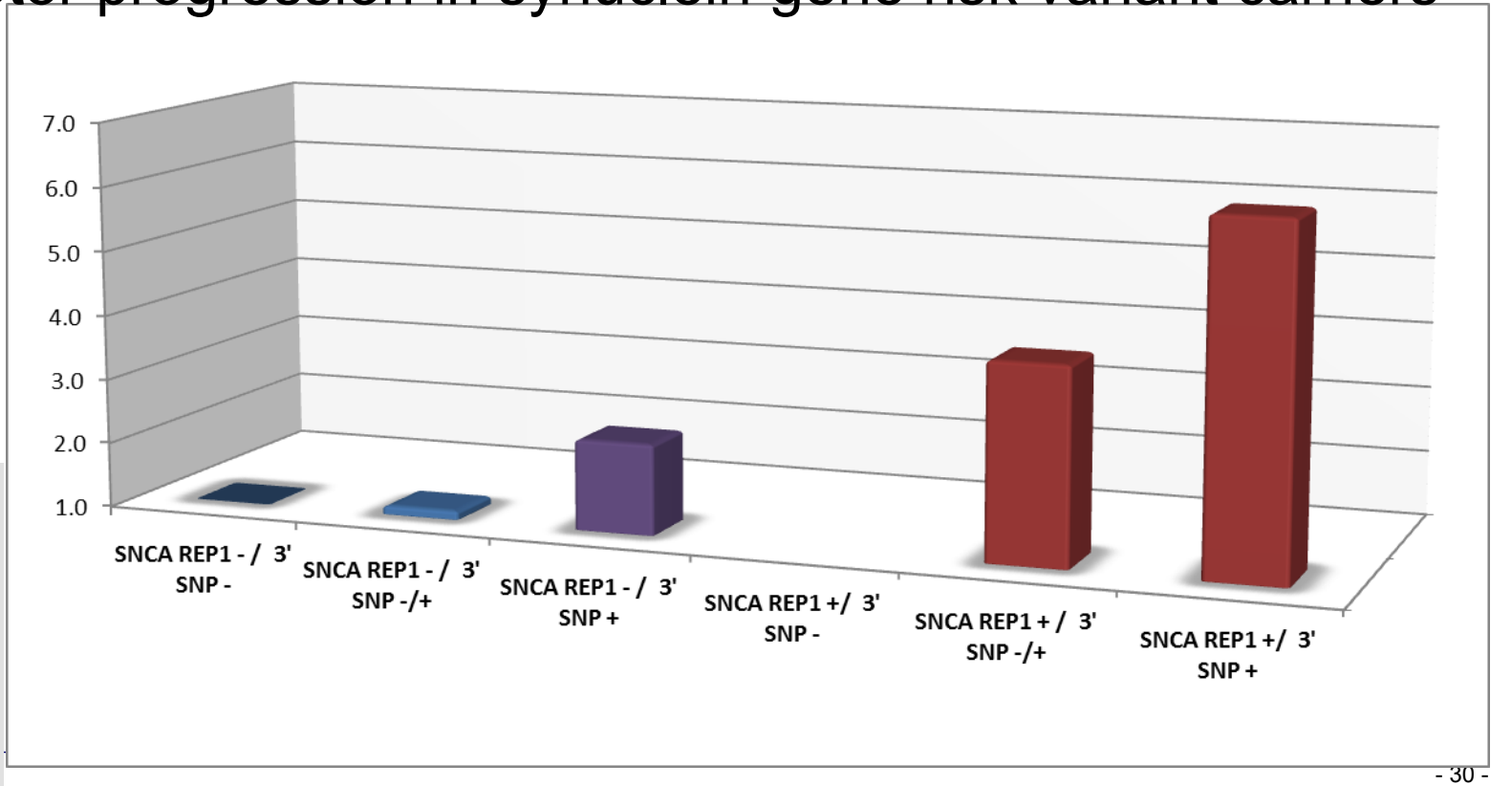
α-Synuclein Genetic Variants Predict Faster Motor Symptom Progression in Idiopathic Parkinson Disease

May 2012 | Volume 7 | Issue 5 | e36199

Beate Ritz[1,2*], **Shannon L. Rhodes**[1], **Yvette Bordelon**[2], **Jeff Bronstein**[2]

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

Journal of Parkinson's Disease xx (20xx) x–xx
DOI 10.3233/JPD-150762
IOS Press

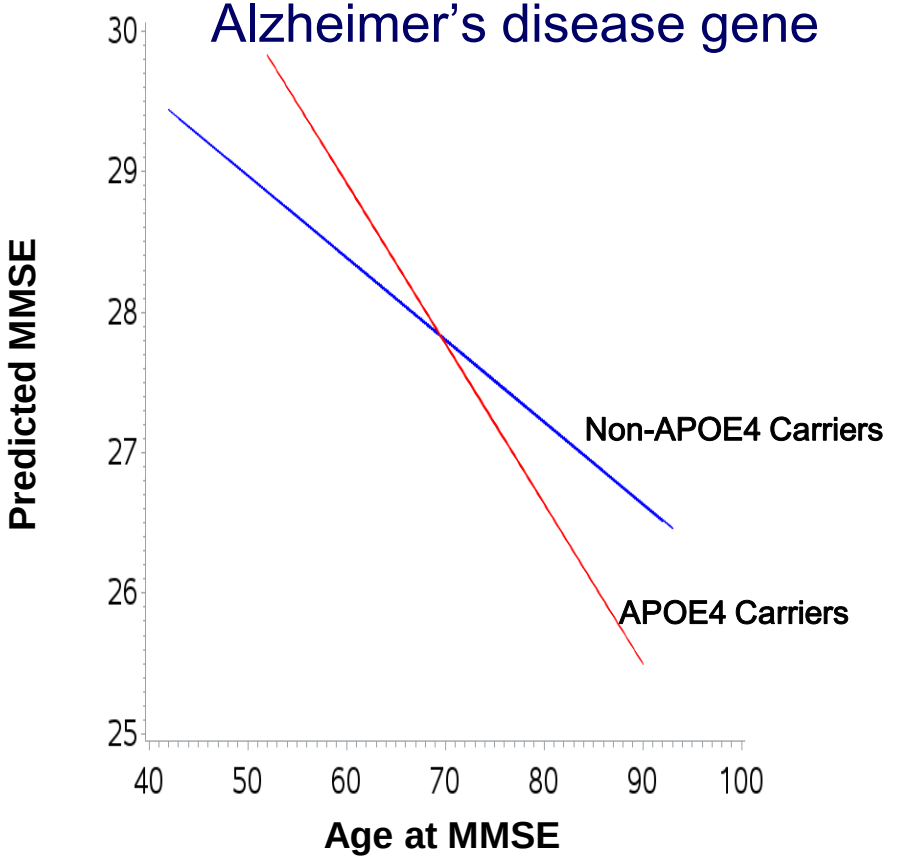
Research Report

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

Kimberly C. Paul[a], Rebecca Rausch[b], Michelle M. Creek[c], Janet S. Sinsheimer[c,d], Jeff M. Bronstein[b], Yvette Bordelon[b] and Beate Ritz[a,b,*]
[a]*Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA*
[b]*Department of Neurology, David Geffen School of Medicine, Los Angeles, CA, USA*
[c]*Department of Biostatistics, UCLA Fielding School of Public Health, Los Angeles, CA, USA*
[d]*Department of Human Genetics, David Geffen School of Medicine, Los Angeles, CA, USA*

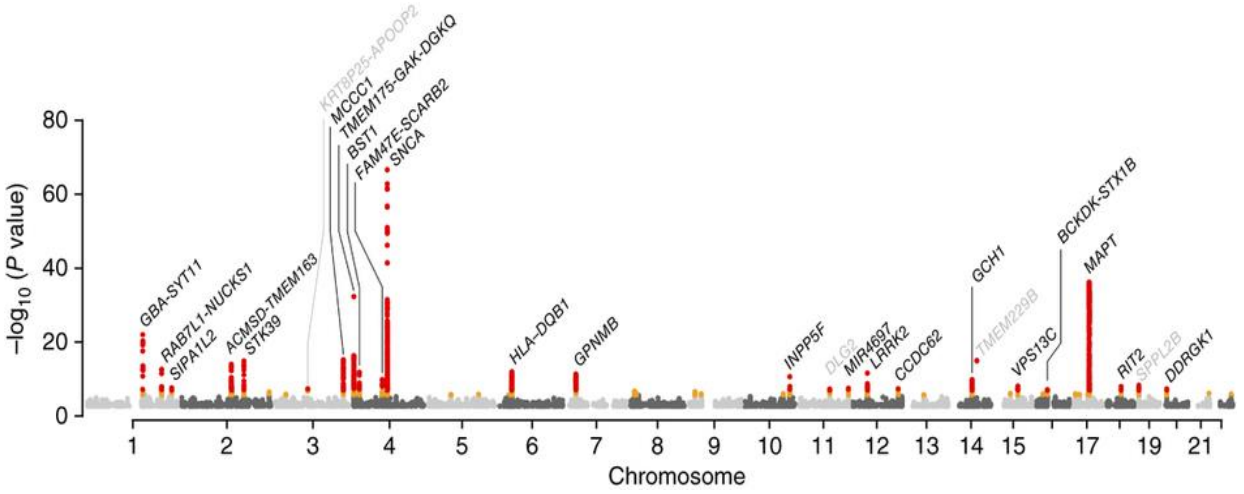
APOE4

Alzheimer's disease gene



Results from linear mixed model, using repeated measures, modeling age as random effect and adjusted for age, sex, race, education

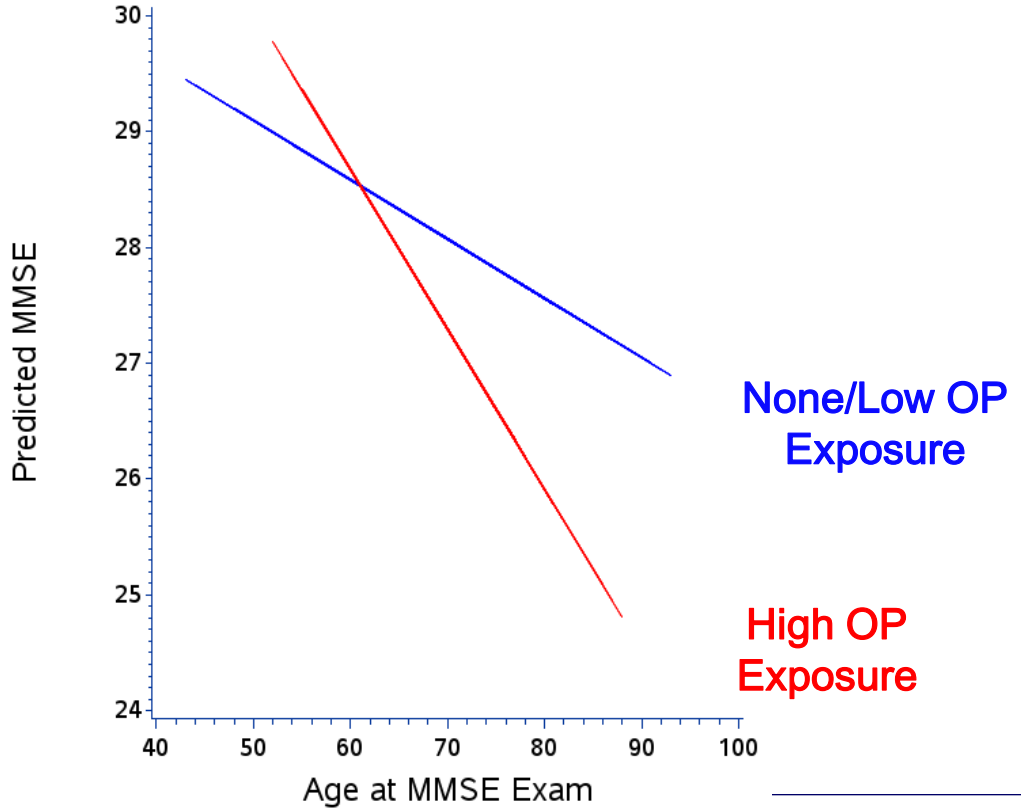
Genetic Predictors of Progression in PD
The Role of PD GWAS Genetic Variants



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

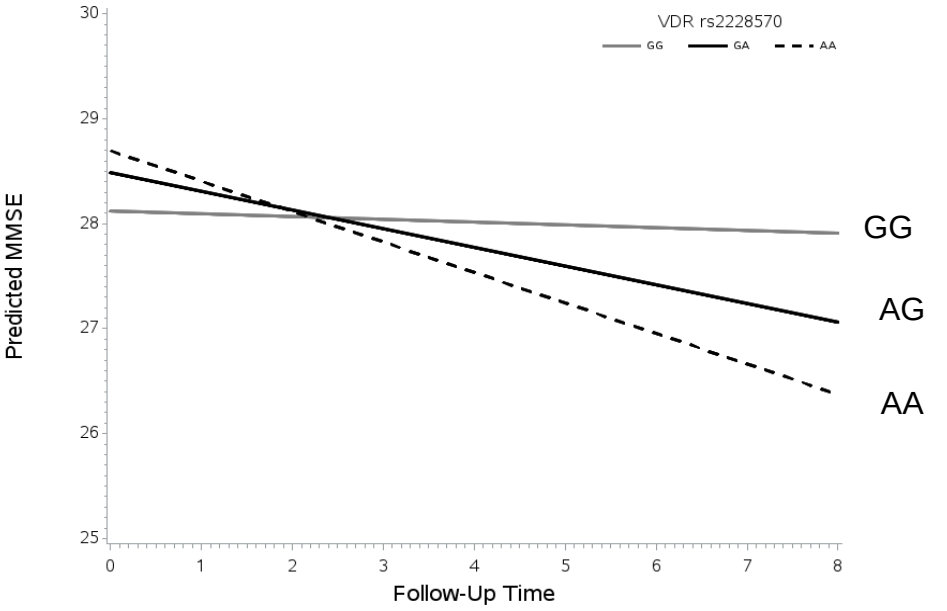
Journal of the Neurological Sciences

Available online 11 September 2016

In Press, Accepted Manuscript — Note to users

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

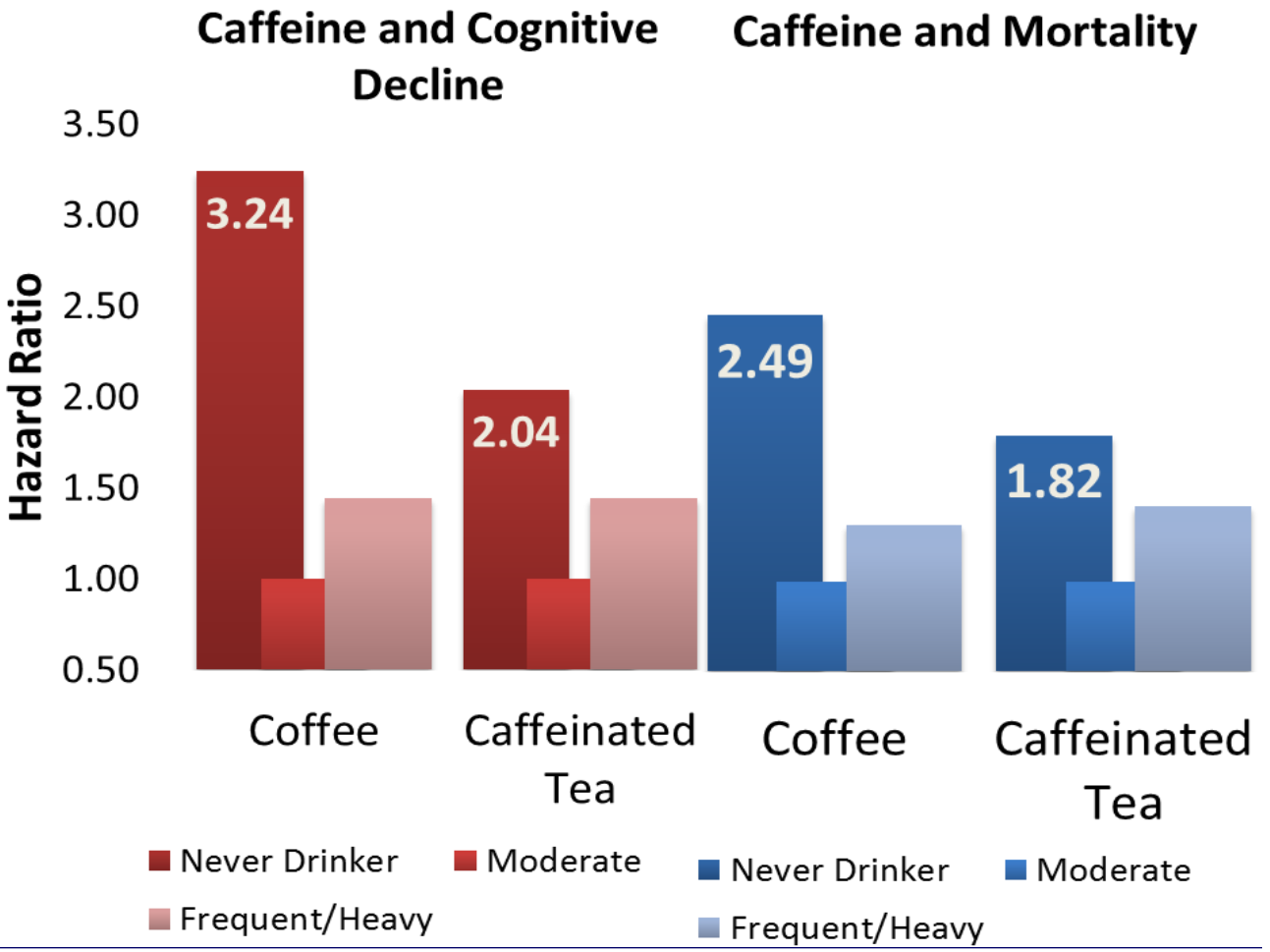
Nicole M. Gatto, MPH, PhD[a], Kimberly C. Paul[b], Janet S. Sinsheimer, PhD[e, f, g], Jeff M. Bronstein, MD, PhD[d], Yvette Bordelon, MD, PhD[d], Rebecca Rausch, PhD[d], Beate Ritz, MD, PhD[b, c, d]



PEG Progression Study

Caffeine and Progression

Caffeinated Coffee and Tea are Protective



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

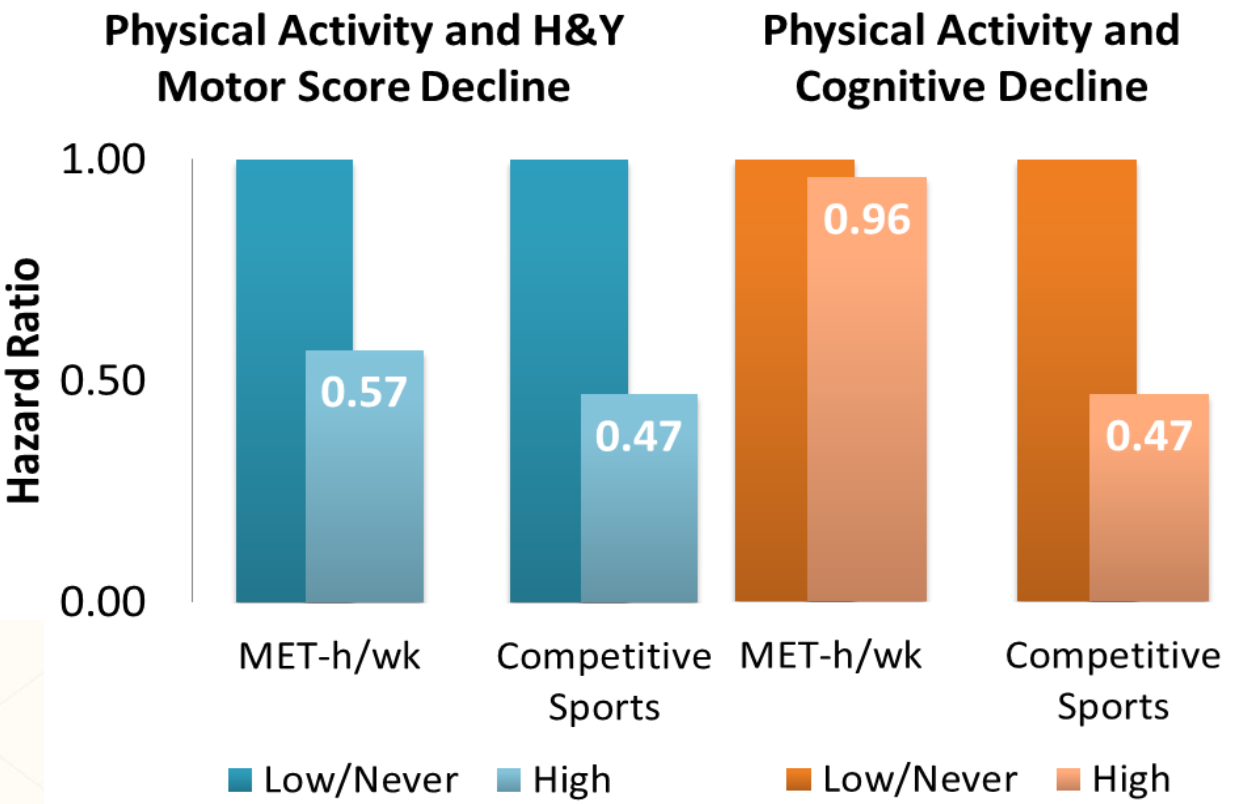
PEG Progression Study

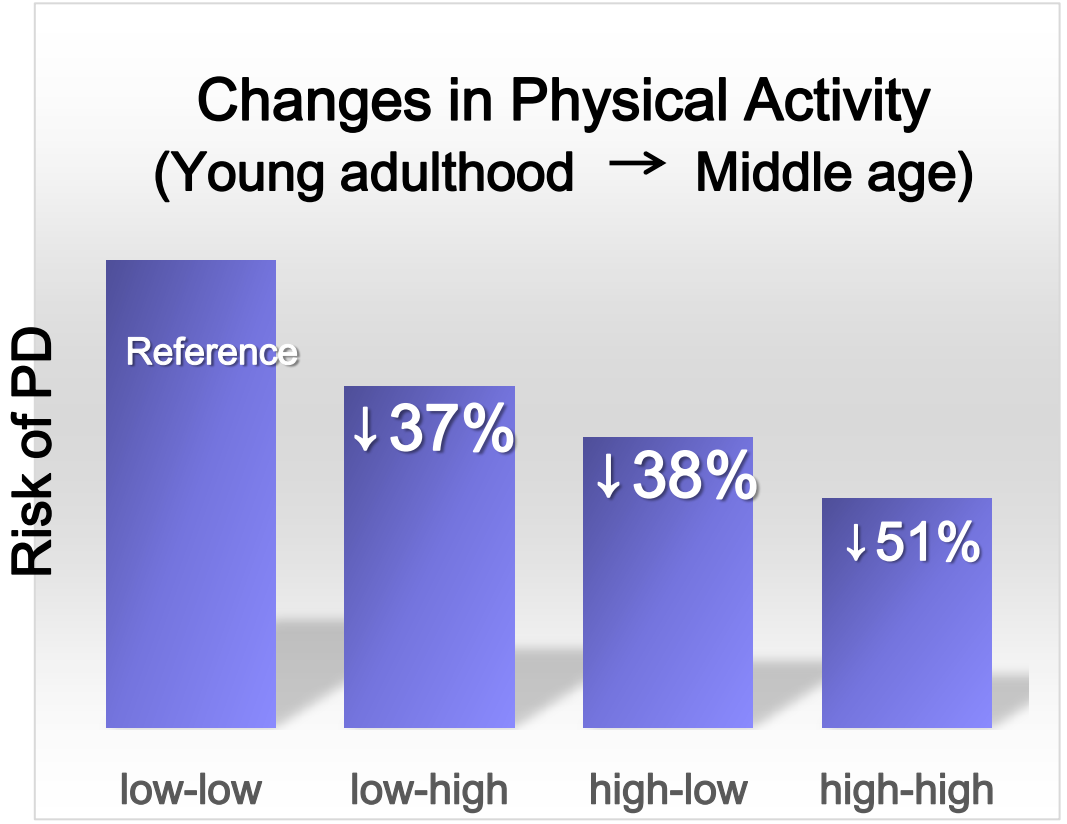
Physical Activity and Symptom Progression

Physical Activity Protects against Motor and Cognitive Decline in PD patients:

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

are both protective





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

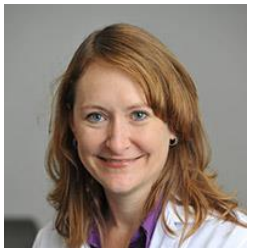
Parkinson's Disease Research Resources

Parkinson's Disease Registry Law in CA signed in 2004

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