2016 Alzheimer Disease Centers
Clinical Core Leaders Meeting

Doing more with genetics: Gene-environment interactions

Haydeh Payami, PhD
On behalf of NeuroGenetics Research Consortium (NGRC)

From: Joseph Quinn quinnj@ohsu.edu

To: haydeh hpayami@uab.edu

Hi Haydeh,

……. would you be willing to give a short talk (20-30 minutes) on your gene-environment work in PD, making the suggestion that this might be a fruitful direction for the ADCs?...

joe

Parkinson's Disease Susceptibility loci

International Collaboration, *Nat Genet* ***2014***

28+ loci explain a fraction of heritability.

NGRC

Found HLA

2nd largest dataset in International Collaboration after 23andMe

Other things we have done with NGRC data

Gene-environment interactions

Genetics of age at onset

Gut Microbiome

Epigenetics

Environmental Exposures & PD

- Pesticides/herbicides (ex. Paraquat) associate with increased risk

- Caffeine
- cigarette smoking
- NSAIDs

associate with reduced risk

Identification of genes that influence the inverse association of caffeine, nicotine and NSAIDs with PD

RATIONALE

- DATA CAN BE COLLECTED AND QUANTIFIED
- POTENTIAL FOR PREVENTION & TREATMENT

  CLINICAL TRIALS FAIL DUE TO LOW AVERAGE EFFICACY. GENOTYPE CAN IDENTIFY RESPONDERS.

APPROACH

- HYPOTHESIS-FREE DISCOVERY

- GENOMEWIDE GENE-ENVIRONMENT INTERACTION IN HUMANS
- GENOME-WIDE INTERACTION ON GENE EXPRESSION IN the FLY
- REPLICATION / VALIDATION

NGRC

HUMAN

Subjects	PD	Controls
N with DNA	2312	2316
GWAS + imputation post QC	2000	1986
smoking data	1600	1506
coffee data	1461	931
NSAIDs data	1570	983

Recruited from neurology clinics in OR (OHSU), WA (UW, VA), GA (Emory) & NY (AMC) using standardized protocols for enrollment, phenotyping, environmental data collection, stool collection.

Uniform methods for sample & data processing, QC, genotyping and data analysis

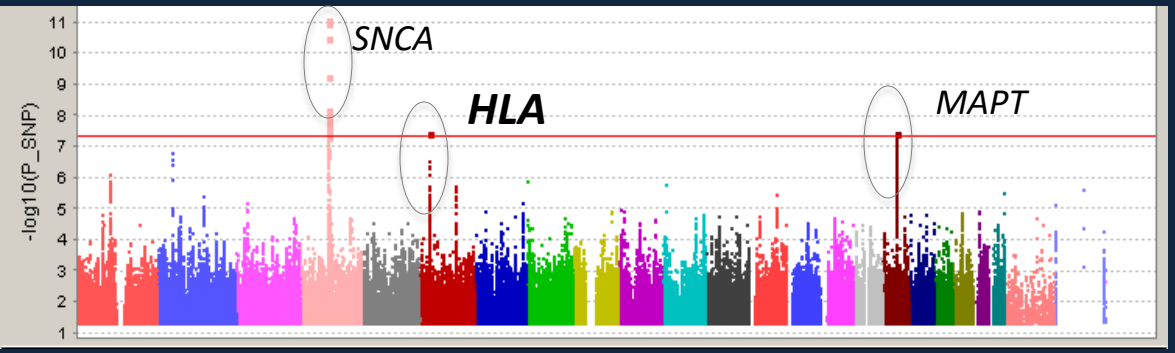
DROSOPHILA

Use paraquat to induce parkinsonism & early death
Use drugs to rescue
Test interaction between paraquat and drug on gene expression in brain

PLOS GENET 2011

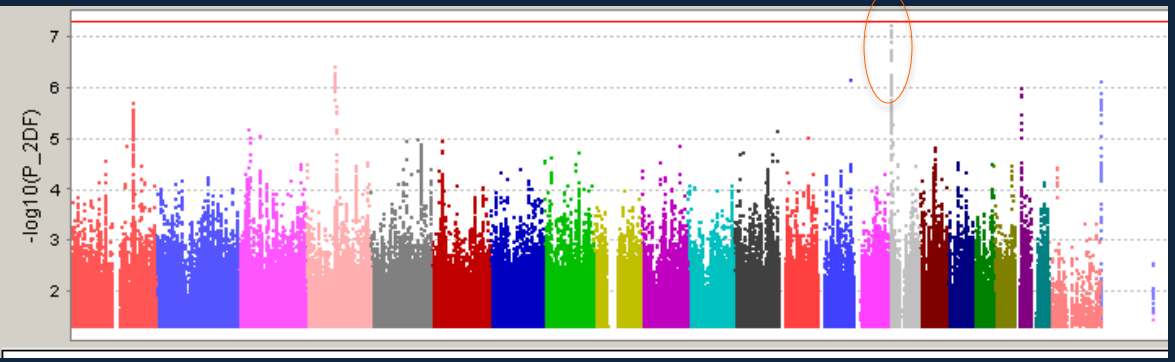
NGRC Dataset under Different Analyses

Nat Genet 2010, PLoS Genet 2011



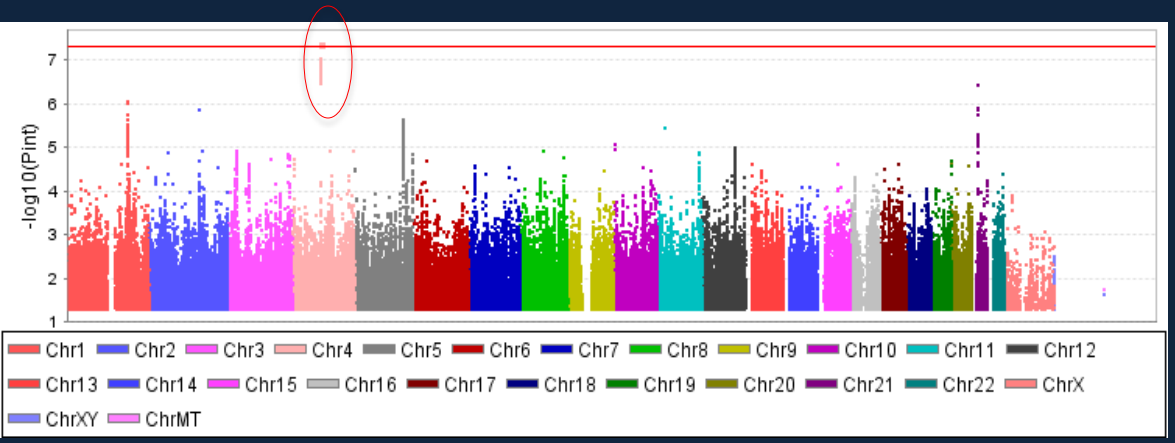
Find SNPs associated with PD (main effect)

GWAS Association



Find SNPs that have a main effect and the effect varies depending on exposure (coffee use).

GWAIS Assoc & Intercation

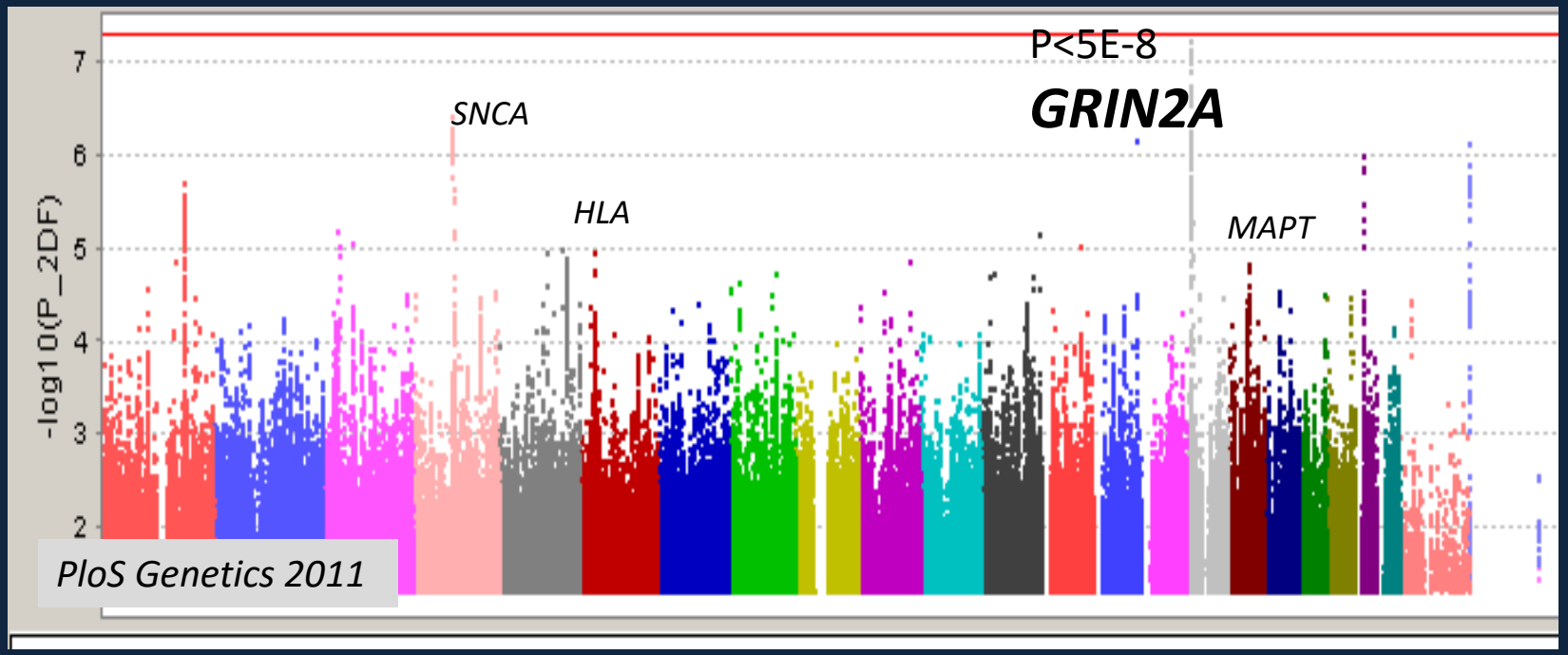


Find SNPs that have diff. assoc. with PD depending on exposure (coffee use).

GWIS Interaction

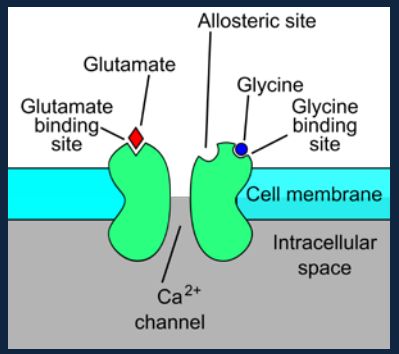
GWAIS Main SNP effect + interaction with coffee

PD ~ covariates + Coffee + SNP + SNPxCoffee vs. PD ~ covariates + Coffee



GRIN2A codes for glutamate receptor NMDA-R2A

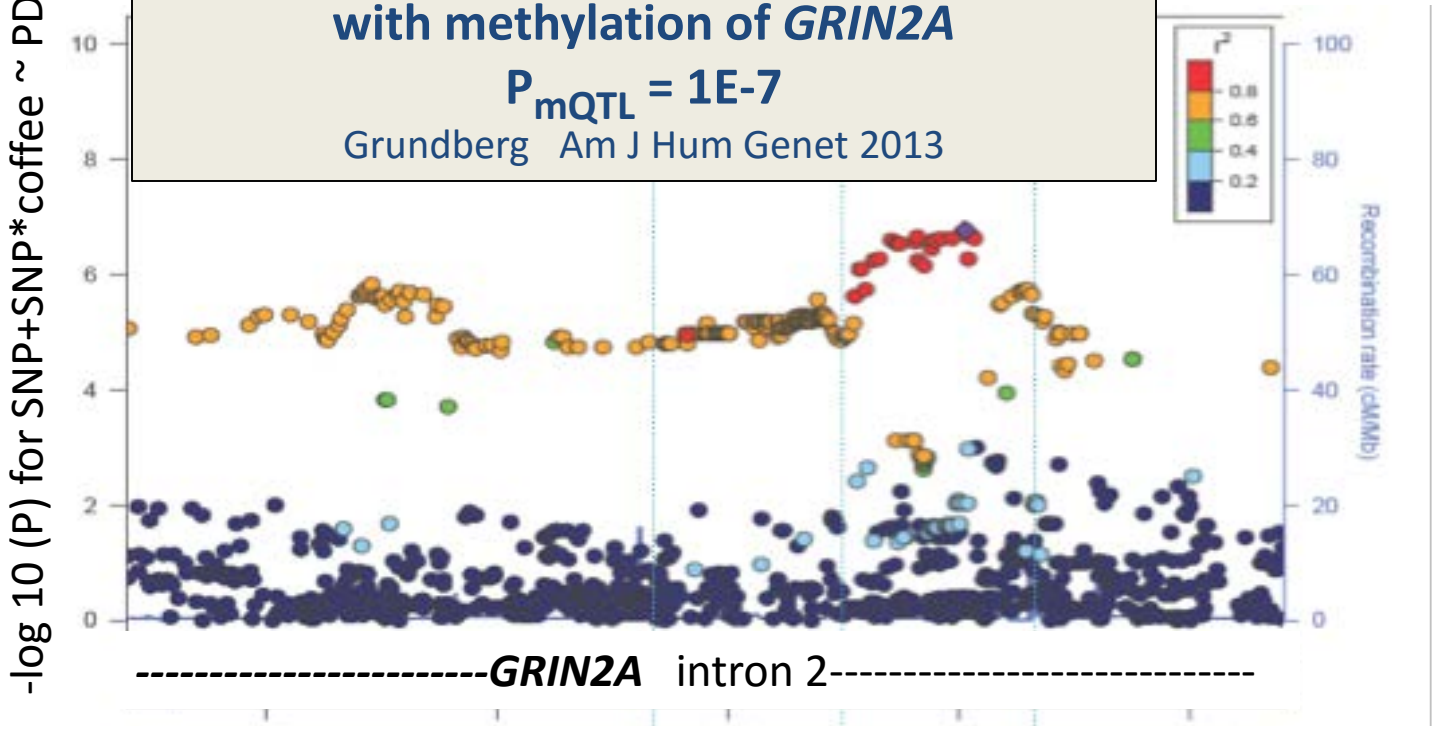
Glutamate is the most prominent excitatory neurotransmitter
Glutamate receptors and glutamate excitoxicity implicated in neurodegenerative diseases



PD-Coffee SNPs in *GRIN2A* are associated with methylation of *GRIN2A*

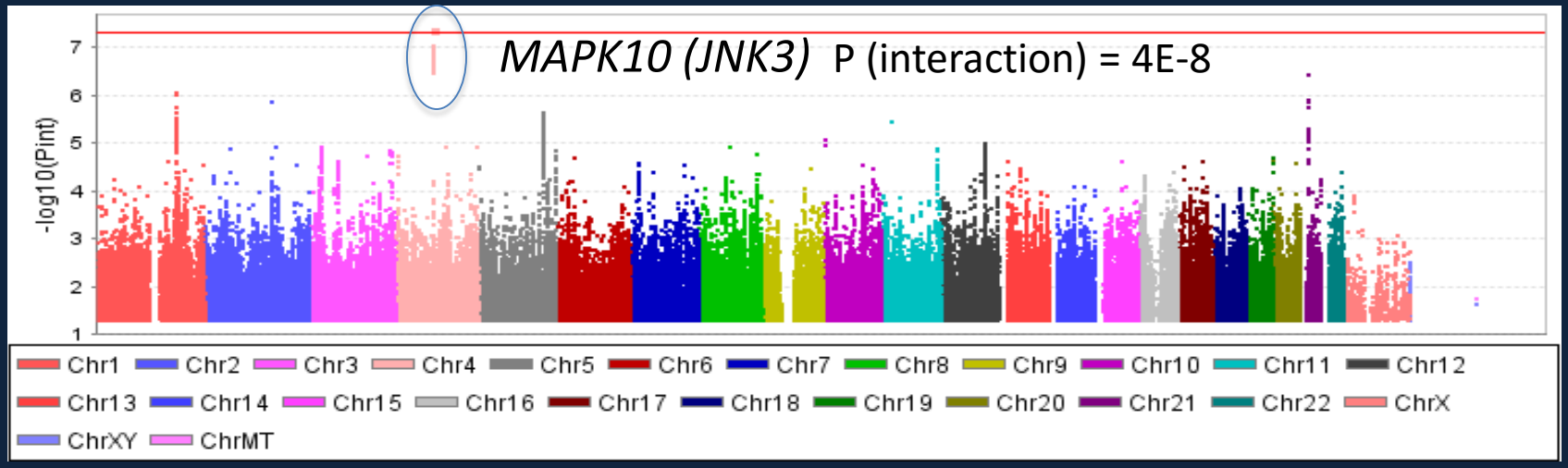
P_{mQTL} = 1E-7

Grundberg Am J Hum Genet 2013



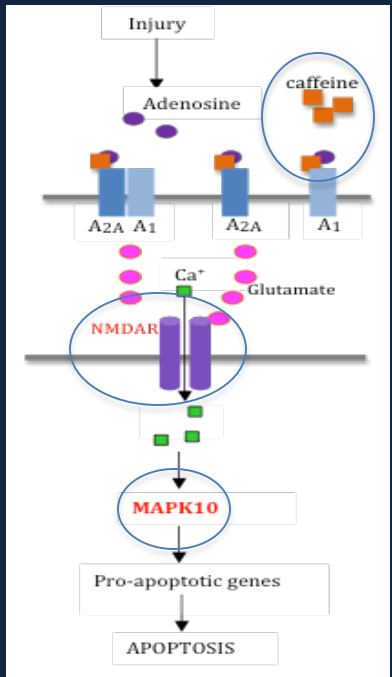
GWIS interaction with coffee

PD ~ covariates + Coffee + SNPxCoffee vs. PD ~ covariates + Coffee



MAPK10 encodes a brain-specific stress-induced kinase required for signaling neuronal apoptosis

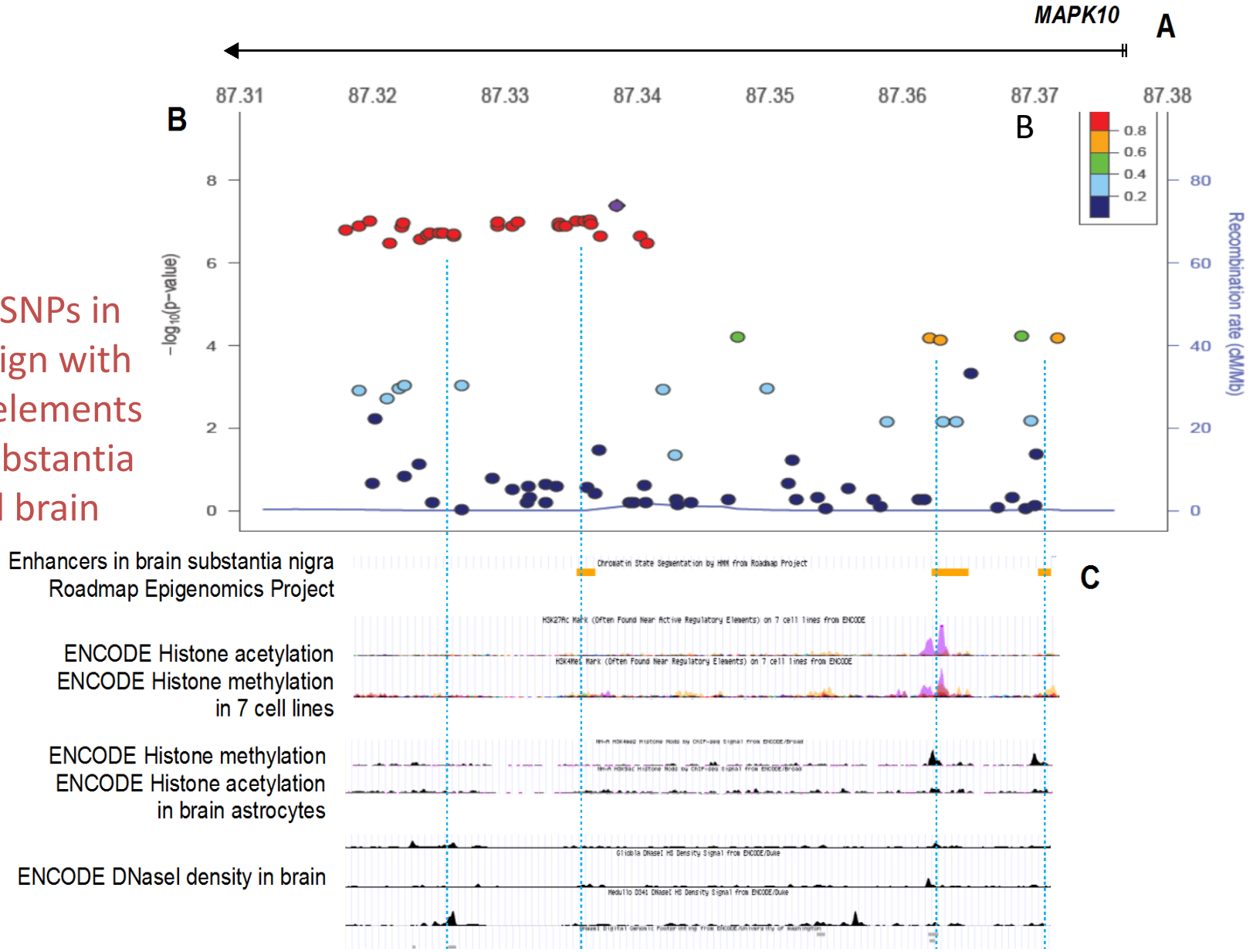
Paraquat, MPTP, rotenone & 6-OHDA induce parkinsonism by activating *MAPK10*, disrupting *MAPK10* prevents dopaminergic neuronal loss and motor deficits



PD-coffee SNPs in *MAPK10* are associated with methylation of *MAPK10*

P_{mQTL}=3E-5 Grundberg Am J Hum Genet 2013

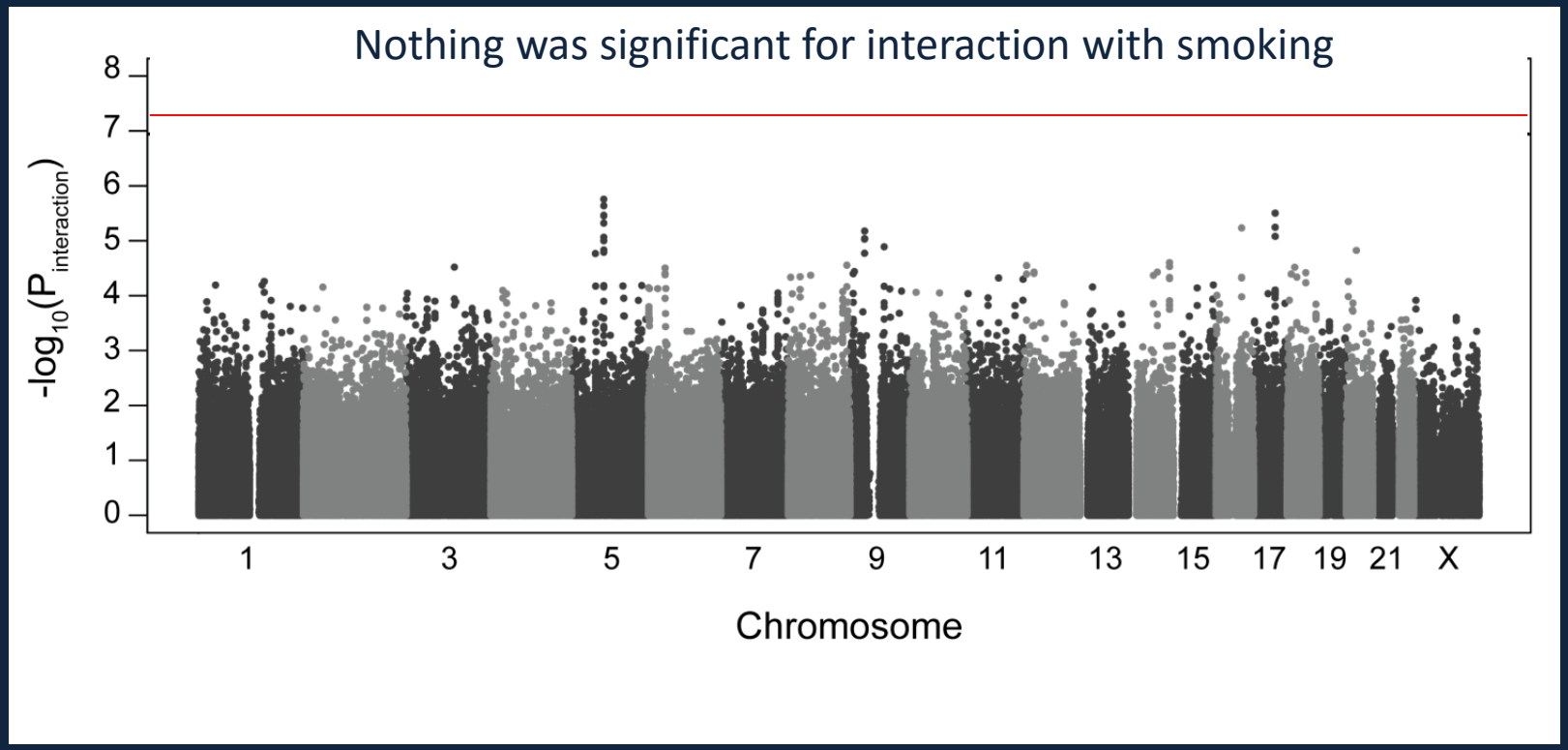
PD-coffee SNPs in *MAPK10* align with regulatory elements active in substantia nigra and brain



Inverse association of coffee with PD stratified by genotype

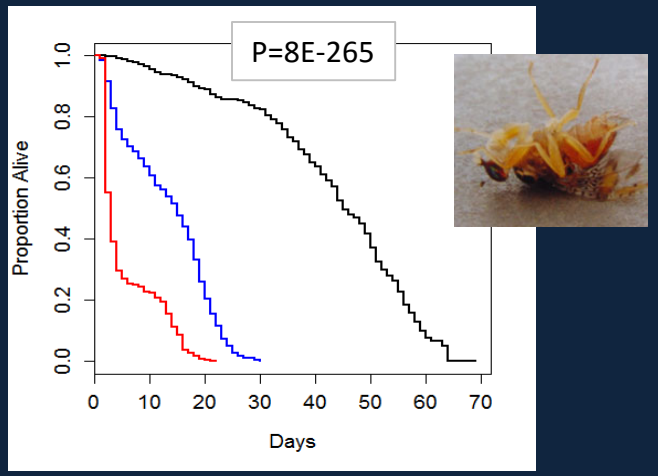
The Pharmacogenomics Journal 2012

Identify genes that significantly enhance or diminish the protective effect of smoking on PD in humans



Paraquat (PQ)

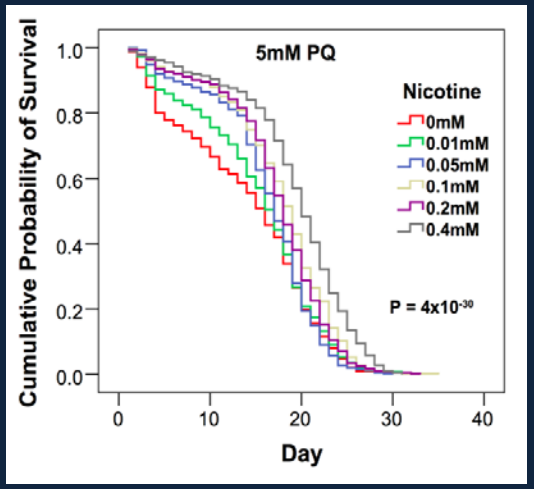
Dose dependent toxicity of PQ

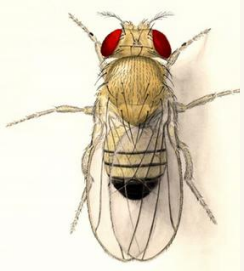


Nicotine

Nicotine + PQ

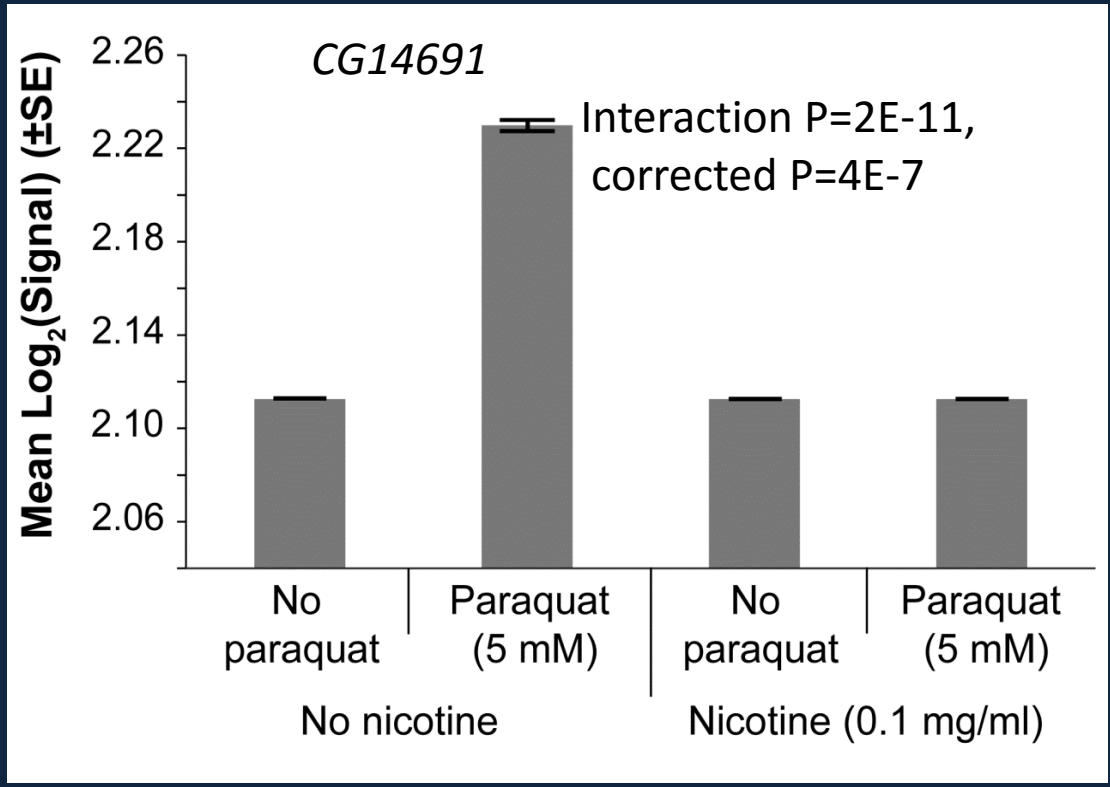
Dose dependent improved survival By nicotine





Genome-wide test of interaction of PQ & nicotine on gene expression in brain

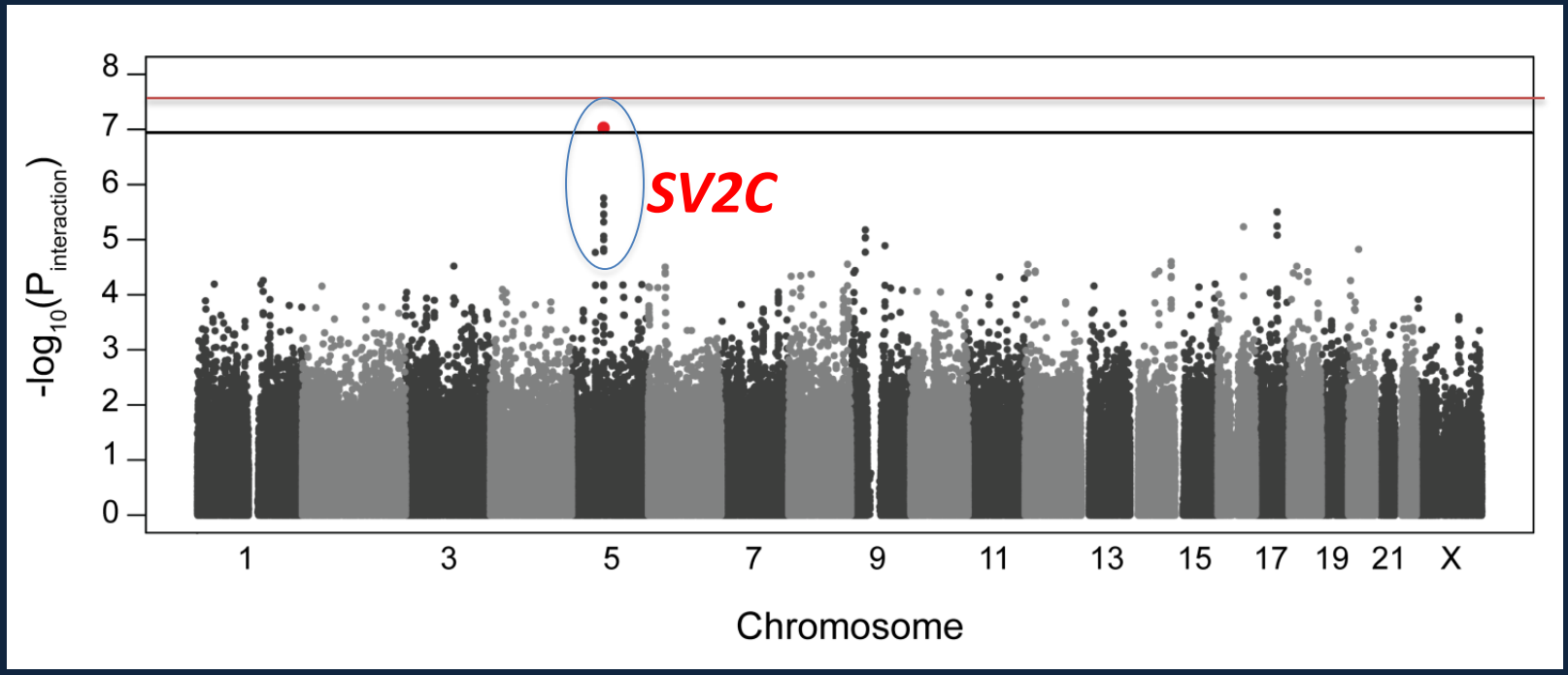
- Flies were treated under 4 conditions:
  1. No drug
  2. PQ
  3. nicotine
  4. PQ and nicotine
- Extracted RNA from heads
- Assessed expression of 18,954 genes
- Genome-wide test of interaction of PQ and nicotine on expression



CG14691 encodes synaptic vesicle protein

Human homologues are *SV2A*/*SV2B*/*SV2C*

GWIS: Identify genes that significantly enhance or diminish the protective effect of smoking on PD in humans



SV2C is densely expressed in dopaminergic cells in substantia nigra
Involved in storage and release of neurotransmitters, dopamine

The variants associated with SV2C expression
mQTL for *SV2C* P=3E-5, *Grundberg Am J Hum Genet 2013*

Association of smoking with PD on average & stratified by genotype

SV2C gene	Genotype Freq	Odds Ratio	Risk reduction By smoking	P
Irrespective of genotype	All subjects	0.81	19% reduction	7E-3

Pharmacogenomics (Epub ahead of print)

Influence of genetic, biological and pharmacological factors on levodopa dose in Parkinson's disease

Aim: Levodopa is first-line treatment of Parkinson's disease motor symptoms but, dose response is highly variable. Therefore, the aim of this study was to determine how much levodopa dose could be explained by biological, pharmacological and genetic factors. Patients & methods: A total of 224 Parkinson's disease patients were genotyped for SV2C and SLC6A3 polymorphisms by allelic discrimination assays. Comedication, demographic and clinical data were also assessed. Results: All variables with $p < 0.20$ were included in a multiple regression analysis for dose prediction. The final model explained 23% of dose variation ($F = 11.54$; $p < 0.000001$). Conclusion: Although a good prediction model was obtained, it still needs to be tested in an independent sample to be validated.

The C allele beneficial in interaction with smoking and here with l-dopa dose

SV2C rs30196	Freq.	L-dopa daily dose
AA	26%	791 ± 333
AC	46%	720 ± 292
CC	28%	639 ± 255

In progress

Pharmacogenomics in treatment trials

SV2C testing in trial of Disease-modifying Potential of Nicotine in Early PD (Wolfgang H. Oertel)

GRIN2A & MAPK10 testing in Clinical trial of Caffeine as Therapeutic Agent in PD (Ronald Postuma)

Prevention

Testing predictive value of genotype in smoking- and caffeine associated reduction in PD incidence in the prospective NIH-AARP Diet and Health Study

ACKNOWLEDGEMENTS

5,000 research volunteers in PD studies of NGRC

The NGRC research team

Jay Nutt, Cyrus Zabetian, Stewart Factor, Erin Hill-Burns et. al.

Honglei Chen, Jeff Vance & Beate Ritz for sharing data

Mel Feany for guidance with fly work

NINDS and MJFF for funding

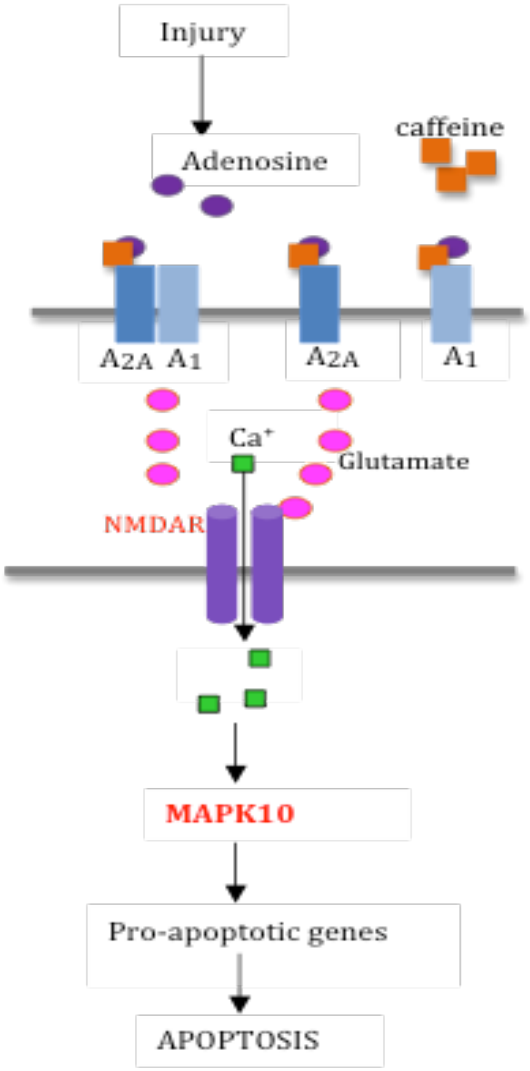
THANK YOU

Relevance to clinical trials

caffeine

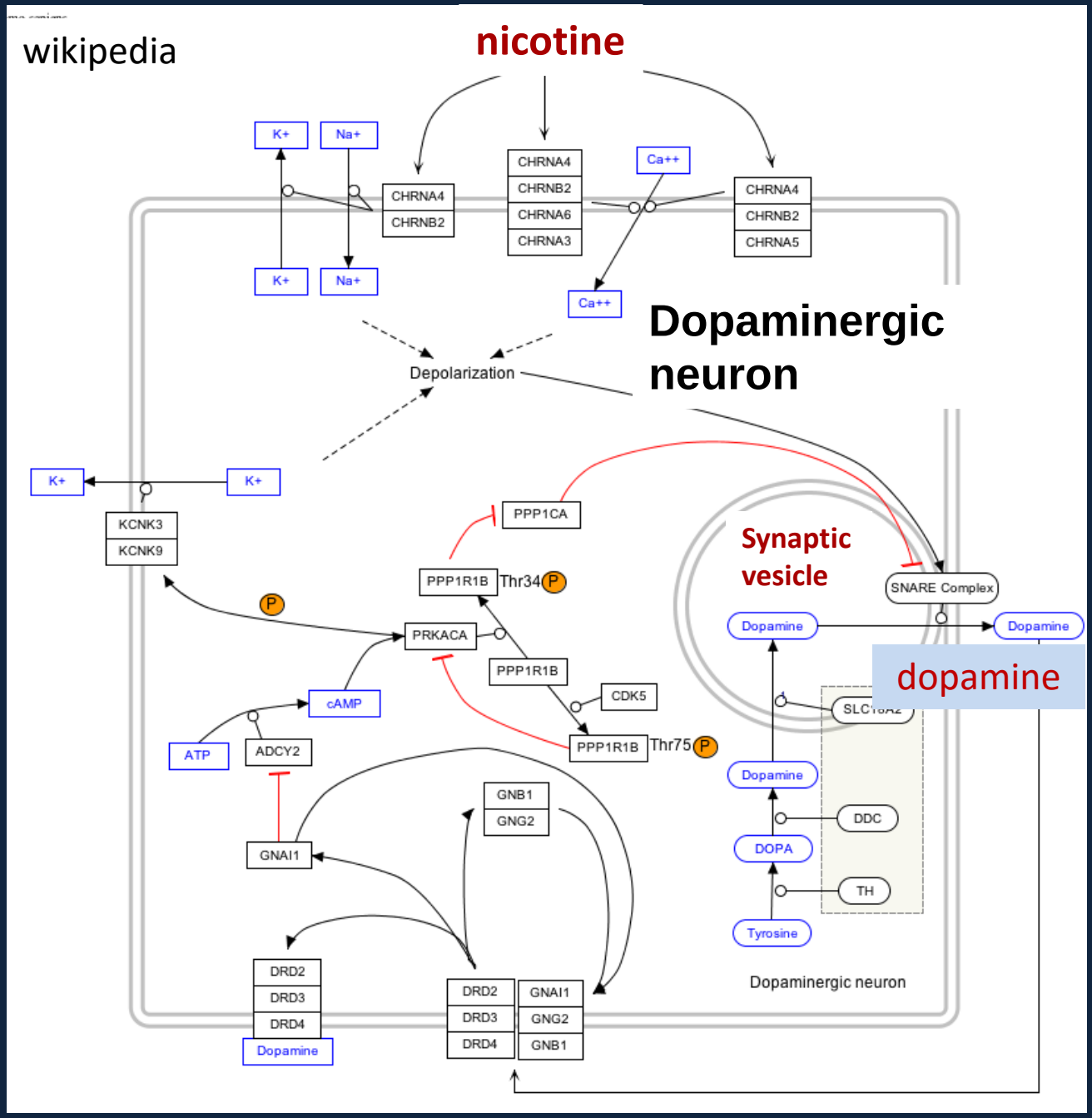
A_{2A} adenosine- & adenosine receptor antagonist

Calcium channel blockers



- Testing predictive value of *GRIN2A* and *MAPK10* in caffeine trial (Ron Postuma)
- Potential to implement in ongoing trials
- Potential of rescuing “failed” trials

wikipedia


nicotine
K+
Na+
CHRNA4
CHRNB2
CHRNA4
CHRNB2
CHRNA6
CHRNA3
Ca++
CHRNA4
CHRNB2
CHRNA5
K+
Na+
Ca++
Dopaminergic neuron
Depolarization
K+
K+
KCNK3
KCNK9
PPP1CA
Synaptic vesicle
SNARE Complex
PPP1R1B
Thr34
P
PRKACA
Dopamine
Dopamine
dopamine
PPP1R1B
CDK5
cAMP
SLC
ATP
ADCY2
PPP1R1B
Thr75
P
Dopamine
GNB1
GNG2
DDC
GNAI1
DOPA
TH
Tyrosine
DRD2
DRD3
DRD4
Dopamine
DRD2
DRD3
DRD4
GNAI1
GNG2
GNB1
Dopaminergic neuron