NIH Common Fund Epigenomics Program

John Satterlee Ph.D.
Epigenomics Program Co-coordinator
National Institute on Drug Abuse/NIH

NIH Council of Councils
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NIH Epigenomics Working Group

Co-Chairs: Nora Volkow (NIDA), Linda Birnbaum (NIEHS), James Battey (NIDCD)

Co-Coordinators: John Satterlee (NIDA), Pat Mastin (NIEHS)

Christine Colvis	NCATS
Carol Pontzer	NCCAM
Grace Ault	NCI
Jennifer Couch	NCI
Paul Okano	NCI
Richard Piekarz	NCI
Sharon Ross	NCI
Mukesh Verma	NCI
Hemin Chin	NEI
Elise Feingold	NHGRI
Mike Pazin	NHGRI
Weiniu Gan	NHLBI
Susan Old	NHLBI
Pothur Srinivas	NHLBI
Anna McCormick	NIA
Suzana Petanceska	NIA
Conrad Malia	NIAID
Nasrin Nabavi	NIAID
Ashley Xia	NIAID
William Sharrock	NIAMS
Guoying Liu	NIBIB
Roderic Pettigrew	NIBIB
Carol Kasten-Sportes	NICHD
Lisa Freund	NICHD
Susan Taymans	NICHD
Mark Caulder	NIDA
Genevieve deAlmeida-Morris	NIDA
Donna Jones	NIDA
Jonathan Pollock	NIDA
Dena Procaccini	NIDA
Joni Rutter	NIDA
David Shurtleff	NIDA
Bracie Watson	NIDCD
Lillian Shum	NIDCR
Kristin Abraham	NIDDK
Olivier Blondel	NIDDK
Jessica Faupel-Badger	NIDDK
Philip Smith	NIDDK
Julie Wallace	NIDDK
Lisa Chadwick	NIEHS
Gwen Collman	NIEHS
Christie Drew	NIEHS
Astrid Haugen	NIEHS
Jerry Heindel	NIEHS
Laurie Johnson	NIEHS
Kimberly McAllister	NIEHS
Srikanth Nadadur	NIEHS
Kristi Pettibone	NIEHS
Fred Tyson	NIEHS
Leroy Worth	NIEHS
Anthony Carter	NIGMS
Andrea Beckel-Mitchener	NIMH
Michelle Freund	NIMH
Thomas Lehner	NIMH
Roger Little	NIMH
Aleksandra Vicentic	NIMH
Robert Riddle	NINDS
Randall Stewart	NINDS
Stephanie Courchesne	OSC
Patricia Labosky	OSC
Johanna Dwyer	ODS
Deborah Olster	OBSSR

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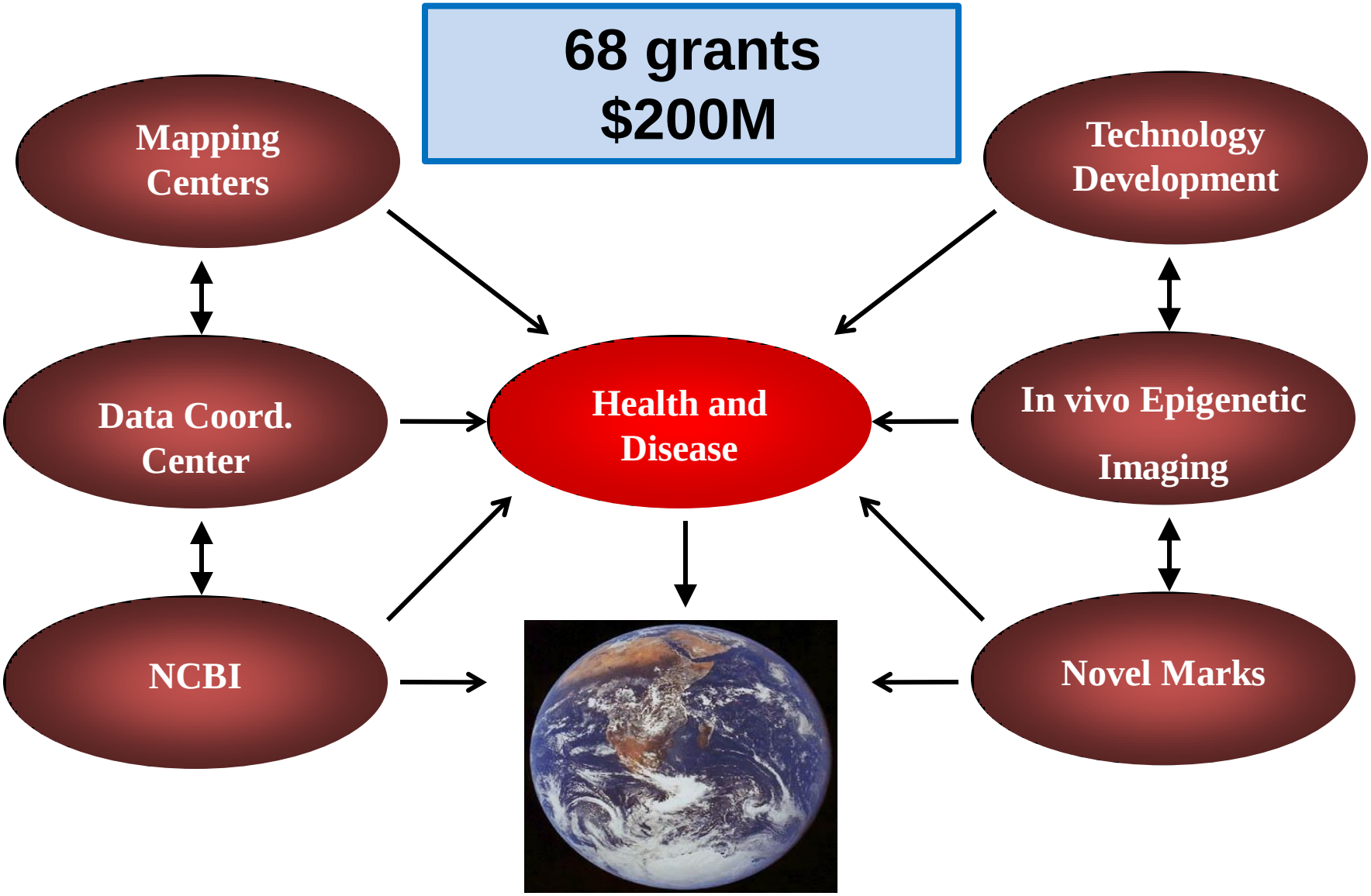
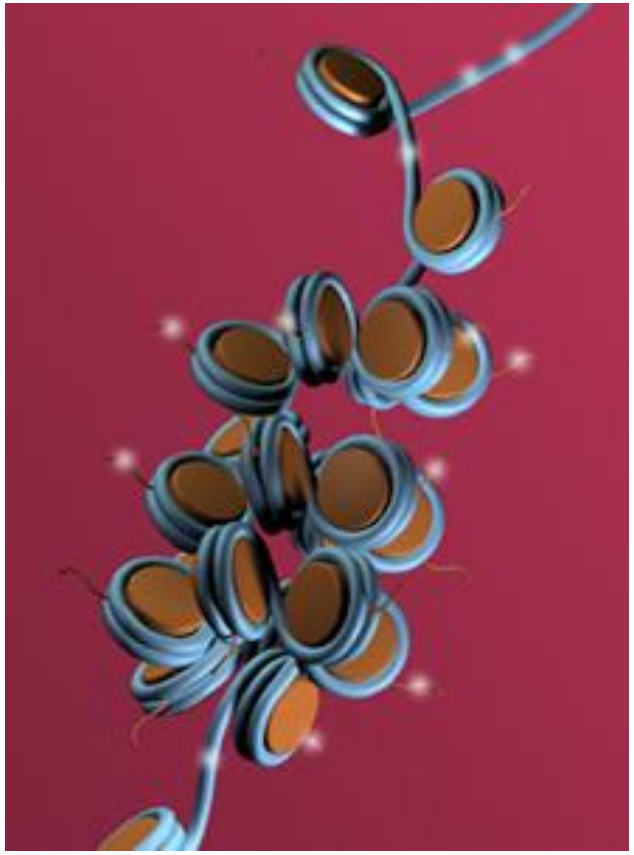


Discovery of Novel Epigenetic Marks

GOAL: **Discover potential novel epigenetic marks**

- **67 new histone modifications**
  Lysine crotonylation
  (Cell, Zhao)

- **Lysine proprionylation**
- **Lysine butyrylation**
- **PolyADP ribosylation**
- **Histone 3 Arginine 2 dimethylation**

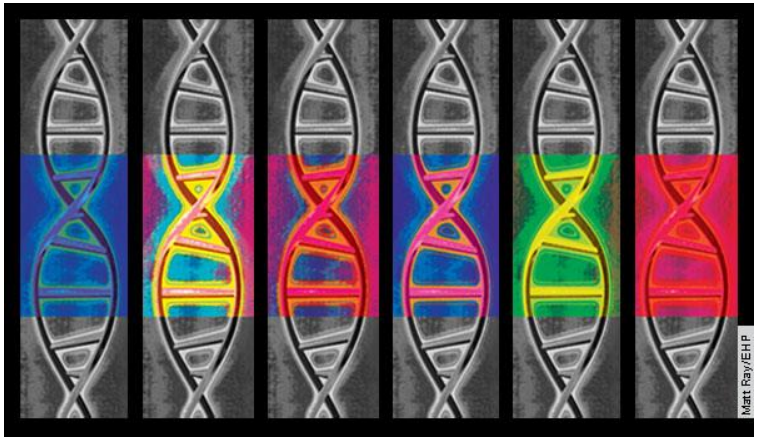


Broad Institute

Epigenomics of Human Health and Disease

GOAL: **Transform our understanding of the epigenomic basis of disease**

- **2009** **CF/IC split**
- **2011** **IC only**



Total: 33 R01s, 12 ICs

Alzheimer's
Cardiovascular
Environmental toxins
Asthma
Cancer
Substance abuse
Psychiatric
Autism
Insulin resistance
Autoimmune
Glaucoma

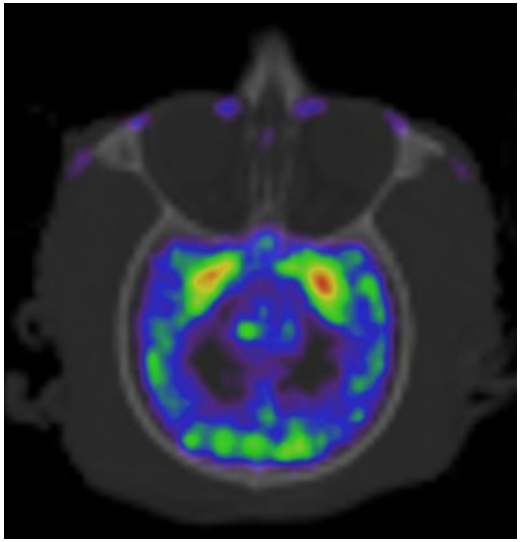
Altered epigenetic states associated with:

- **Gestational age at birth** ***(Feinberg/Fallin)***
- **Hepatocellular carcinoma** ***(Meltzer)***
- **Breast cancer** ***(Huang)***
- **Schizophrenia and bipolar disorder** ***(Mill)***
- **Alzheimer's disease** ***(De Jager/Bennett)***

Technology Development in Epigenetics

GOAL: **Develop revolutionary technologies with the potential to significantly change epigenetics research.**

- **2008 General epigenetic technologies**
- **2011 Epigenetic imaging**
- **2013 Epigenetic manipulation (new)**



Gelovani lab

- **Histone dynamics *(Science, Henikoff)***
- **Single molecule epigenomics *(PNAS, Soloway)***
- **SXRT of epigenomic organization *(Cell, Larabell/Lomvardas)***
- **PET imaging of histone deacetylases *(Neuroimage, Gelovani)***

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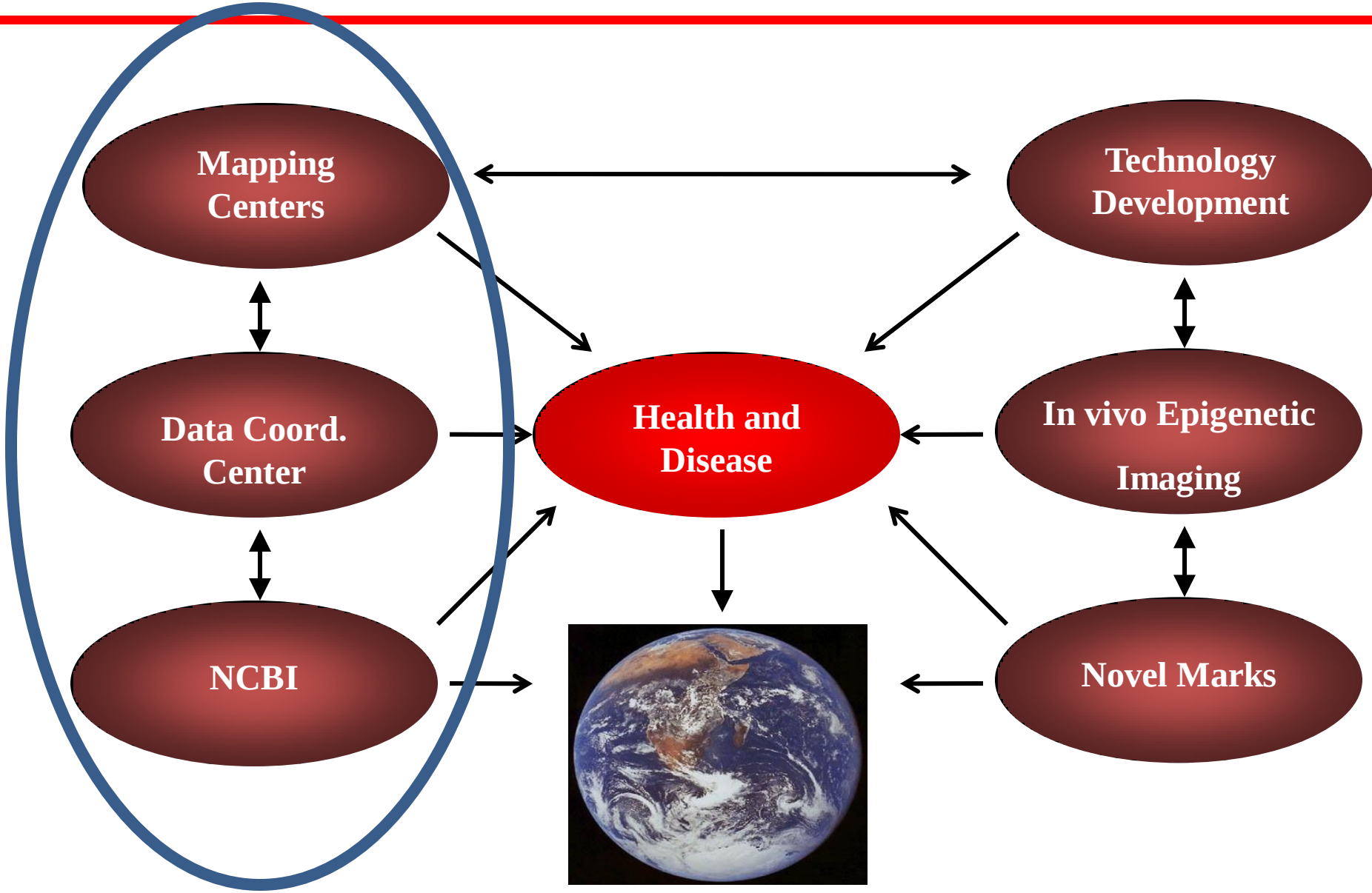
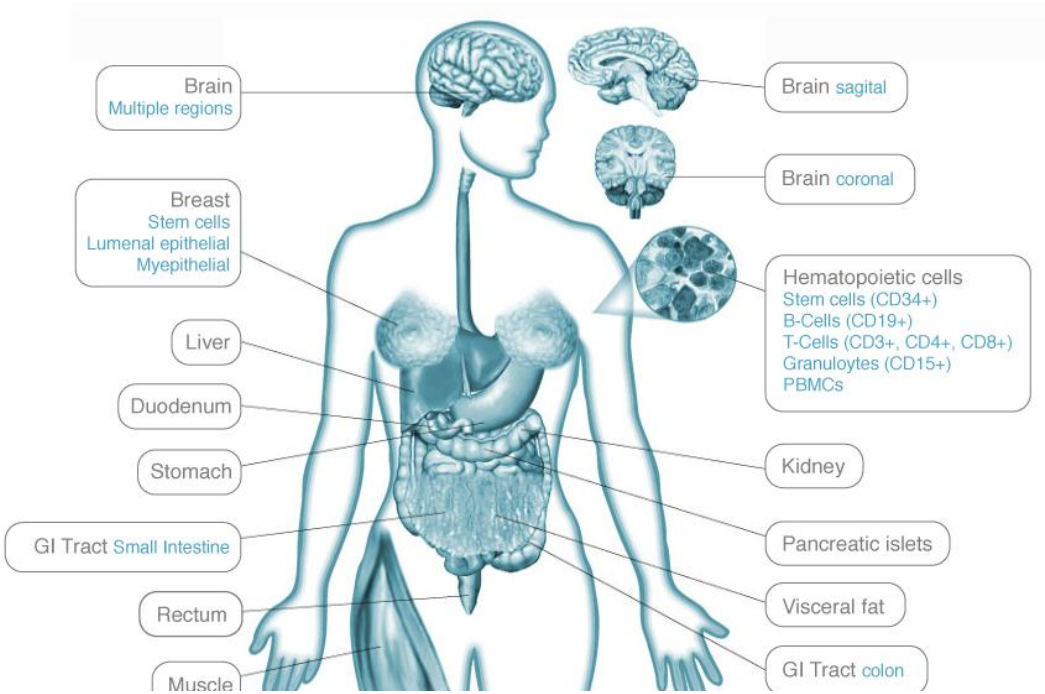


Reference Epigenome Mapping Centers

GOAL: **Generate comprehensive epigenomic maps for "normal" human cells and tissues**



- **First human methylomes (*Nature* 2009)**
- **42 methylomes completed**
- **79 comprehensive epigenome datasets**
- **Data publically accessible: http://www.roadmapepigenomics.org/**

Program Integration and Outreach

Yearly "Investigators" Meetings:

Next: Oct 20-21, 2013 Boston, MA

Workshops:

ENCODE/Epigenomics Programs co-sponsored tutorial on using these datasets (ASHG)

International Efforts:

Members:
CF Epigenomics,
European Union,
Canada, Germany,
Japan, Italy, South Korea

Future: Transition and Translation

Transition from Common Fund to NIH ICs

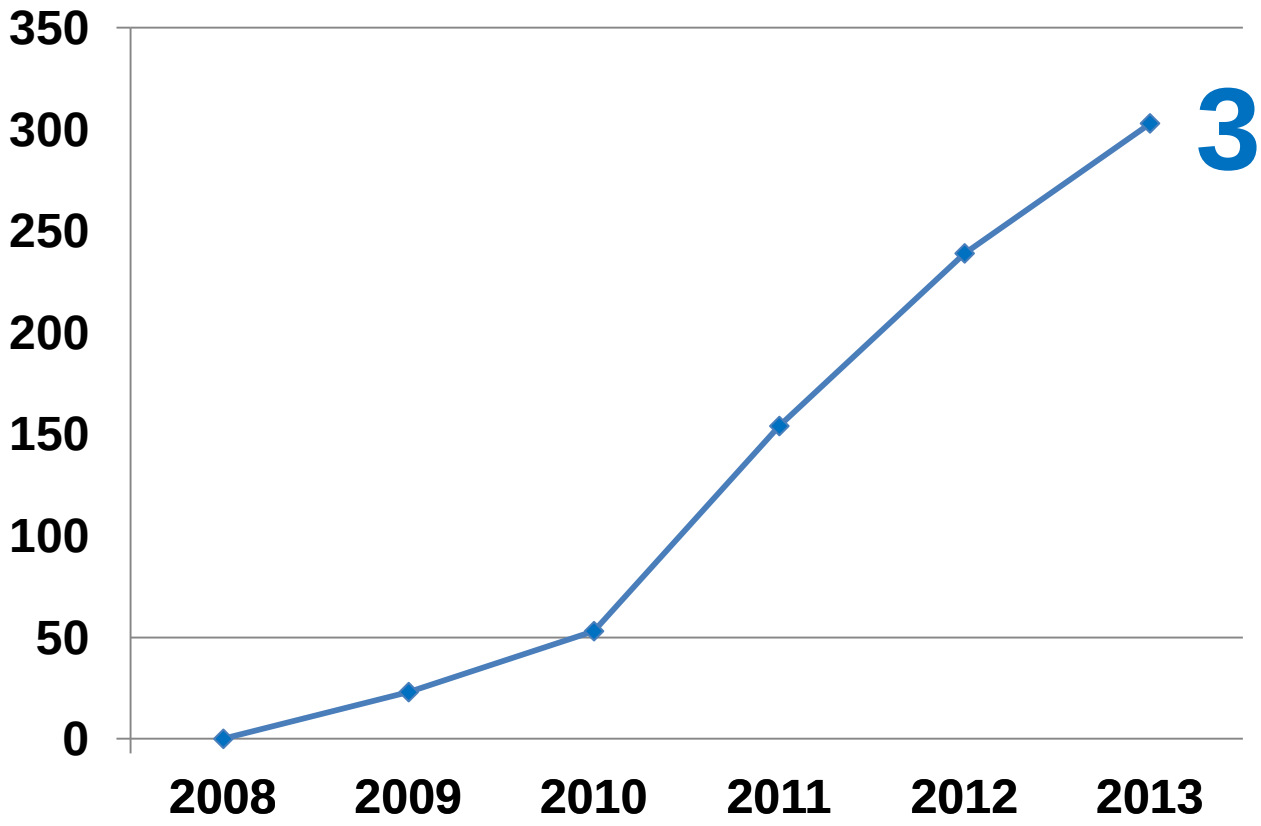
NICHD 2009	Epigenetic Processes in Development (R21)
NINR 2010	Epigenetic Factors Associated with Complications of Chronic Disorders (R01)
NIDA 2010	Exploring Epigenomic Processes and Non-Coding RNAs in HIV/AIDS (R01 and R21)
NIMH 2011	Epigenomic Modifications in Neurodevelopment (R01)
NIEHS 2012	Chromatin Structure, Genomics, and Transcriptional Responses to the Environment (R01)
NIDA 2012	Drugs of Abuse and Transgenerational Phenotypes (R01)
NIEHS 2012	Transgenerational Inheritance in Mammals After Environmental Exposure (R01)
NIAAA 2012	Transgenerational Effects of Alcohol (R01 and R21)
NIDCR 2013	Epigenomics of Virus-Associated Oral Diseases (R01)

The Potential for Translational Epigenomics

Workshop 2011: 'From Epigenomic Discovery to Improvements in Human Health"

Diagnostics, Therapeutics, Prevention for IC-specific Diseases

Epigenomics Program Publications to Date



Nature 10
Cell 13
Science 2
Nat. Biotech. 6

Using Epigenomics Data to Interpret GWAS Hits

Systematic Localization of Common Disease-Associated Variation in Regulatory DNA

Matthew T. Maurano,[1*] Richard Humbert,[1*] Eric Rynes,[1*] Robert E. Thurman,[1] Eric Haugen,[1] Hao Wang,[1] Alex P. Reynolds,[1] Richard Sandstrom,[1] Hongzhu Qu,[1,2] Jennifer Brody,[3] Anthony Shafer,[1] Fidencio Neri,[1] Kristen Lee,[1] Tanya Kutyavin,[1] Sandra Stehling-Sun,[1] Audra K. Johnson,[1] Theresa K. Canfield,[1] Erika Giste,[1] Morgan Diegel,[1] Daniel Bates,[1] R. Scott Hansen,[4] Shane Neph,[1] Peter J. Sabo,[1] Shelly Heimfeld,[5] Antony Raubitschek,[6] Steven Ziegler,[6] [illegible] Cotsapas,[7,8] Nona [illegible]dehnia,[3,9] Ian Glass,[10] Shamil R. Sunyaev,[11] Rajinder Kaul,[4] John A. Stamatoyannopoulos[1,12]†

Genome-wide association studies have identified many noncoding variants associated with common diseases and traits. We show that these variants are concentrated in regulatory DNA marked by deoxyribonuclease I (DNase I) hypersensitive sites (DHSs). Eighty-eight percent of such DHSs are active during fetal development and are enriched in variants associated with gestational exposure–related phenotypes. We identified distant gene targets for hundreds of variant-containing DHSs that may explain phenotype associations. Disease-associated variants systematically perturb transcription factor recognition sequences, frequently alter allelic chromatin states, and form regulatory networks. We also demonstrated tissue-selective enrichment of more weakly disease-associated variants within DHSs and the de novo identification of pathogenic cell types for Crohn's disease, multiple sclerosis, and an electrocardiogram trait, without prior knowledge of physiological mechanisms. Our results suggest pervasive involvement of regulatory DNA variation in common human disease and provide pathogenic insights into diverse disorders.

nome. In total, we identified 3,899,693 distinct DHS positions along the genome (collectively spanning 42.2%), each of which was detected in one or more cell or tissue types (median = 5).

Disease- and trait-associated variants are concentrated in regulatory DNA. We examined the distribution of 5654 noncoding genome-wide significant associations [5134 unique single-nucleotide polymorphisms (SNPs); fig. S1 and table S2] for 207 diseases and 447 quantitative traits (*2*) with the deep genome-scale maps of regulatory DNA marked by DHSs. This revealed a collective 40% enrichment of GWAS SNPs in DHSs (fig. S1C, $P < 10^{-55}$, binomial, compared to the distribution of HapMap SNPs). Fully 76.6% of all noncoding GWAS SNPs either lie within a DHS (57.1%, 2931 SNPs) or are in complete linkage disequilibrium (LD) with SNPs in a nearby DHS (19.5%, 999 SNPs) (Fig. 1A) (*12*). To confirm this enrichment, we sampled variants from the 1000 Genomes Project (*13*) with the same genomic feature localization (intronic versus intergenic), distance from the nearest transcriptional start site, and allele frequency in individuals of European ancestry. We confirmed significant enrichment both for SNPs within DHSs ($P < 10^{-59}$, simulation) and also including variants in complete LD ($r^2 = 1$) with SNPs in DHSs ($P < 10^{-37}$, simulation) (fig. S2).

In total, 47.5% of GWAS SNPs fall within

Science, 2012, 489:83-90