Genetics Core Update

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For the Genetics Core/Working Groups

ADNI Steering Committee

April 18, 2016

Vancouver BC

INDIANA UNIVERSITY SCHOOL OF MEDICINE

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Outline of Genetics Core update

ADNI-2 progress & use of genetics data

- Available data review
- 32 additional WGS from Carlos Cruchaga
- 10 more GWAS ADNI-2 / ADNI-DoD APOE and GWAS on 160 coming soon
- Methylation coming later this year
- *** Metabolomics update
- ADNI-3 Aims – What's new (Genetics Core proposal)
- Focus on genetic enrichment of clinical trials
- Candidate genes & polygenic scoring
- Incorporating rare variants – as emerge from IGAP, ADSP etc
- Multi-omics and systems biology
- Epigenetics and the methylation study
- 1719 advanced methylation arrays on 649 unique participants
- See email table from Sungeun with demographics
- PBMC collection for iPSC and other purposes
- Explain possible uses and why its important – mention blood vs brain
- So far close correspondence not seen in one report on AD (Yu et al 2016)
- ---- But data from PD and an epilepsy surgery/schizophrenia study are encouraging
- Family history and pedigrees, potential call back
- Future directions

Genetics Core Goals for ADNI-3

- Overall: To identify and validate genetic markers to enhance clinical trial design and drug discovery.
- Aim 1: Continue sample collection, processing, banking, curation and dissemination.
- Aim 2: Continue to provide genome-wide genotyping data to the scientific community.
- Aim 3: Continue to perform and facilitate bioinformatics analyses of ADNI genetics and quantitative phenotype data and test scientific hypotheses related to the goals of ADNI-3.
- Aim 4: Continue to provide organization, collaboration and leadership for genomic studies of quantitative biomarker phenotypes.

Oct. 2015

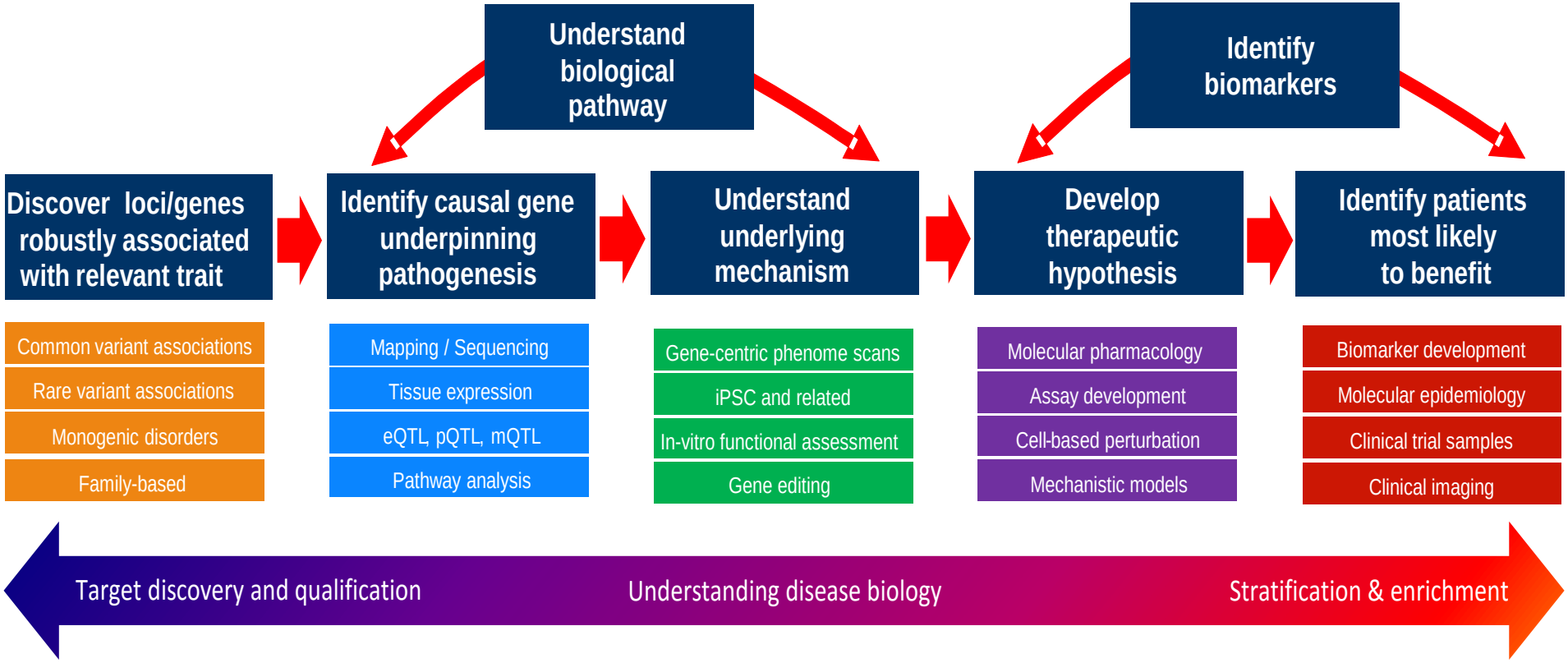
New Aspects

- Aim I: PBMC collection
  - *Enabling iPSC and functional assays for mechanistic and drug development efforts*
- Aim 2: Next generation GWAS & other assays
  - New arrays by the time of enrollment, WGS costs decreasing, additional –omics
- Aim 3: Bioinformatics analyses of quantitative phenotype data & test scientific hypotheses
  - Focus on trial enrichment & systems biology
- Aim 4: Continue to support collaborative research
  - New working groups: systems biology, methylation, etc.
  - With Clinical Core: ascertain more family history

Major themes & hypotheses

- H1: The efficiency of clinical trials can be improved by **enrichment with genetic markers beyond *APOE***, reducing sample size, time to complete trials, and lowering costs;
- H2: **Systems biology** modeling of multi-omics data, yielding polygenic risk scores and gene pathway- and network-based metrics, will prove more powerful than single variants in predicting disease progression and outcomes;
- H3: **Variation in the *MAPT* gene and other pathways will be associated with [18F]AV-1451 tau PET**; and
- H4: Genetic variation influences **proteomics and metabolomics biomarker assays** and controlling for genetic effects will improve the performance of –omics biomarkers in predicting disease progression and outcomes.

Path from genetic signal to targeted therapeutics: key applications to drug discovery and development



Core Report: Alzheimer's & Dementia 11 (2015) 792-814

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

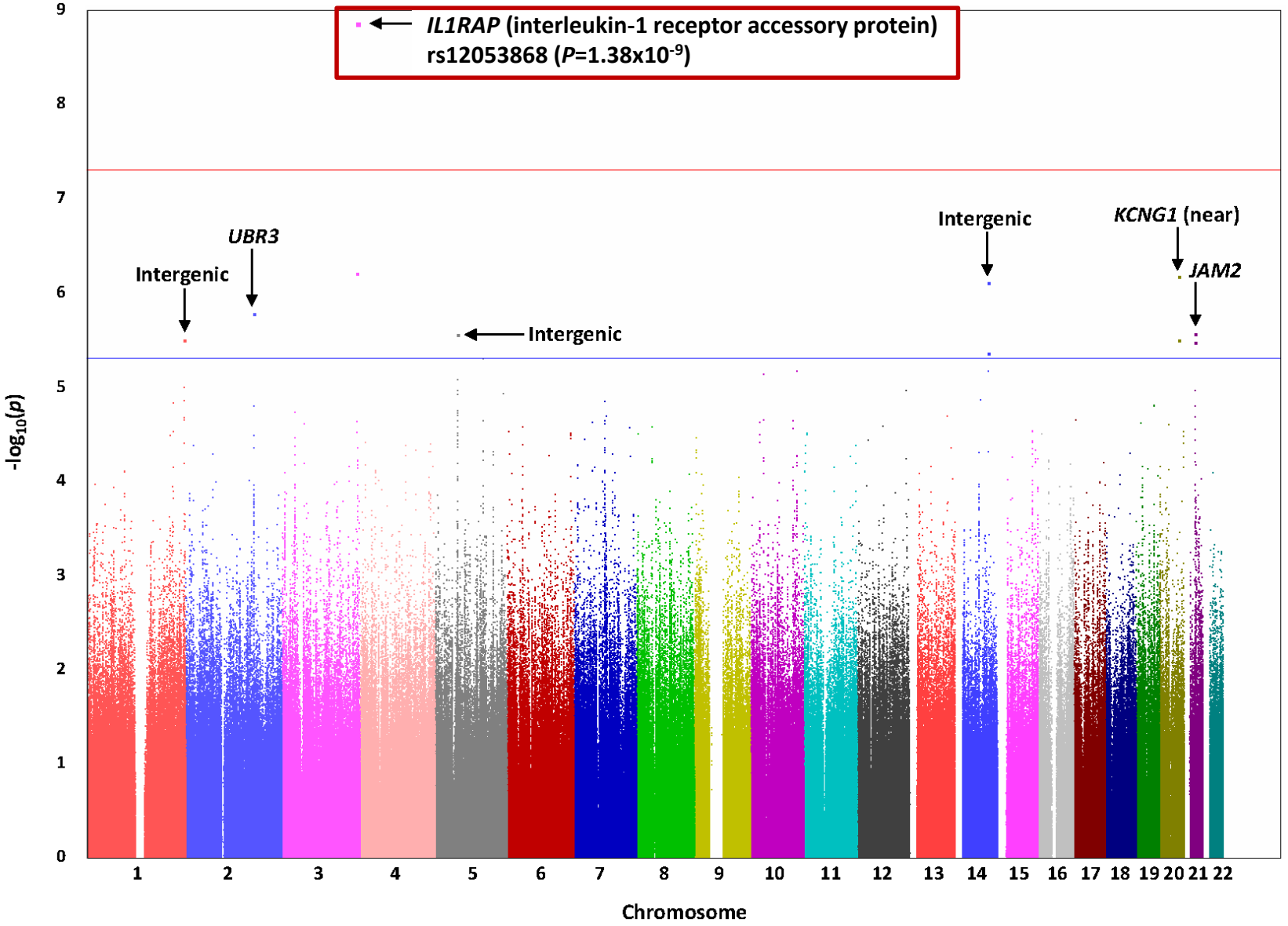
- 1. ***Strategies to decrease heterogeneity*** – Selecting patients with baseline measurements in a narrow range (decreased inter-patient variability) and excluding patients whose disease or symptoms improve spontaneously or whose measurements are highly variable (less intra-patient variability).

- 2. ***Prognostic enrichment strategies*** – choosing patients with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints); increase absolute effect between groups.

- 3. ***Predictive enrichment strategies*** – choosing patients more likely to respond to the drug treatment than other patients with the condition being treated. Such selection can lead to a larger effect size (both absolute and relative) and permit use of a smaller study population.

FDA, 2012

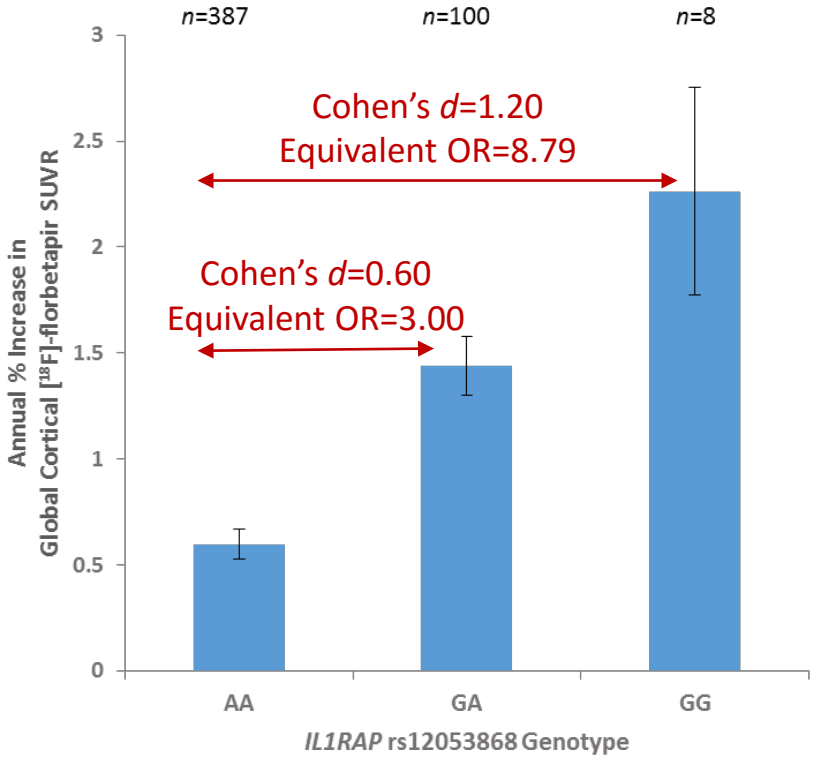
IL1RAP Candidate - Longitudinal Amyloid PET



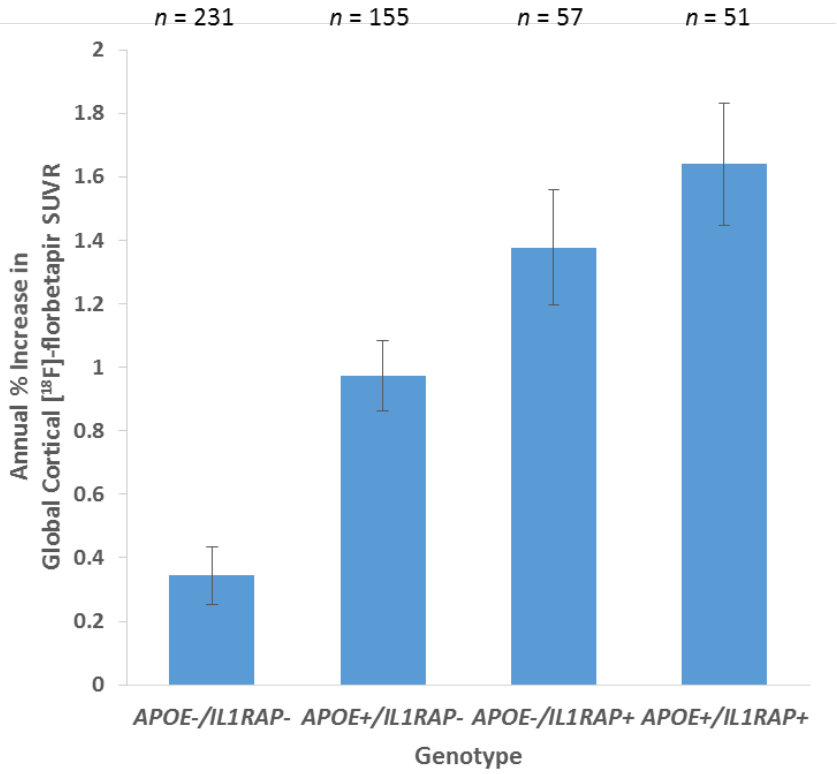
Ramanan et al., *Brain* Oct. 2015

Effect of *IL1RAP* rs12053868

***IL1RAP* rs12053868-G is associated with higher rates of amyloid accumulation**



***IL1RAP* rs12053868-G and *APOE* ε4 exert independent, additive effects**



-*IL1RAP* (7.1%) + *APOE* ε4 (3.4%) explain 10.5% of the phenotypic variance (age and gender explain 0.9%)

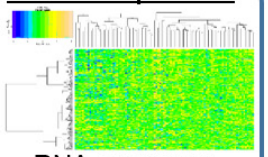
-*IL1RAP* association remains genome-wide significant (P=5.80x10^{-9}) with additional covariates of *APOE* ε4 status, baseline diagnosis, education, baseline amyloid burden and its square, and PCA eigenvectors

Ramanan et al., *Brain* Oct. 2015

Converging –*omics* & Systems Biology

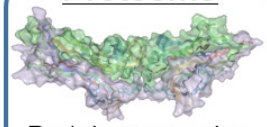
ADNI

Transcriptome**



RNA sequence and expression

Proteome*

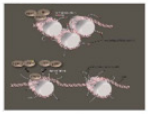


Protein expression, structure, and function

Metabolome*,†

Metabolite / enzyme profile

Epigenome†



DNA methylation and histone modification

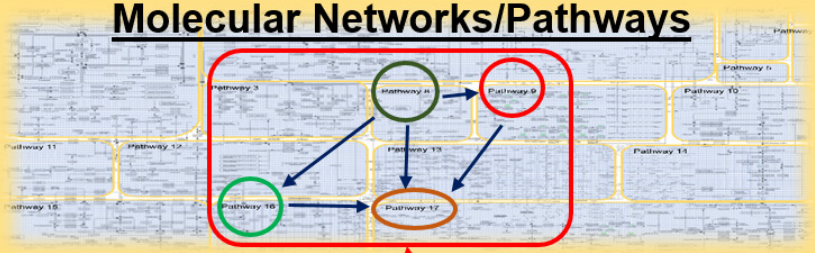
Genome*,**

DNA sequence and variation

Exposome*,**

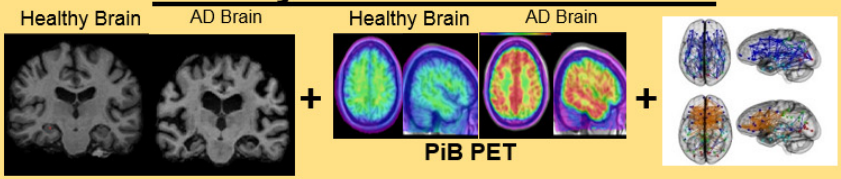
Environment, life style, diet, drug, age

Molecular Networks/Pathways



Perturbed biochemical networks/pathways

Healthy vs Disordered Brains‡

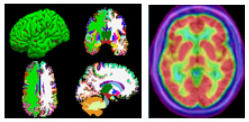


Systems Biology Approach

Interactome†

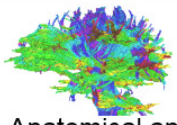
Interaction (e.g., gene-gene, gene-protein)

Brain structure & function*,**



Structural and functional brain imaging

Connectome**



Anatomical and functional brain connectivity

*: ADNI-1
**: ADNI-GO/2

Image sources
†: upload.wikimedia.org.
‡: www.uphs.upenn.edu

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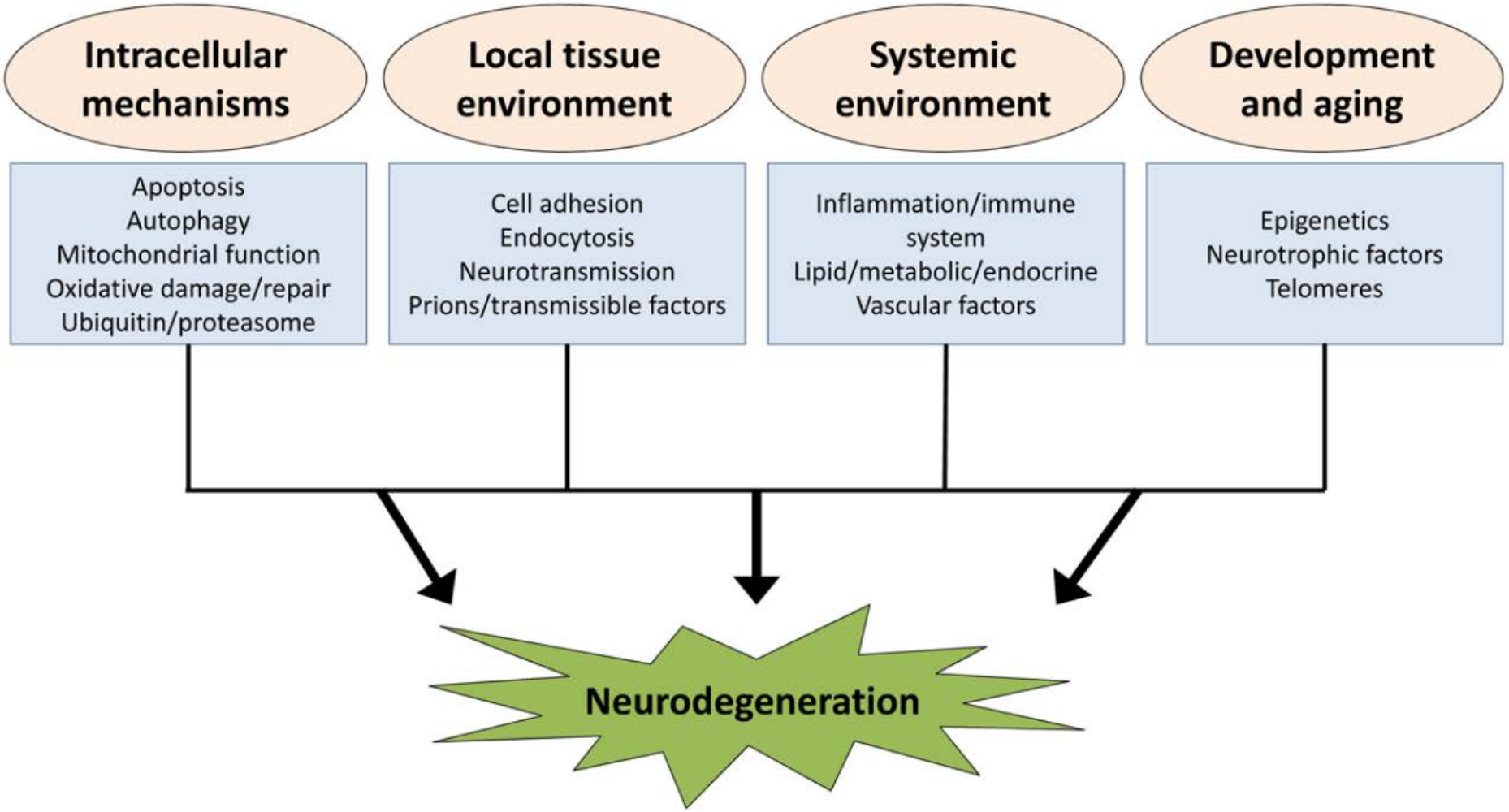
Genetics Core – Saykin et al Alzheimer's & Dementia 11 (2015) 792-814

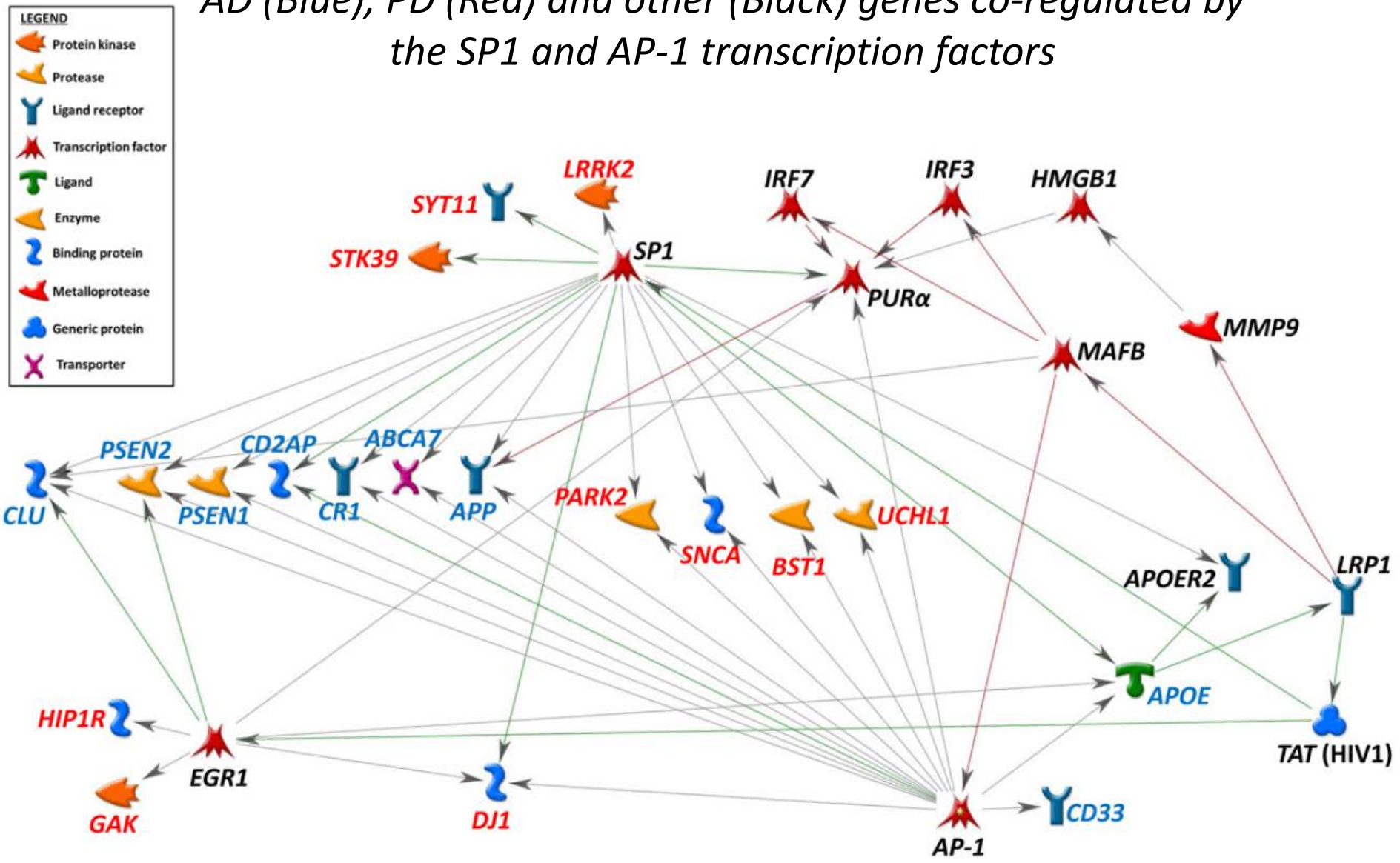
Systems Biology Approach
Pathways to Neurodegeneration



Ramanan & Saykin, Am J Neurodegener Dis 2013;2(3):145-175

Neurodegeneration Pathways in AD & PD

AD (Blue), PD (Red) and other (Black) genes co-regulated by the SP1 and AP-1 transcription factors



Ramanan & Saykin, Am J Neurodegener Dis 2013;2(3):145-175

ADNI Methylation Study Update

Genetics Core Methylation Working Group

***Wade Davis**, Aparna Vasanthakumar, Jeffrey Waring (AbbVie)*
Charles O'Donnell, Marc Muskavitch (Biogen)
Qingqin Li (J&J)
Nadeem Sarwar (Eisai)
***Sungeun Kim**, Kwangsik Nho, Liana Apostolova, Andrew Saykin (Indiana University)*
with help from the PPSB Chairs & FNIH

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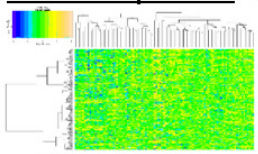

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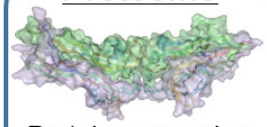

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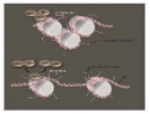

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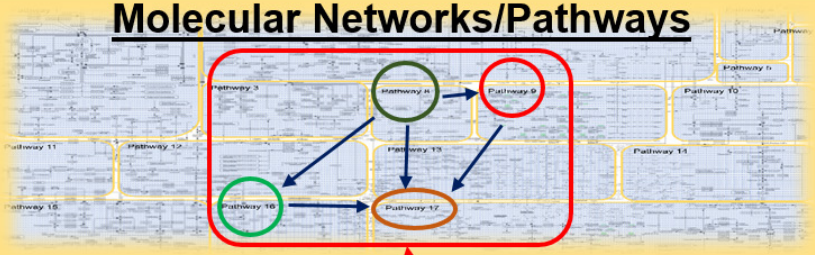

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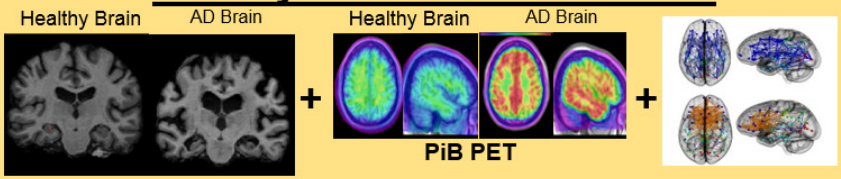

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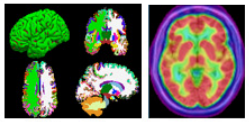

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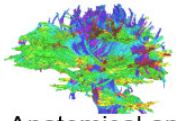

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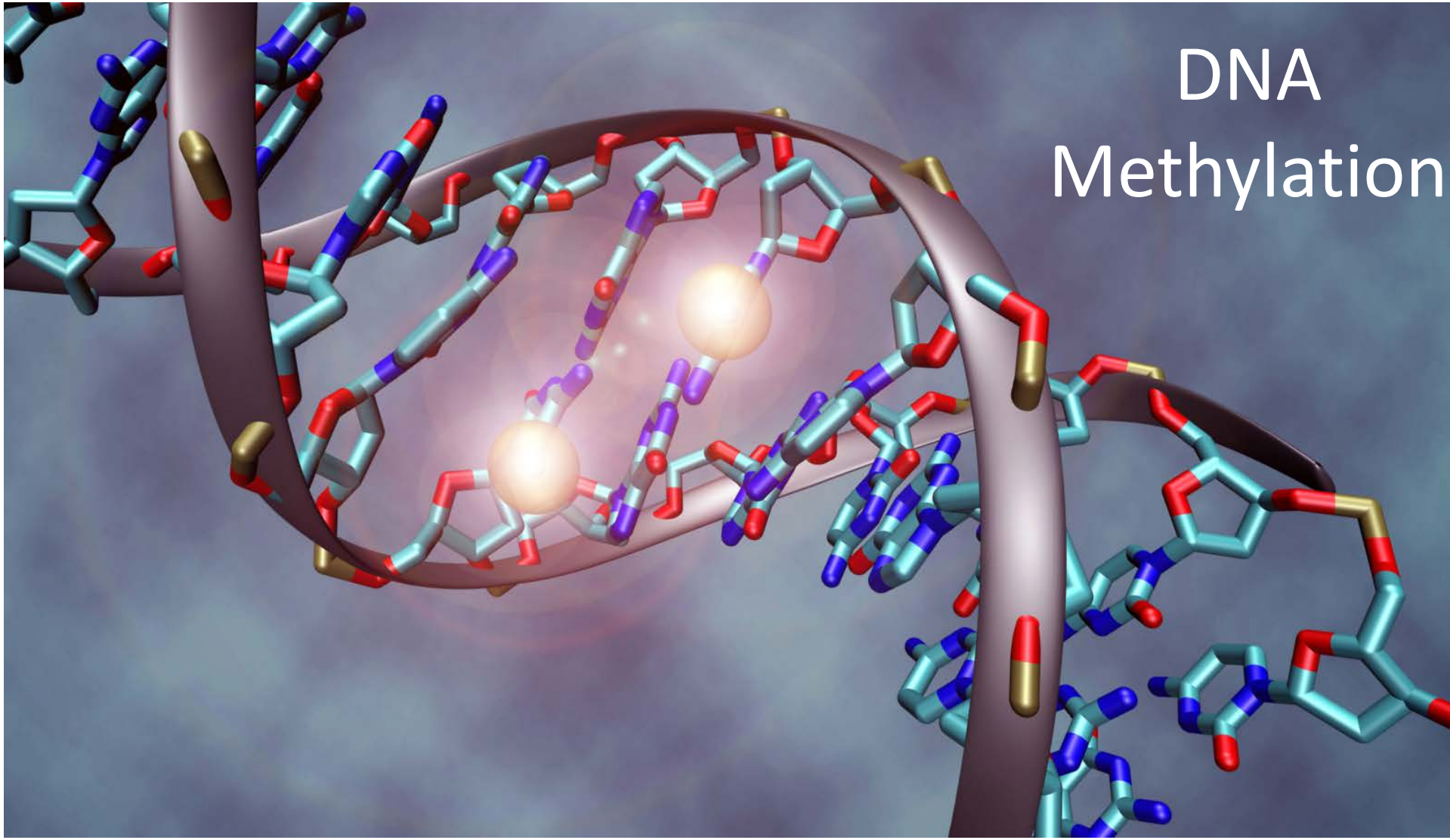
Epigenetics

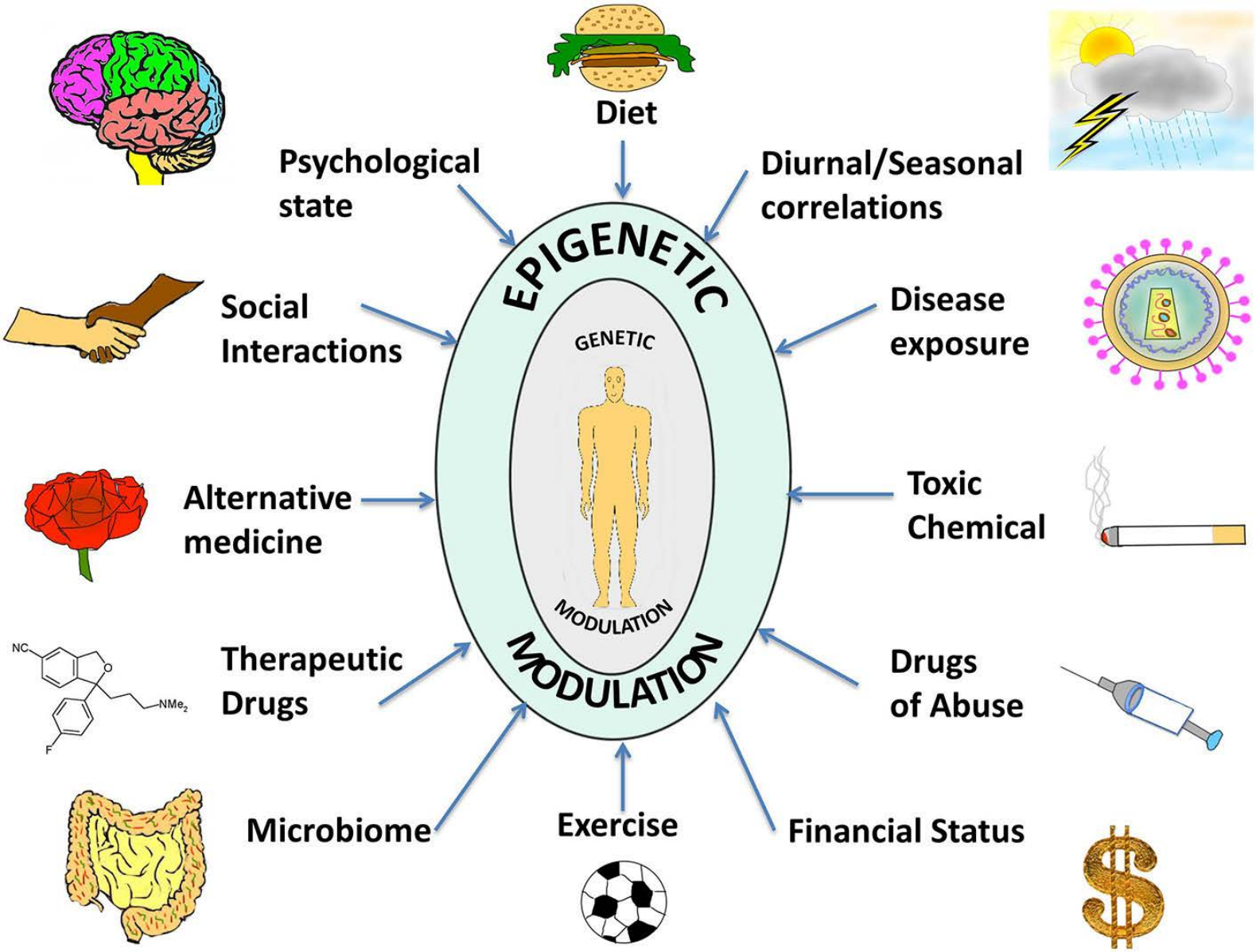
- MZ twins discordant for heritable diseases like AD
- Epigenetics includes heritable changes in gene expression caused by environmental and G x E factors rather than changes in DNA sequence
- Functionally relevant changes in phenotype without a change in genotype
- Consensus definition of *epigenetic trait* (Cold Spring Harbor 2008): "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence"
- Major roles: differentiation, development and disease

http://www.whatisepigenetics.com/
https://en.wikipedia.org/wiki/Epigenetics



DNA molecule that is methylated on both strands on the center cytosine. The crystal structure of a short DNA helix with sequence "accgcCGgcgcc", which is methylated on both strands at the center cytosine. Christoph Bock (Max Planck Institute for Informatics)

Sources of Epigenetic Changes



Kanherkar et al. (2014), Frontiers in Cell Dev Biol

Methylation Sample Characteristics

Study Design	Age (years; Mean, SD)	Male (N, %)	APOE ε4 positive (N,%)
Cross-sectional (All Individuals)*			
Cognitively Nornal (n=221)	76.27 (6.63)	111 (50%)	57 (26%)
Mild Cognitive Impairment (n=335)	72.58 (7.82)	188 (56%)	153 (46%)
Alzheimer's Disease (n=93)	77.19 (7.69)	60 (65%)	63 (68%)
Longitudinal design*			
Cognitively Nornal (n=195)	75.96 (6.54)	97 (50%)	50 (26%)
Mild Cognitive Impairment (n=283)	72.23 (7.73)	157 (55%)	117 (41%)
Alzheimer's Disease (n=93)	77.19 (7.69)	60 (65%)	63 (68%)
Pre-/post-conversion			
MCI to AD (n=110)	74.5 (7.89)	62 (56%)	71 (65%)
NL to AD (n=10)	78.8 (4.05)	7 (70%)	4 (40%)
NL to MCI (n=42)	78.71 (6.9)	21 (50%)	13 (31%)

* 80 cross-sectional samples were included

Selection criteria: WGS & GWAS, RNA profiling, $\geq$ 2 year clinical follow-up, MRI and PET imaging data; converters, longitudinal DNA availability (except 80 cross sectional)

Updated 4/11/2016, Sungeun Kim

Future Directions

- These will require additional support before they can be fully realized, but within available resources, work will continue to develop these important areas:
- A) Work with other parties to find resources for WGS, transcriptome and epigenetic profiling of ADNI's longitudinal DNA and RNA samples;
- B) Provide a forum to work on issues of return of research results to participants;
- C) Work with the Clinical Core to develop new call back and family studies of ADNI participants;
- D) Facilitate replication studies with other cohorts/data sets;
- E) Collaborate with academic and industry partners on *molecular and functional validation* follow-up studies; and
- F) Collaborate with the Neuropathology Core to relate differential pathological features to genetic variation.

Genetics Core/Working Groups

Indiana University

- Imaging Genomics Lab
  - Andrew Saykin (Leader)
  - **Li Shen (co-Leader)**
  - Liana Apostolova
  - Sungeun Kim
  - Kwangsik Nho
  - Shannon Risacher
  - Vijay Ramanan
- National Cell Repository for AD
  - **Tatiana Foroud (co-Leader)**
  - Kelley Faber

PPSB Working Groups

- **Nadeem Sarwar***
- PPSB Chairs
- FNIH Team

* Genetics Core Liaison

- Core Collaborators/Consultants
  - **Steven Potkin (UCI; co-Leader)**
  - **Robert Green (BWH)**
  - **Paul Thompson (USC)**
- Other Collaborators – RNA and NGS Projects:
  - Keoni Kauwe (BYU)
  - Yunlong Liu (Indiana)
  - Fabio Macciardi (UC Irvine)

2015