Lucile Packard Children's Hospital AT STANFORD

Data-driven Systems and Personalized Medicine

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Department of Medicine, and, by courtesy,
Computer Science

Center for Pediatric Bioinformatics, LPCH

Stanford University

Butte Lab
Systems Medicine • Stanford Pediatrics • Packard Children's Hospital

Disclosures

- Scientific founder and advisory board membership
  - Genstruct
  - NuMedii
  - Personalis
- Past or present consultancy
  - Lilly
  - NuMedii
  - Johnson and Johnson
  - Genstruct
  - Tercica
  - Ansh Labs
  - Prevendia
- Honoraria
  - Lilly
  - Siemens

Total 800,000 microarrays available

Doubles every two years

Butte AJ. Translational Bioinformatics: coming of age. *JAMIA*, 2008.

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Home » Pharmacology

Bone Models

Bone Metastases
Osteoarthritis
Osteoporosis

Cardiovascular Models

Atrial Arrhythmias
Coronary Artery Disease
Hypertension
Ischemia
Myocardial Infarction
Restenosis
Ventricular Tachycardia

Dermatology Models

Acne
Atopic Dermatitis
Hair Growth
Lupus
Psoriasis
Rosacea
Skin Graft
Wound Healing

Diabetes Models

BB/W Rats
Food Intake
Goto-Kakizaki Rats
Non Obese Diabetic Mice
Obese Mice
Primate Diabetes
Streptozotocin Mice
Streptozotocin Rats
More...

Genitourinary Models

Chronic Kidney Disease
Cystometry
Endometriosis
IGA Glomerulonephritis
Interstitial Cystitis
Spinalized Rats

In Vitro Models

In Vitro Bone Models
In Vitro CVD Models
In Vitro Diabetes Models
In Vitro Eye Models
In Vitro Oncology Models
In Vitro Skin Models

In Vivo Technologies

Cognition
EEG
Electrophysiology
Imaging
Microdialysis

Infectious Disease

Bacterial Infection
Dengue Virus
Hepatitis C Virus
Influenza
LCMV Mouse
Malaria

Inflammation Models

Arthritis
Delayed Type Hypersens
Edema
Hemophilia
Irritable Bowel Disease
Irritant
LPS Acute Response
Mucositis
More...

Neurological Models

Alzheimer's Disease
Anxiety
Behavioral Tests
Cerebral Palsy
Circadian Profiling
Depression
Epilepsy
Olfactory Testing
More...

Oncology Models

Angiogenesis
Cachexia

Ophthalmic Models

Cataract
Corneal Dystrophy

Otology Models

Hearing Loss
Meniere's Disease

Pain Models

General Pain
Inflammatory Pain

Respiratory Models

Ascaris Lung Allergy
Cough

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Home » Pharmacology » Diabetes and Obesity » Obese Mice

ob/ob Diabetes Model - 16 Mice

Service Description

Provider: Links Biosciences is a US company with laboratories in Hangzhou, China. The laboratory has been offering exploratory (non-GLP) pharmacology services to US and Chinese biopharma since 2004.

Background: The obese mutant mouse model was first reported by Ingalls A *et al* from the Jackson Laboratory in 1951 (Obese, a New Mutation in the House Mouse [164 KB]). The obese mouse resulted from a spontaneous mutation in a gene that was named *ob* in the V stock. Mice homozygous for the obese spontaneous mutation, (Lep^ob^; commonly referred to as *ob* or *ob/ob*), are first recognizable at about 4 weeks of age. Homozygous mutant mice gain weight rapidly and may reach three times the weight of wild-type controls. In addition to obesity, mutant mice exhibit hyperphagia, a diabetes-like syndrome of hyperglycemia, glucose intolerance, elevated plasma insulin, subfertility, impaired wound healing, and an increase in hormone production from both pituitary and adrenal glands. Friedman J *et al* reported leptin in 1994, and demonstrated that leptin, the product of the *ob* gene, was produced in white adipose tissue and served as the peripheral signal to the central nervous system of nutritional status.

Service Details: This service offers a 28 day db/db mouse model of T2DM and obesity. Customer has various options that are conveyed to Links Biosciences using a Service Order Form. Customer assigns up to 16 mice to

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Home » Pharmacology » Diabetes and Obesity » Obese Mice

ob/ob Diabetes Model - 16 Mice

$9,000.00 USD
per service

9 week
turn around time

Provided By
Links Biosciences

Request Info

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Validation methods are increasingly commoditized

Scroll down to browse a list of available research models for **Type I and Type II diabetes, hyperglycemia, insulin resistance, diet-induced obesity and related diseases**. Use the filters on the left to refine the list and then click on any listing to view technical information or to ask a question.

Click on the Vendors tab to view a complete list of CROs that offer diabetes and obesity pharmacology models.

VIEW SERVICES | VIEW VENDORS | 133 results | get help

Search Filters

Diabetes and Obesity

- BB/W Rats
- Food Intake
- Goto-Kakizaki Rats
- Non Obese Diabetic Mice
- Obese Mice
- Obese Primates
- Primate Diabetes
- Streptozotocin Mice
- Streptozotocin Rats
- db/db Diabetic Mice
- fa/fa Zucker Diabetic Rats

Certifications help

- GLP (48)
- AAALAC (28)
- GMP (20)
- ISO 9001 (7)
- GCP (7)
- FDA (5)
- USDA (4)

more

Locations

United States (64)

Univ. of Maryland School of Medicine Obesity and Diabetes Research Center

University of Maryland School of Medicine Obesity and Diabetes Research Center focuses on research of obesity, diabetes, and aging in nonhuman primates.

vendor info | Add

Transgenic Rabbit Models

Transgenic Rabbit Models offers transgenic rabbit models for the study of atherosclerosis, ophtalmology, hypertrophic myopathies, diabetes, obesity, hemostasis, respiratory diseases, AIDS, and cancer.

vendor info | Add

Ophthy-DS

Ophthy-DS offers ophthalmic model services for macular degeneration, diabetes, uveitis, and dry eye.

vendor info | Add

PharmaNess

PharmaNess offers pharmacokinetics, pharmacodynamics, formulations, behavioral assay, in vivo screening, ex vivo screening, microscopy, stereology and histology staining services.

vendor info | Add

Wisconsin National Primate Research Center

Wisconsin National Primate Research Center focuses on research of regenerative medicine, reproduction, immunology, virology, aging, and metabolic diseases.

vendor info | Add

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Search PubMed for "Diabetes and Obesity" using BioWizard.

Selected Vendors

Translational Pipeline

Clinical and Molecular Measurements

Translational Question or Trial

Statistical/Computational methods

Validating drug or biomarker

Translational Pipeline

Clinical and Molecular Measurements

Commodity

↓↑

Translational Question or Trial

↓

Statistical/Computational methods

↓

Validating drug or biomarker

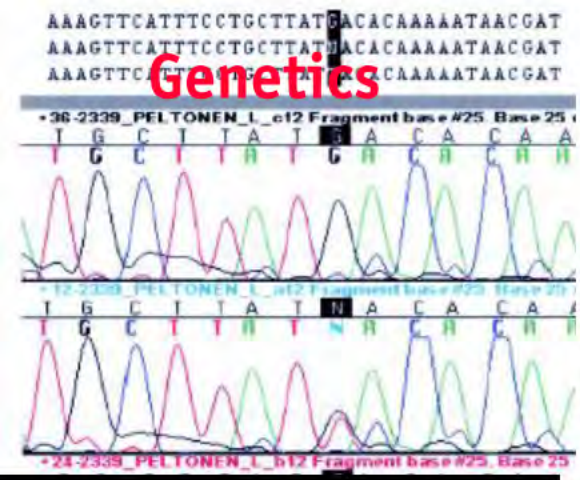
Commodity

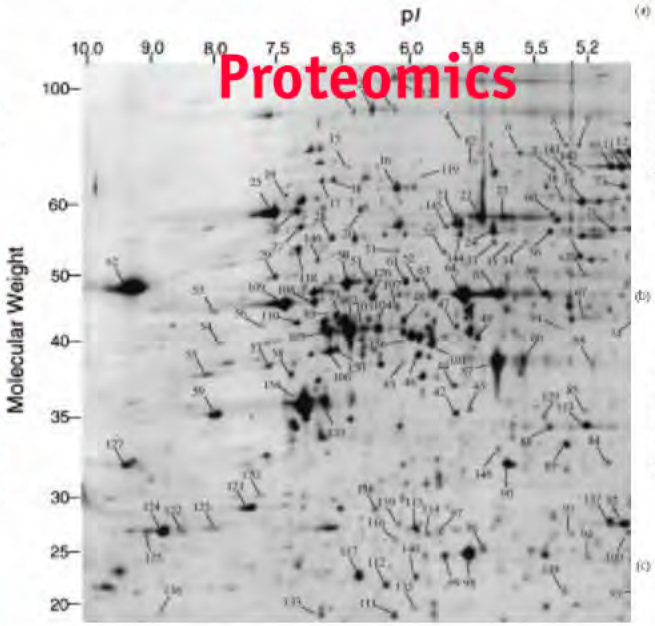
We are used to starting computer, IT, and Internet companies in garages...

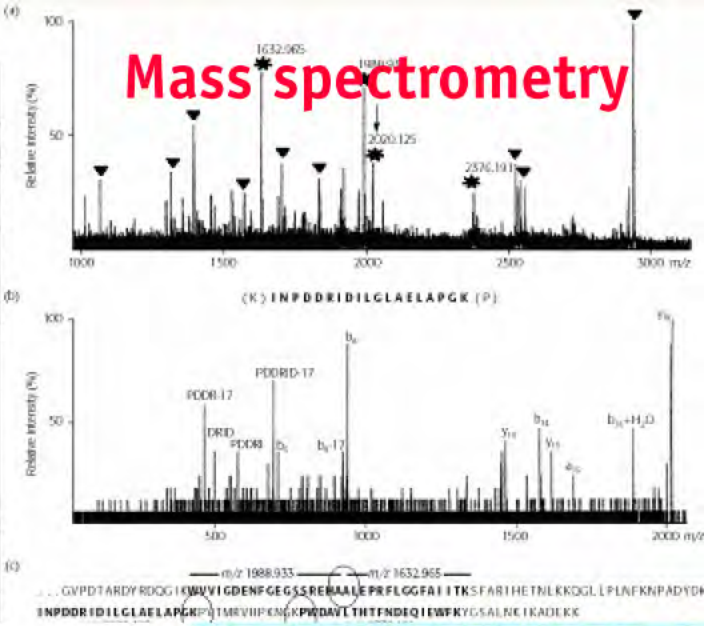
Potentials for starting a "garage biotech"?

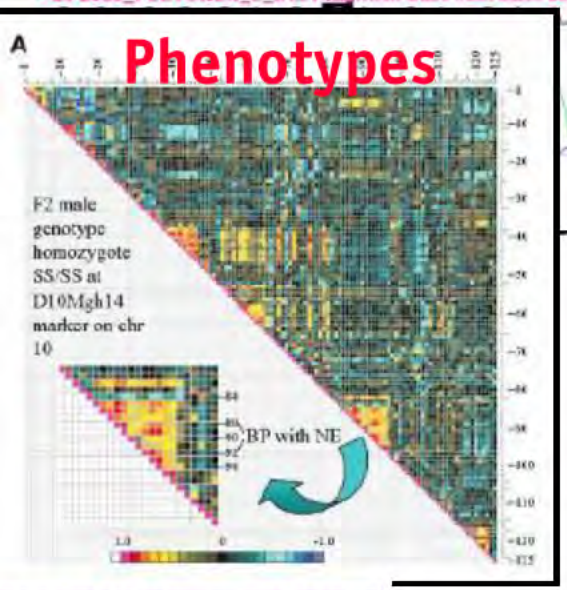
Agenda

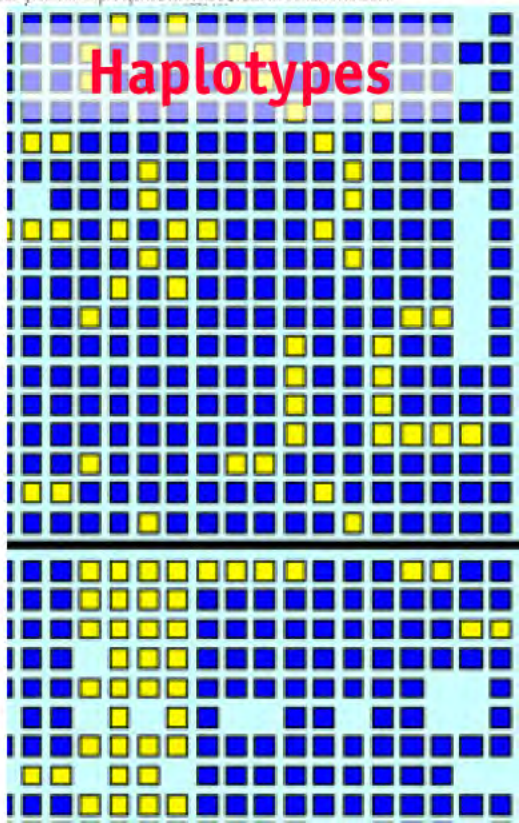
- Integrative genomics to find causal factors for complex disorders Link
- Genomic nosology and drug/diagnostic discovery Link
- Personalized disease-risk prediction and prevention Link

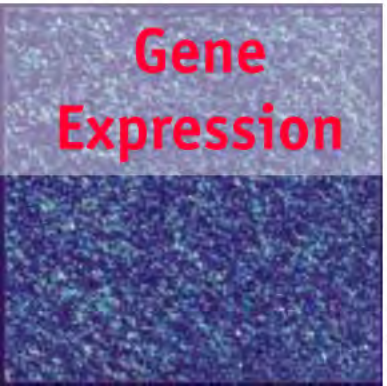


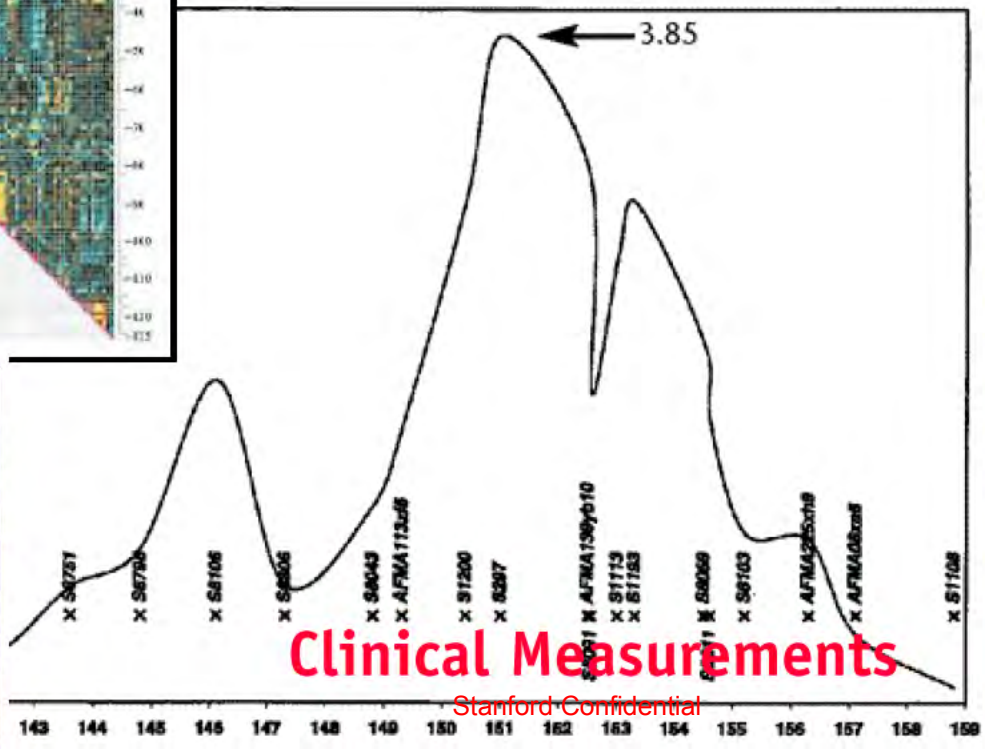


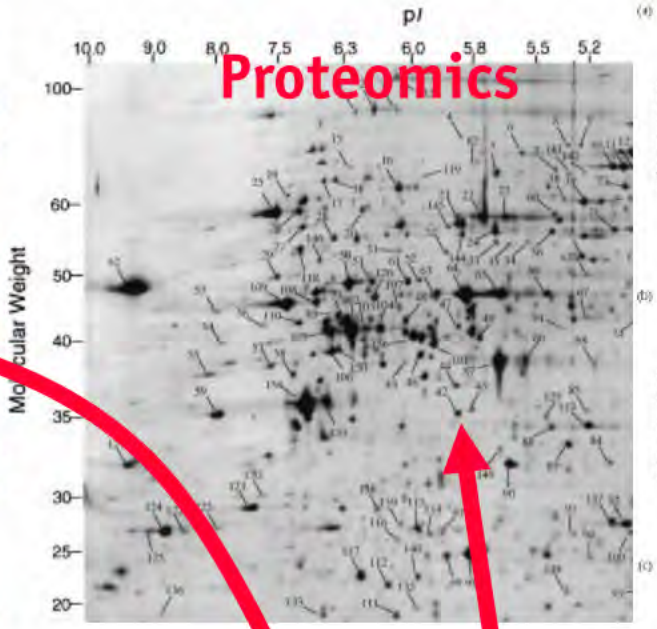


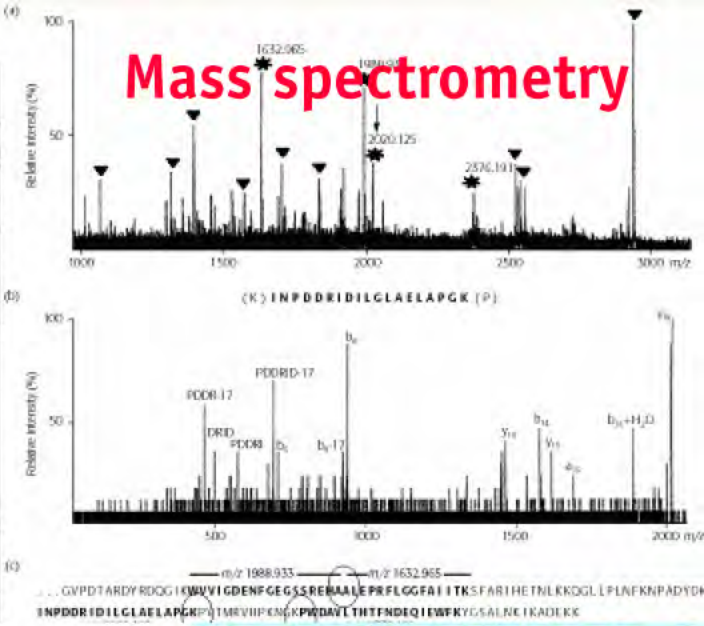


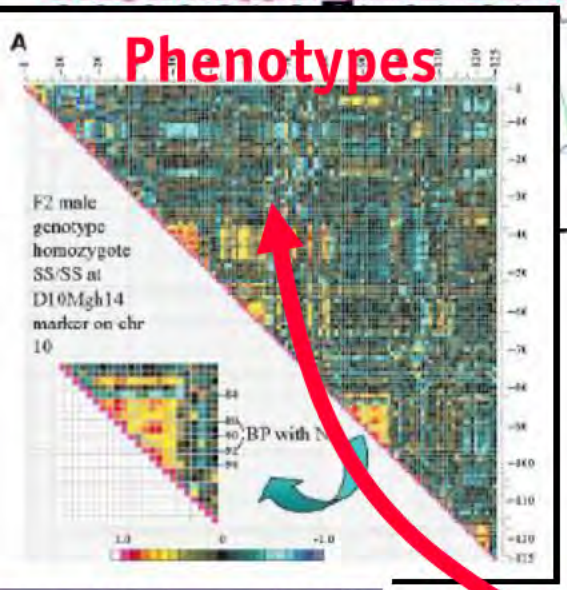


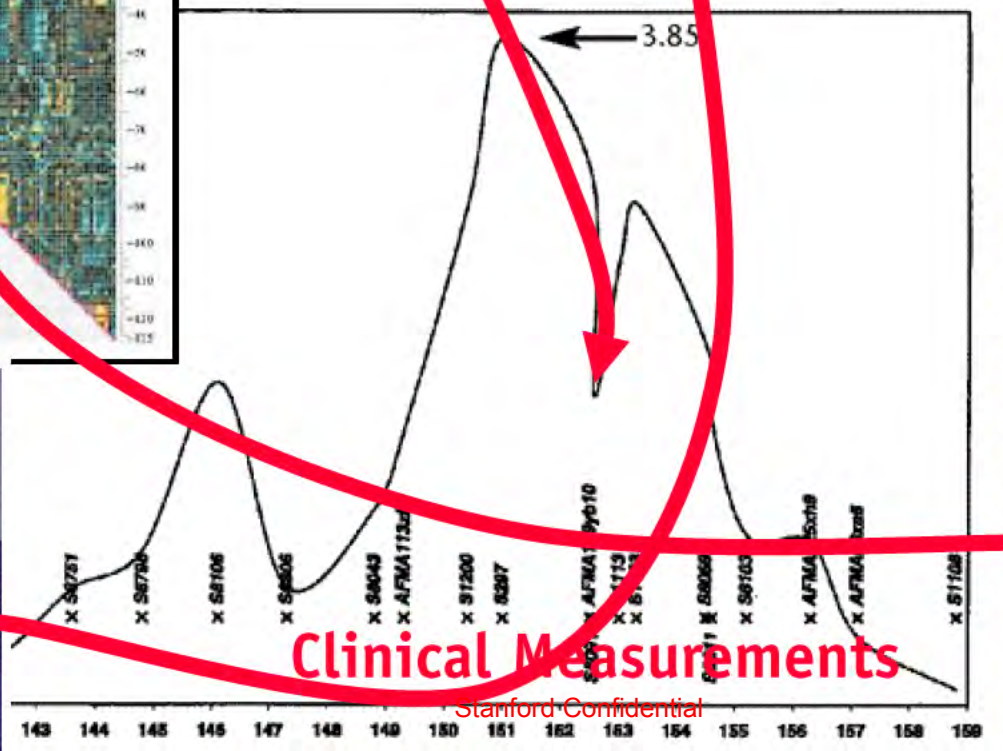


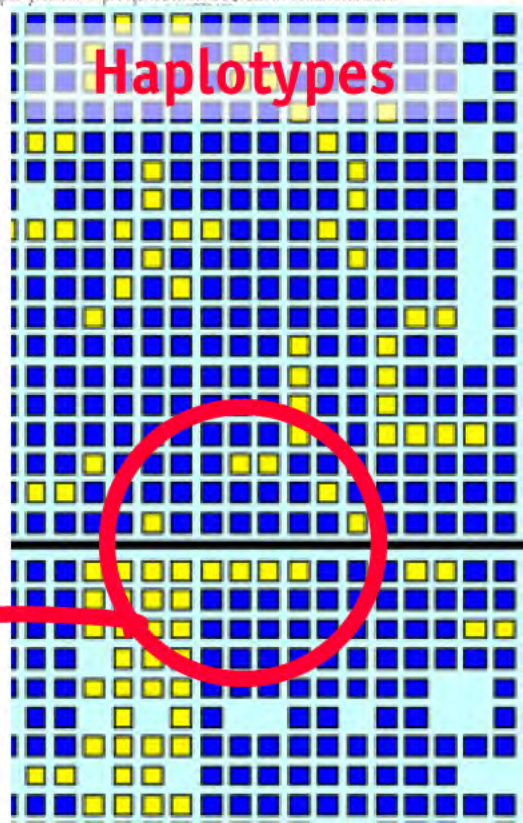


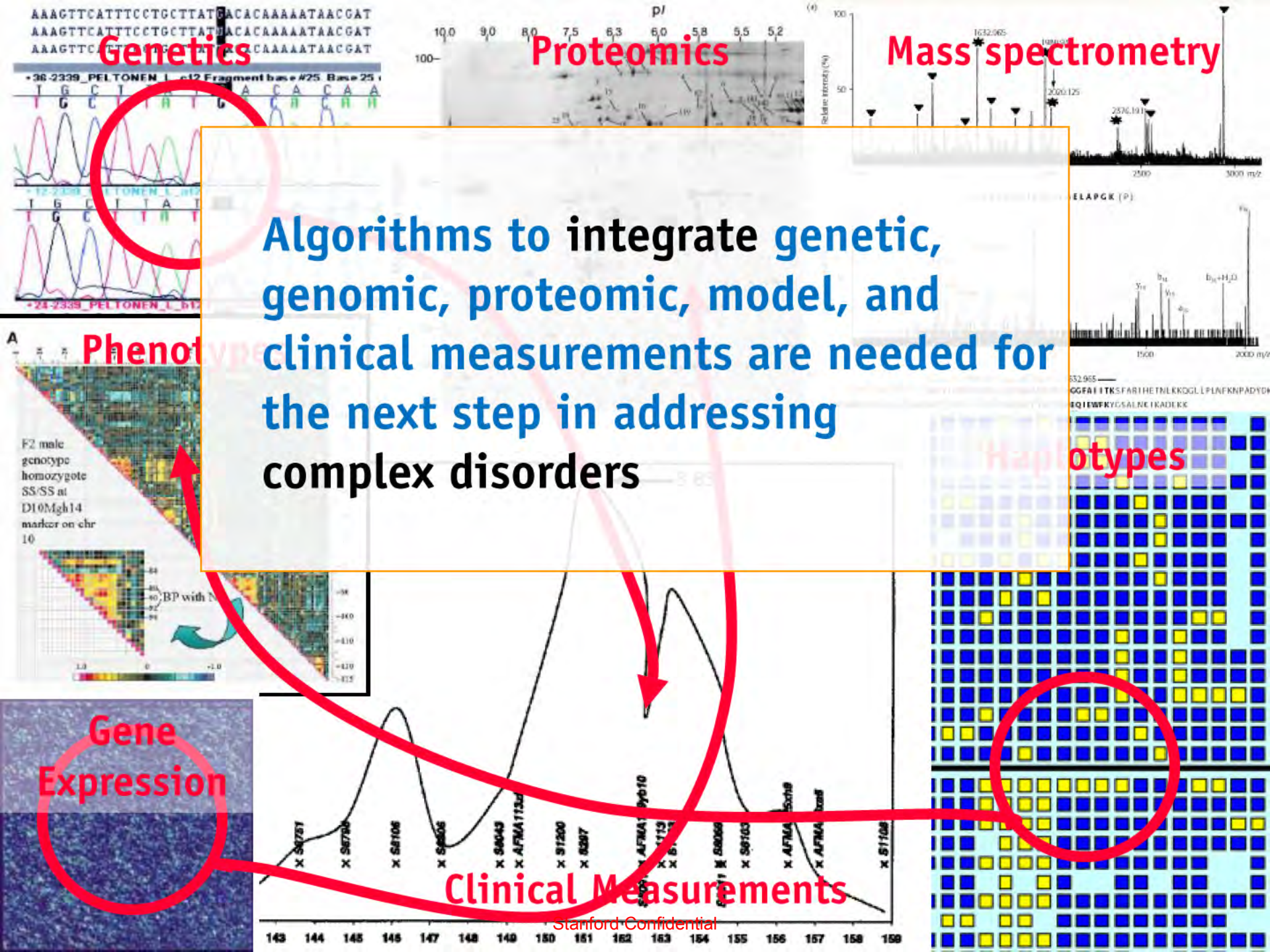











Genetics
Proteomics
Mass spectrometry
Phenotypes
Haplotypes
Gene Expression
Clinical Measurements
Algorithms to integrate genetic, genomic, proteomic, model, and clinical measurements are needed for the next step in addressing complex disorders
F2 male genotype homozygote SS/SS at D10Mgh14 marker on chr 10
Stanford Confidential

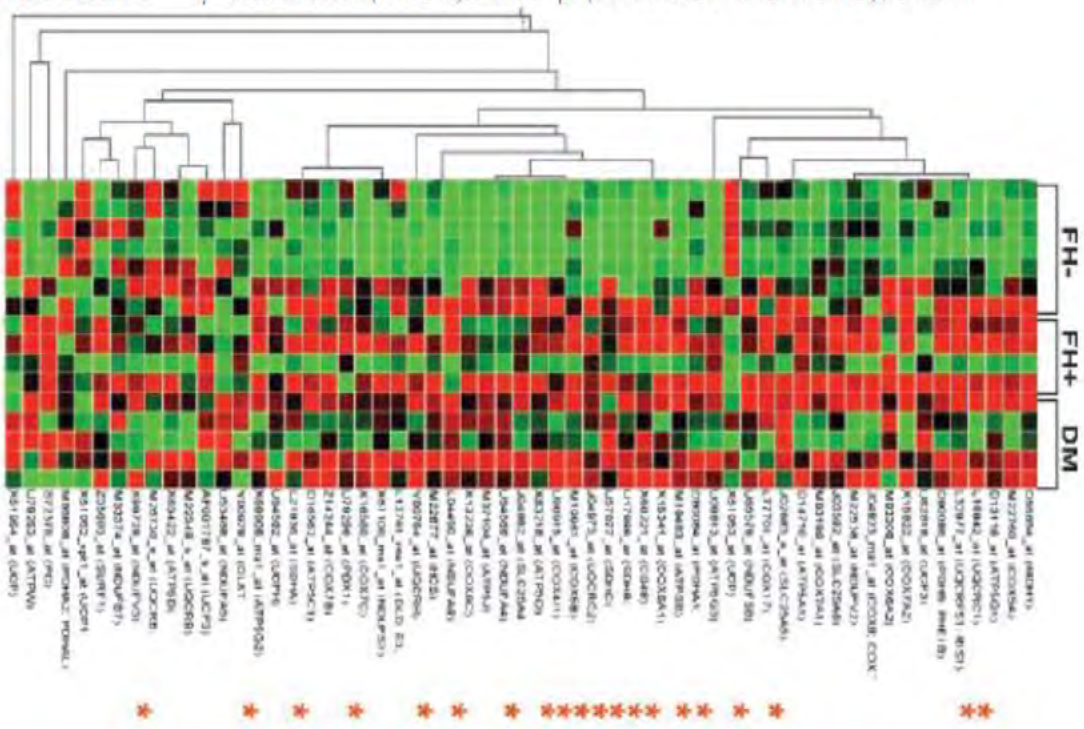
Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of *PGC1* and *NRF1*

Mary Elizabeth Patti*†‡, Atul J. Butte*†§, Sarah Crunkhorn*, Kenneth Cusi¶, Rachele Berria¶, Sangeeta Kashyap¶, Yoshinori Miyazaki¶, Isaac Kohane§, Maura Costello*, Robert Saccone*, Edwin J. Landaker*, Allison B. Goldfine*, Edward Mun‖, Ralph DeFronzo¶, Jean Finlayson¶, C. Ronald Kahn*, and Lawrence J. Mandarino¶

*Research Division, Joslin Diabetes Center, Boston, MA 02215; §Division of Informatics and Endocrinology, Children's Hospital, Boston, MA 02115; Department of Surgery, Beth Israel Deaconess Medical Center, Boston, MA 02215; and ¶University of Texas Health Science Center, San Antonio, TX 78229

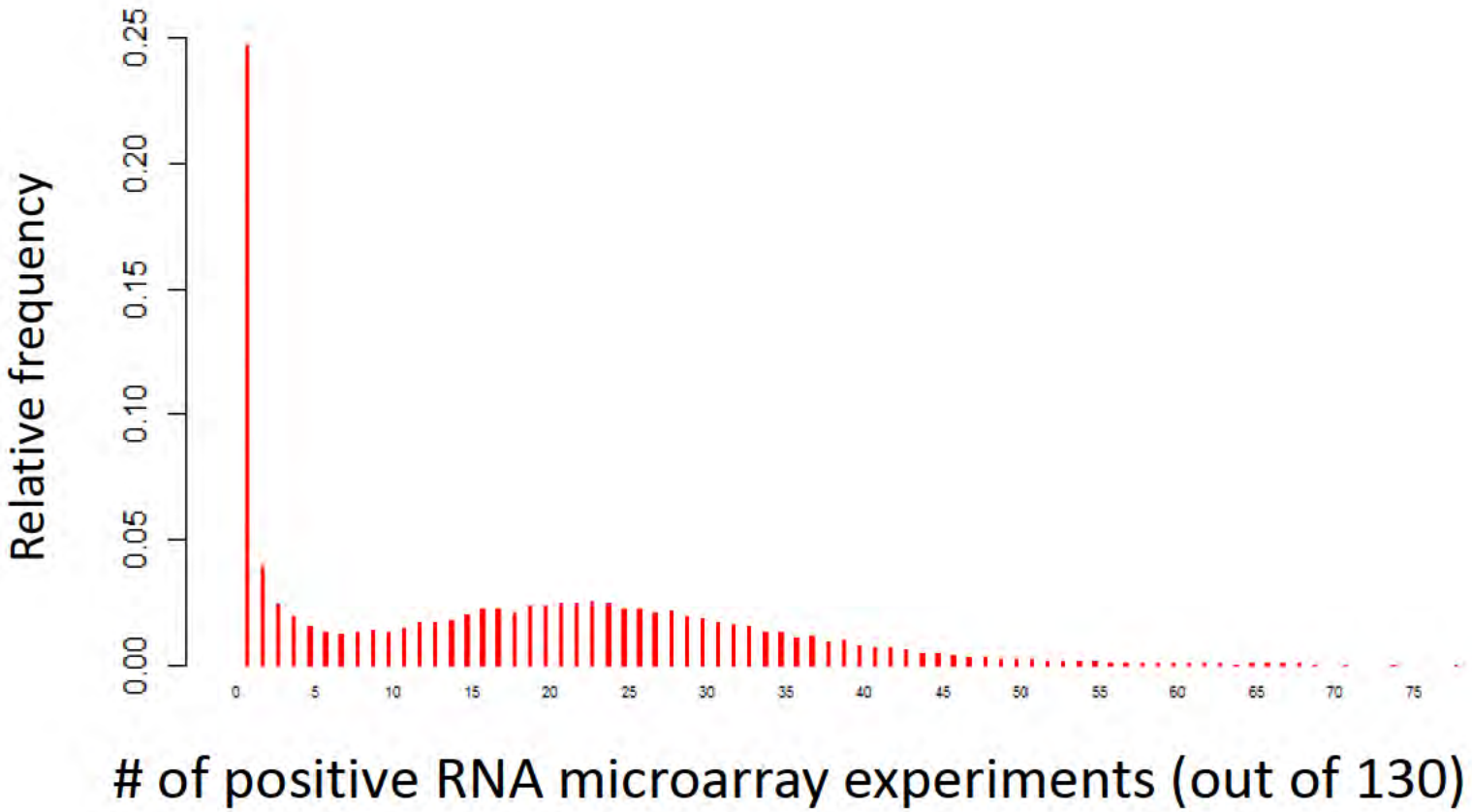
Contributed by C. Ronald Kahn, May 14, 2003

Type 2 diabetes mellitus (DM) is characterized by insulin resistance and pancreatic β cell dysfunction. In high-risk subjects, the earliest detectable abnormality is insulin resistance in ske Impaired insulin-mediated signaling, gene expressi synthesis, and accumulation of intramyocellular trigl all been linked with insulin resistance, but no sp responsible for insulin resistance and DM has been humans. To identify genes potentially important in t esis of DM, we analyzed gene expression in skeletal more, expression of peroxisomal proliferator activator receptor γ coactivator (*PGC1*)α and -β (*PPARGC1* and *PERC*), coacti-



- One example of a microarray experiment with diabetes and control samples
- 187 genes differentially expressed

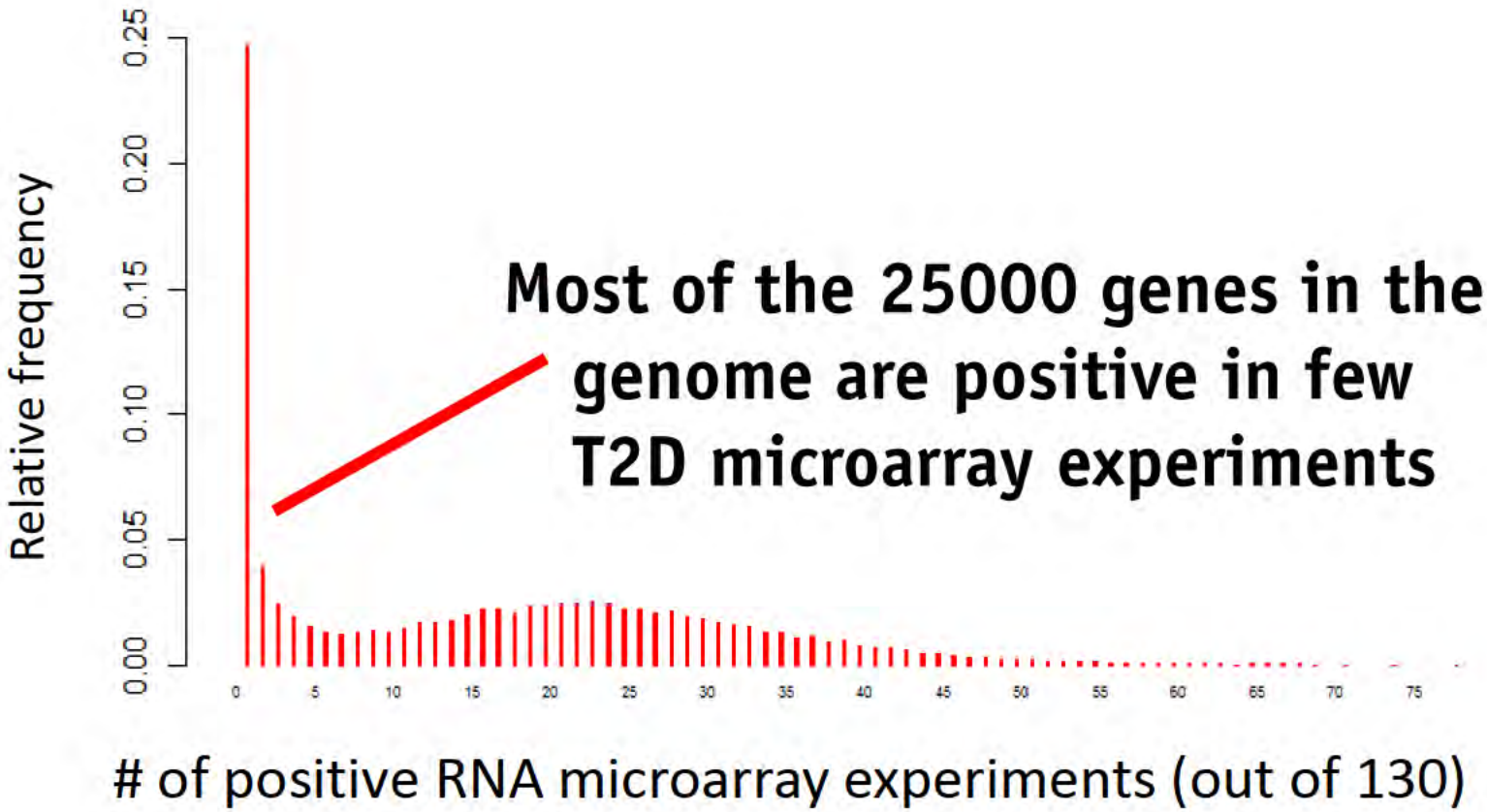
Intersect 130 T2D microarray experiments



Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Keiichi Kodama

Intersect 130 T2D microarray experiments

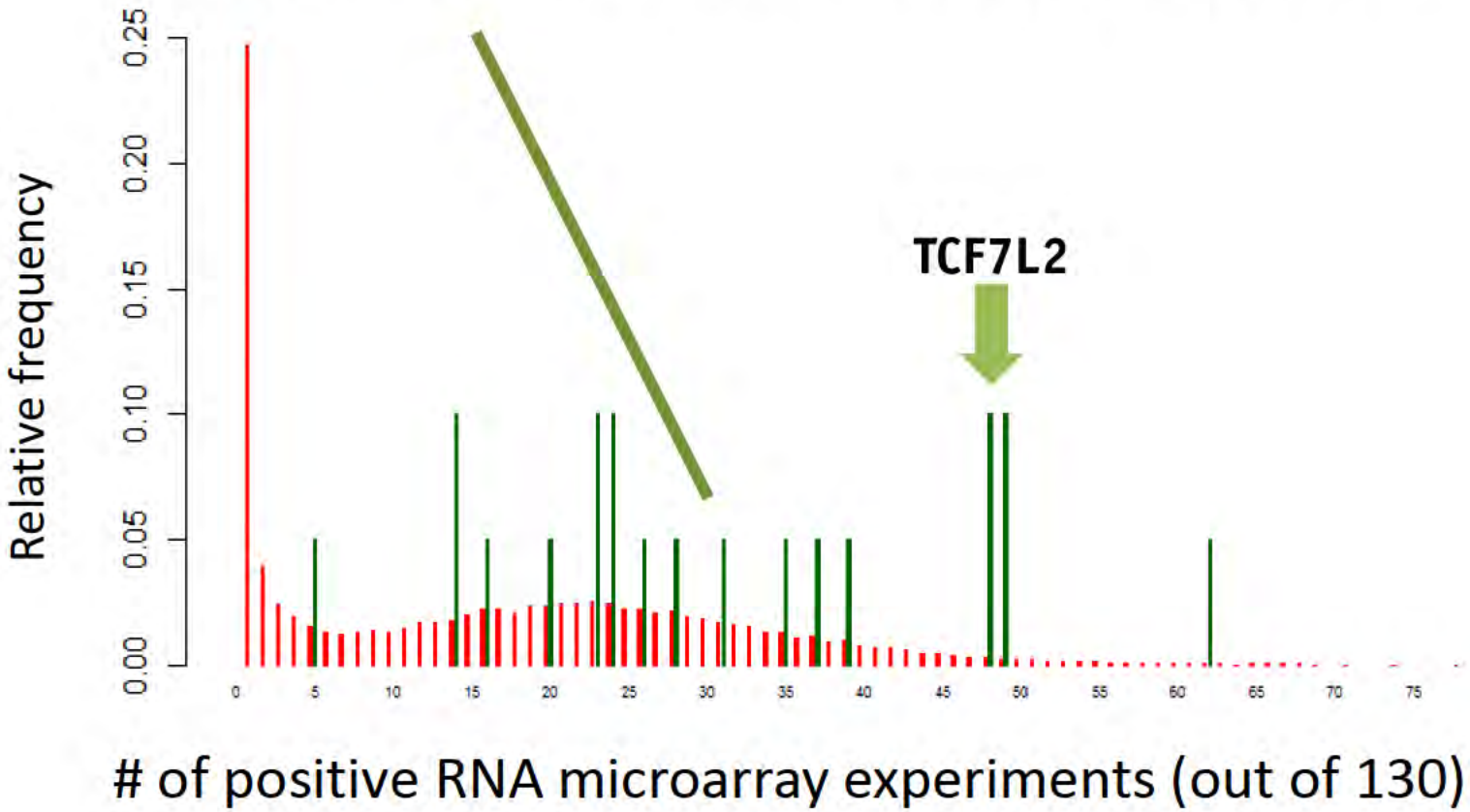


Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Keiichi Kodama

Intersect 130 T2D microarray experiments

The 20 best known genes with DNA variants (from GWAS) are positive in more experiments...



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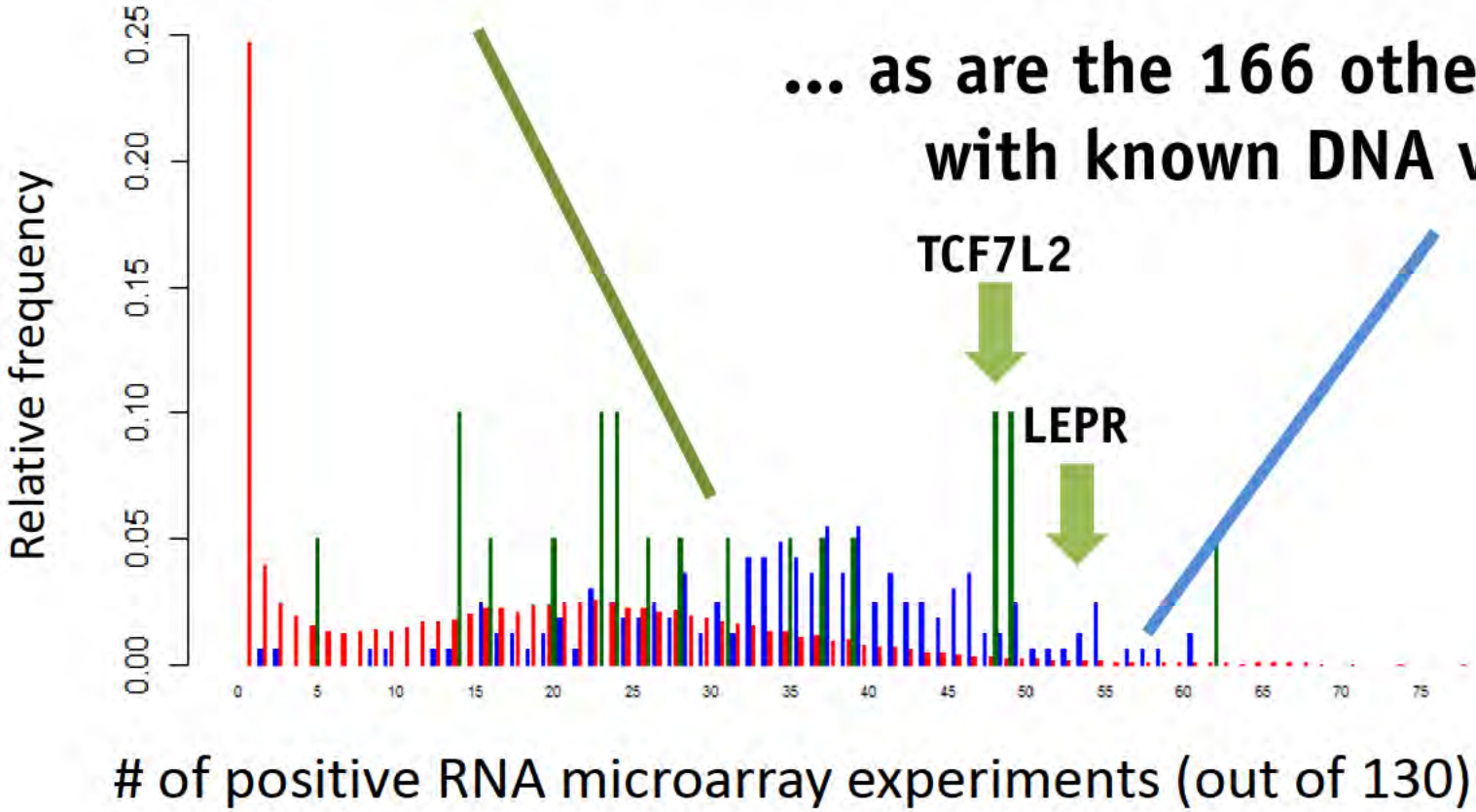
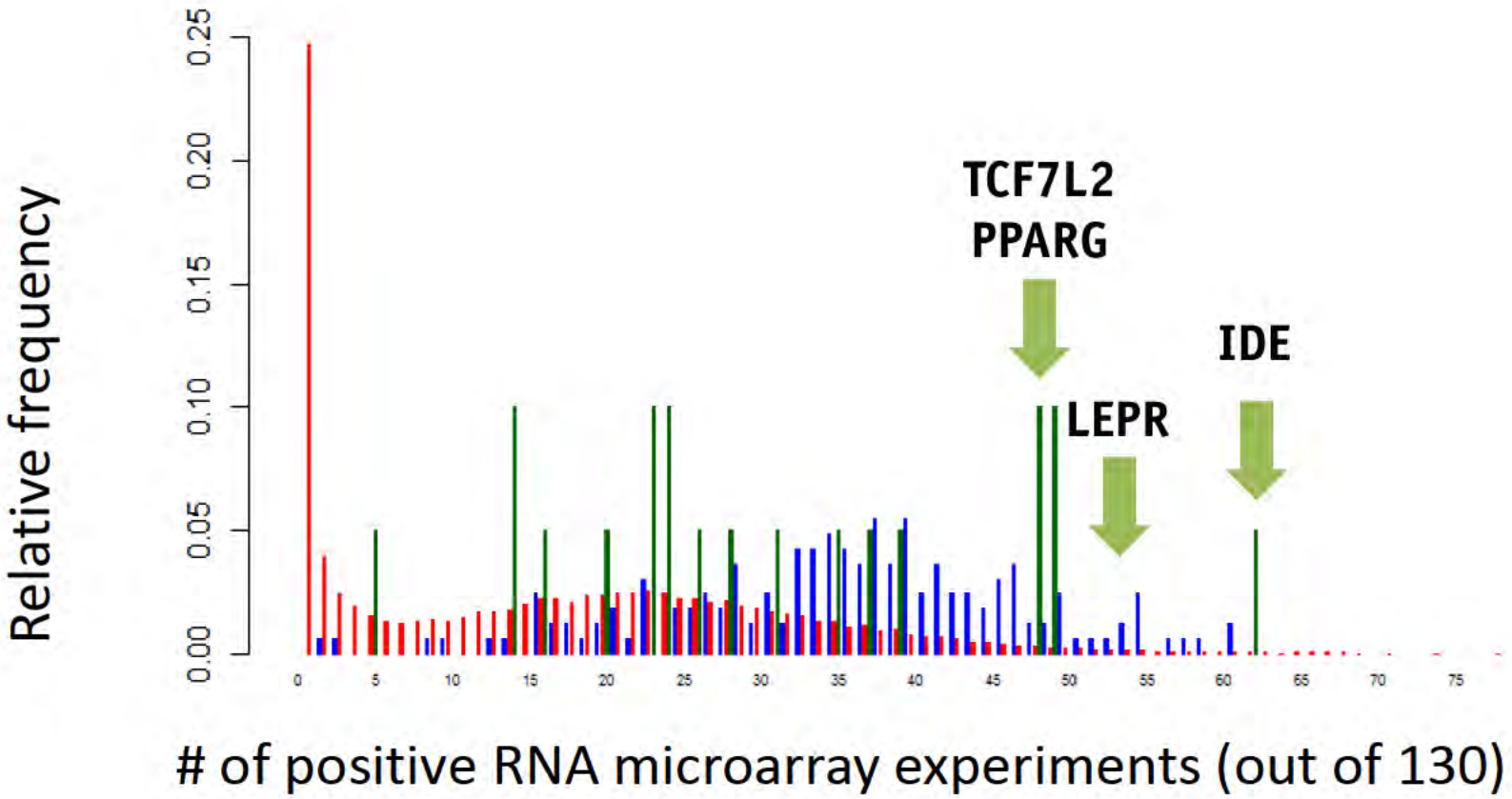


Intersect 130 T2D microarray experiments



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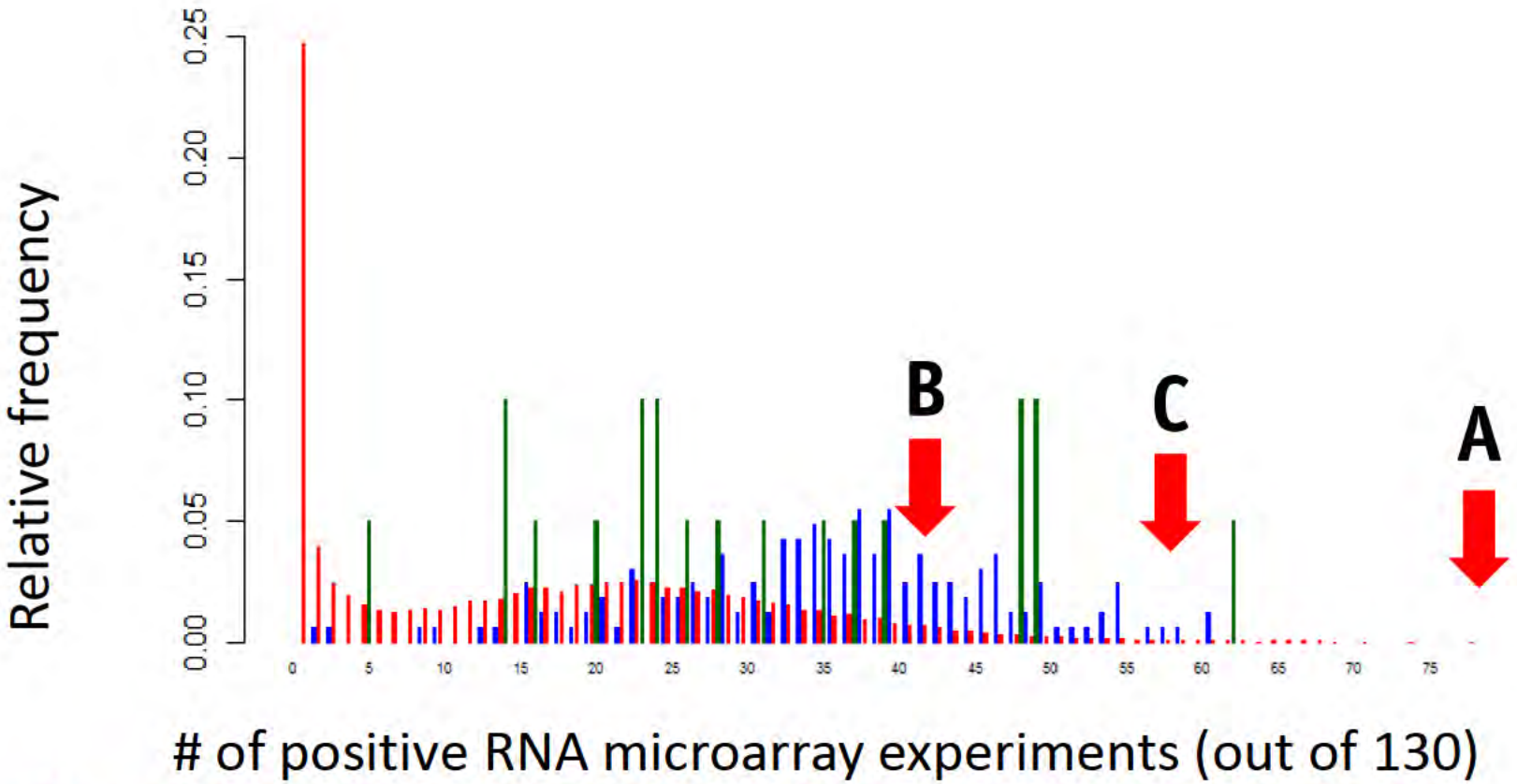
Intersect 130 T2D microarray experiments



Close collaboration with Dr. Takashi Kadowaki, Momoko Horikoshi, Kazuo Hara, University of Tokyo

Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

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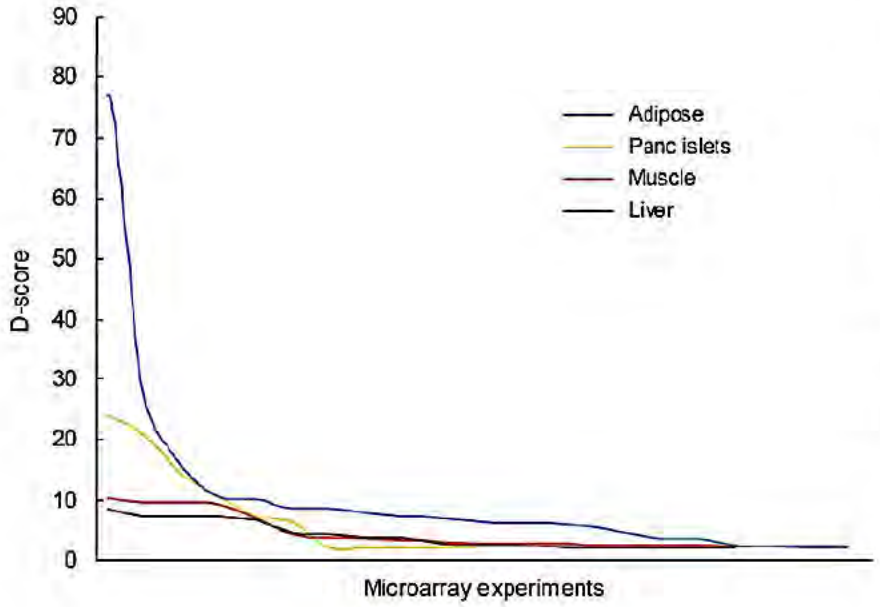
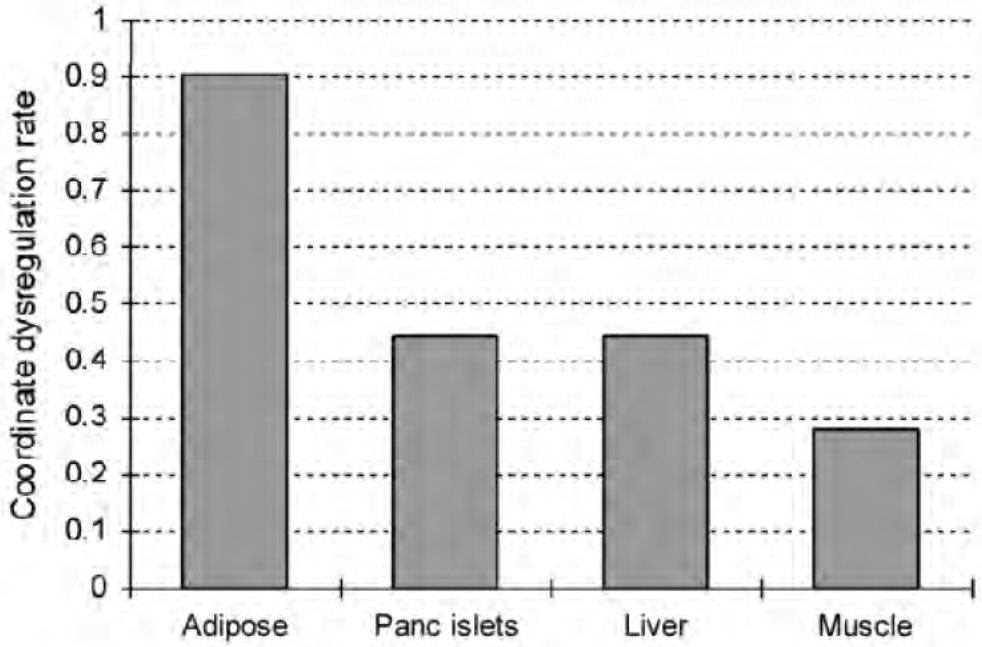
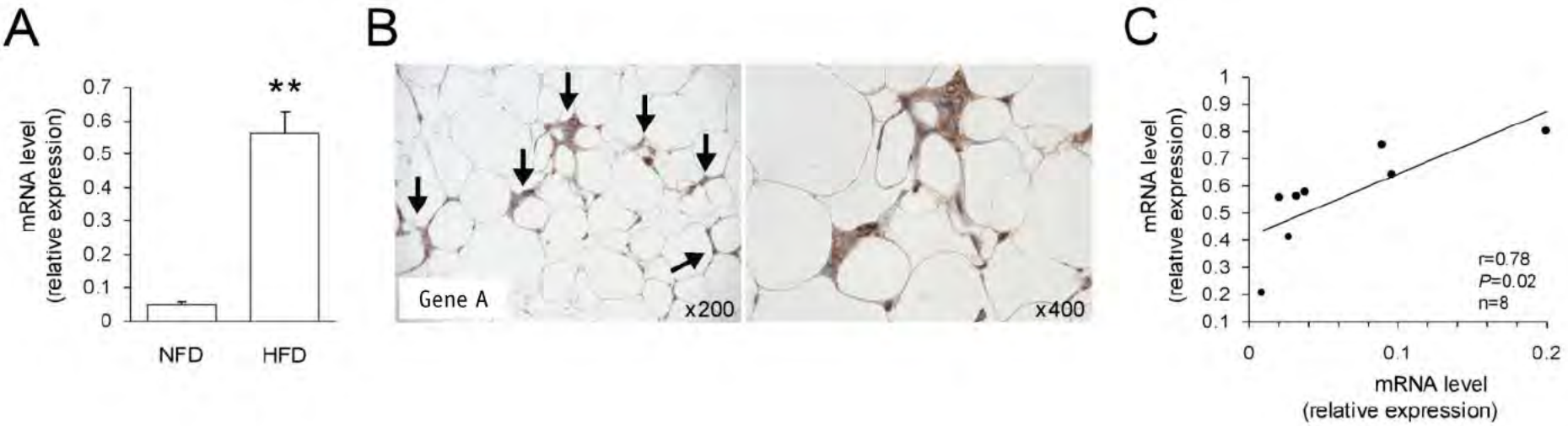
- Gene A changes the most in adipose tissue and islet experiments
- Adipose and islets also show Gene C change





Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Gene A is higher in high fat diet
Gene A is expressed in mouse fat infiltrate
Gene A and C are co-expressed in fat



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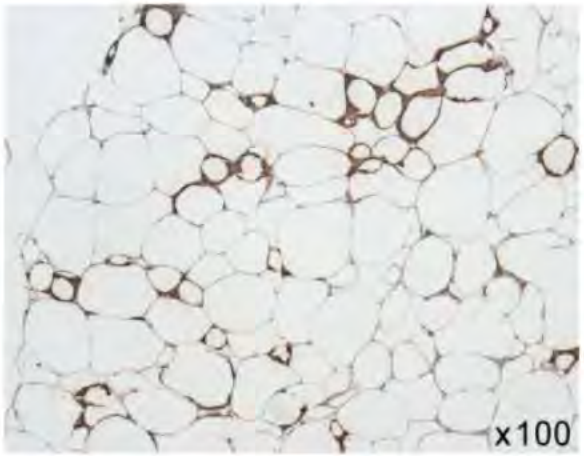
Kyoko Toda

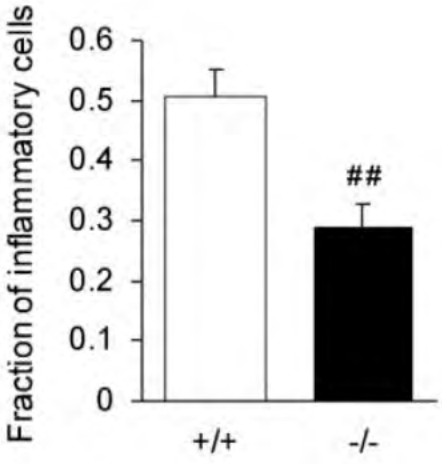
Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Gene A knockout has reduced infiltrate in fat

- **Mac-2 stain**

HFD





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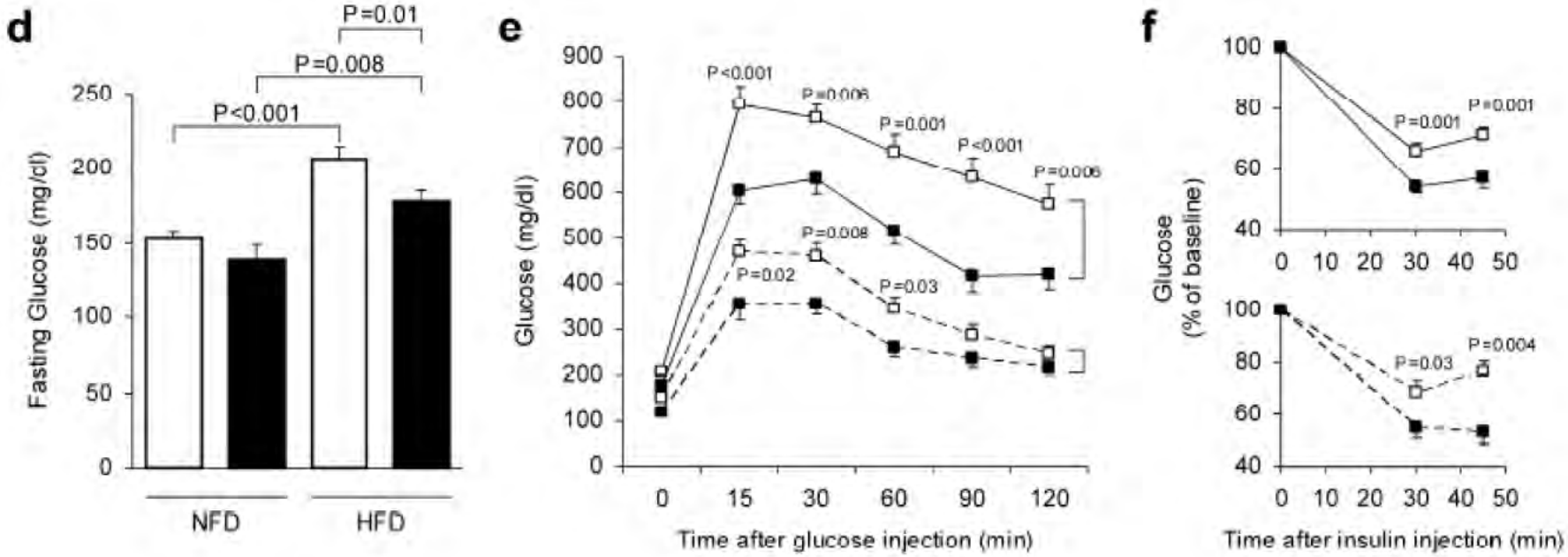
Kyoko Toda

Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Gene A knockout has increased insulin sensitivity



- **No change in weight gain**

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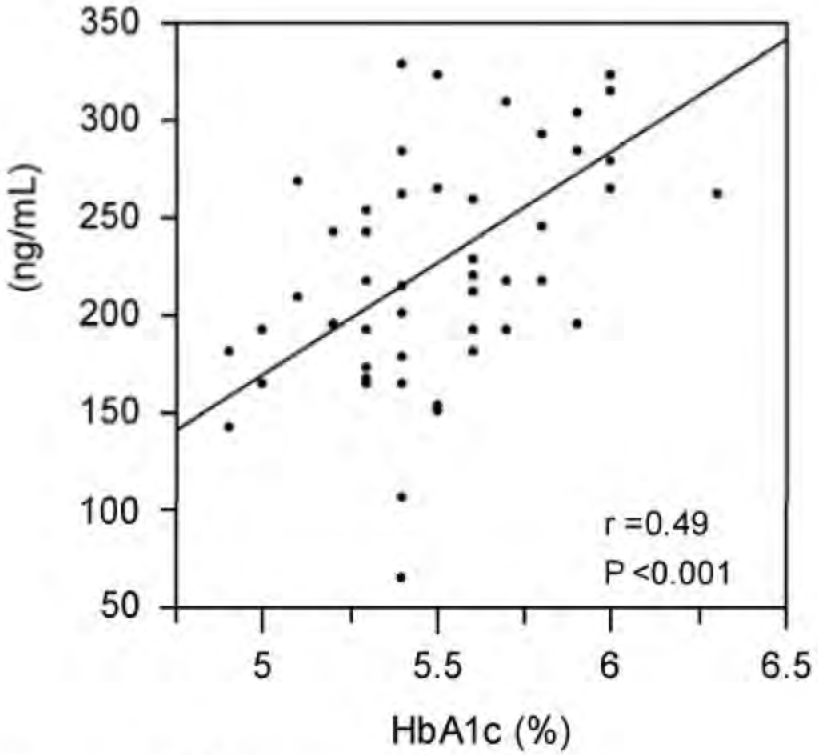
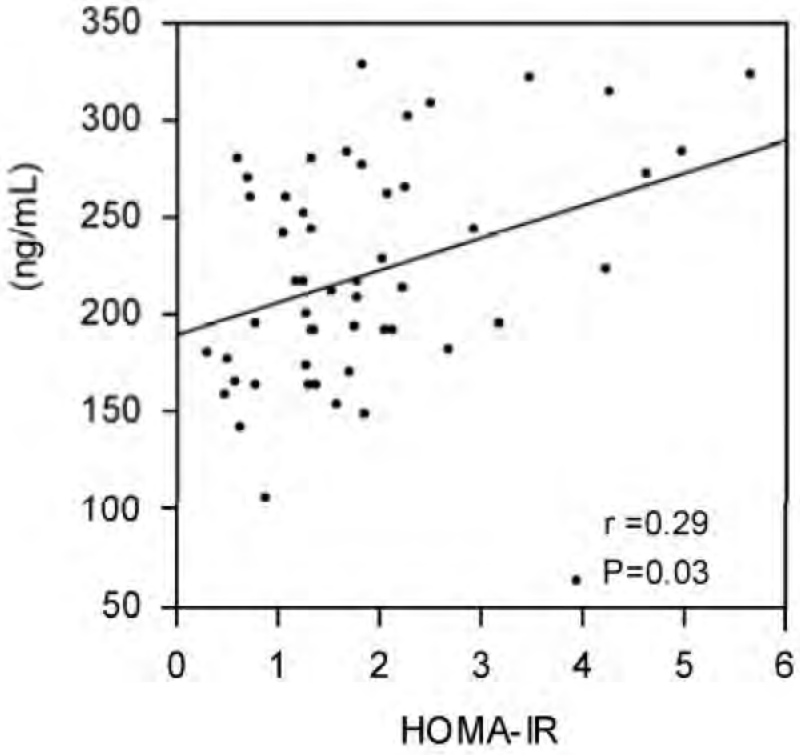
Kyoko Toda

Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Serum soluble Gene A protein correlates with human HbA1c and insulin resistance





- n = 55 non-diabetics
- 60.3 years of age ± 15, 36 males, 19 females
- BMI 23.2 ± 4.3 kg/m^2

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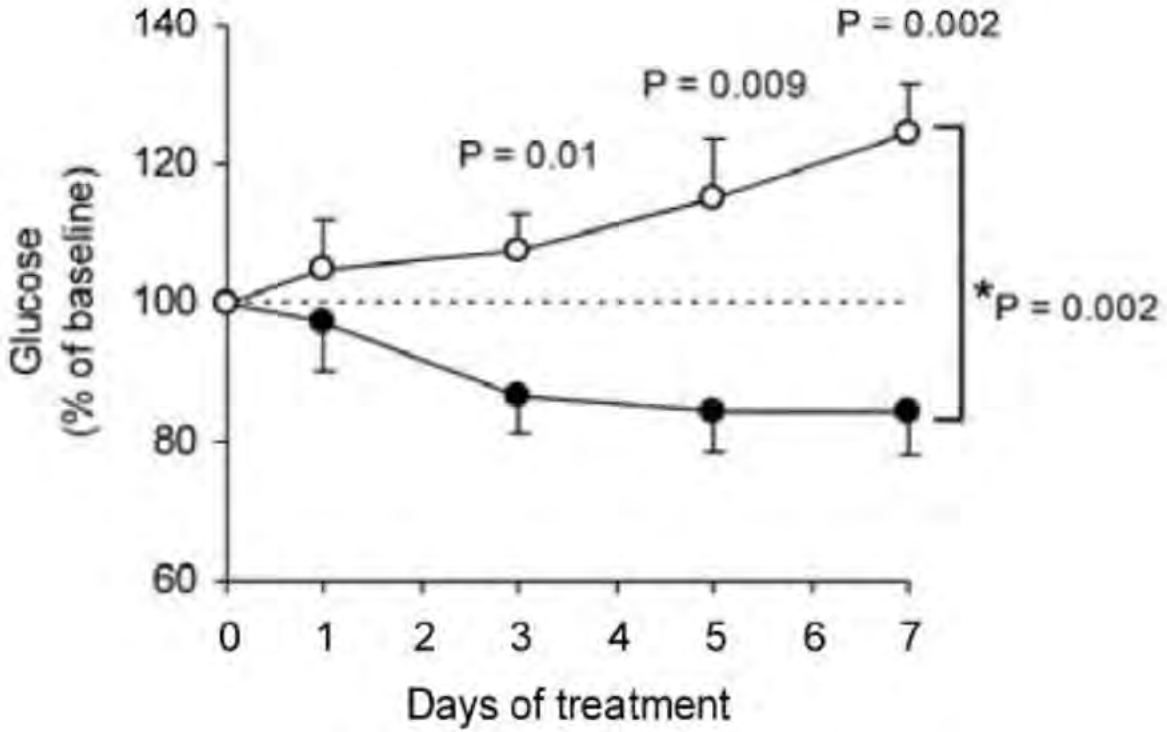
Momoko Horikoshi

Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Therapeutic antibody against Gene A → reduces glucose



- C57BL6/6J fed high-fat diet for 18 weeks
- Intraperitoneal injection of rat anti-mouse anti-A antibody (n=8) or isotype control (n=8)
- 100 µg at day 0 and 50 µg at day 1-7

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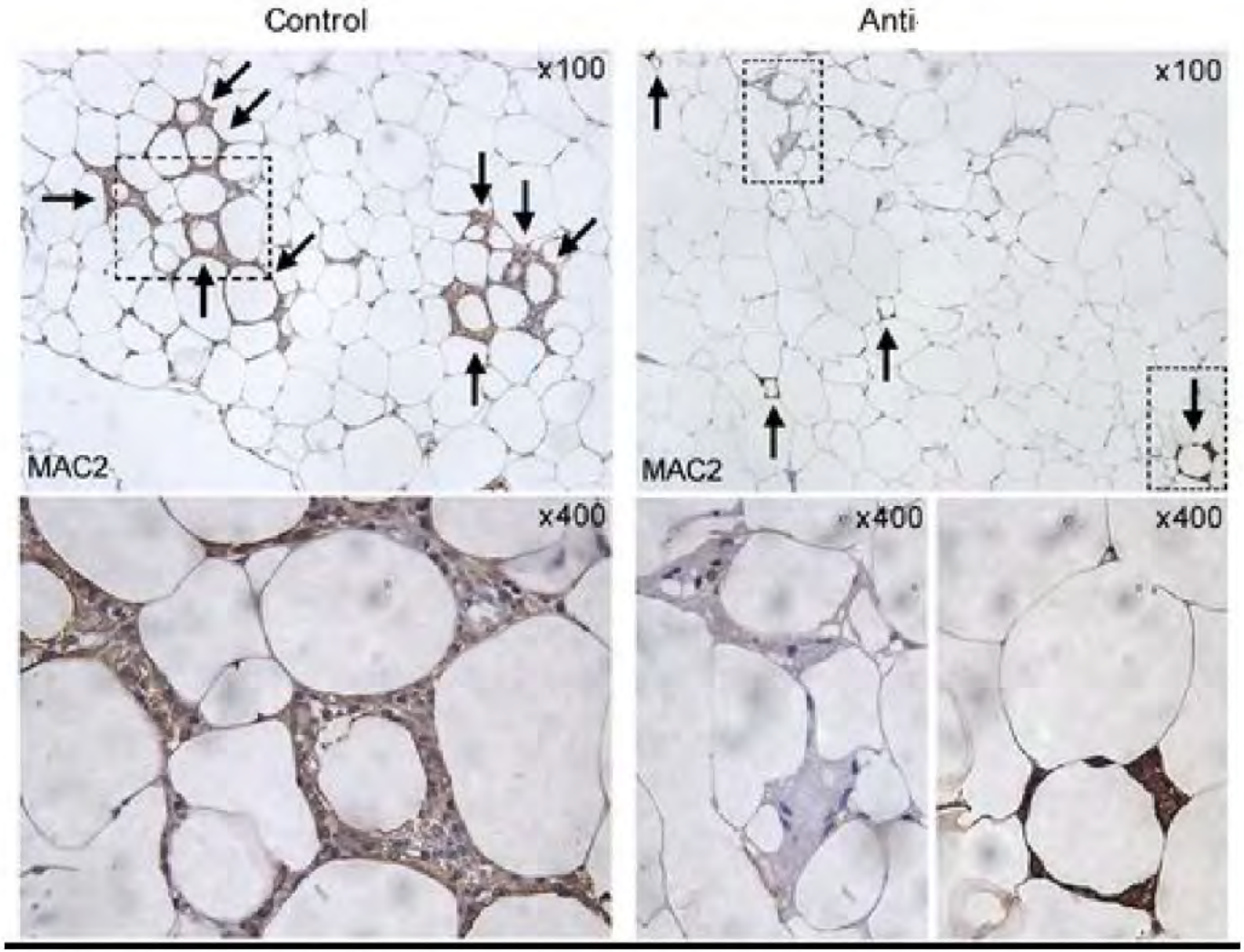
Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Therapeutic antibody against Gene A → reduces fat inflammatory infiltrate



Keiichi Kodama

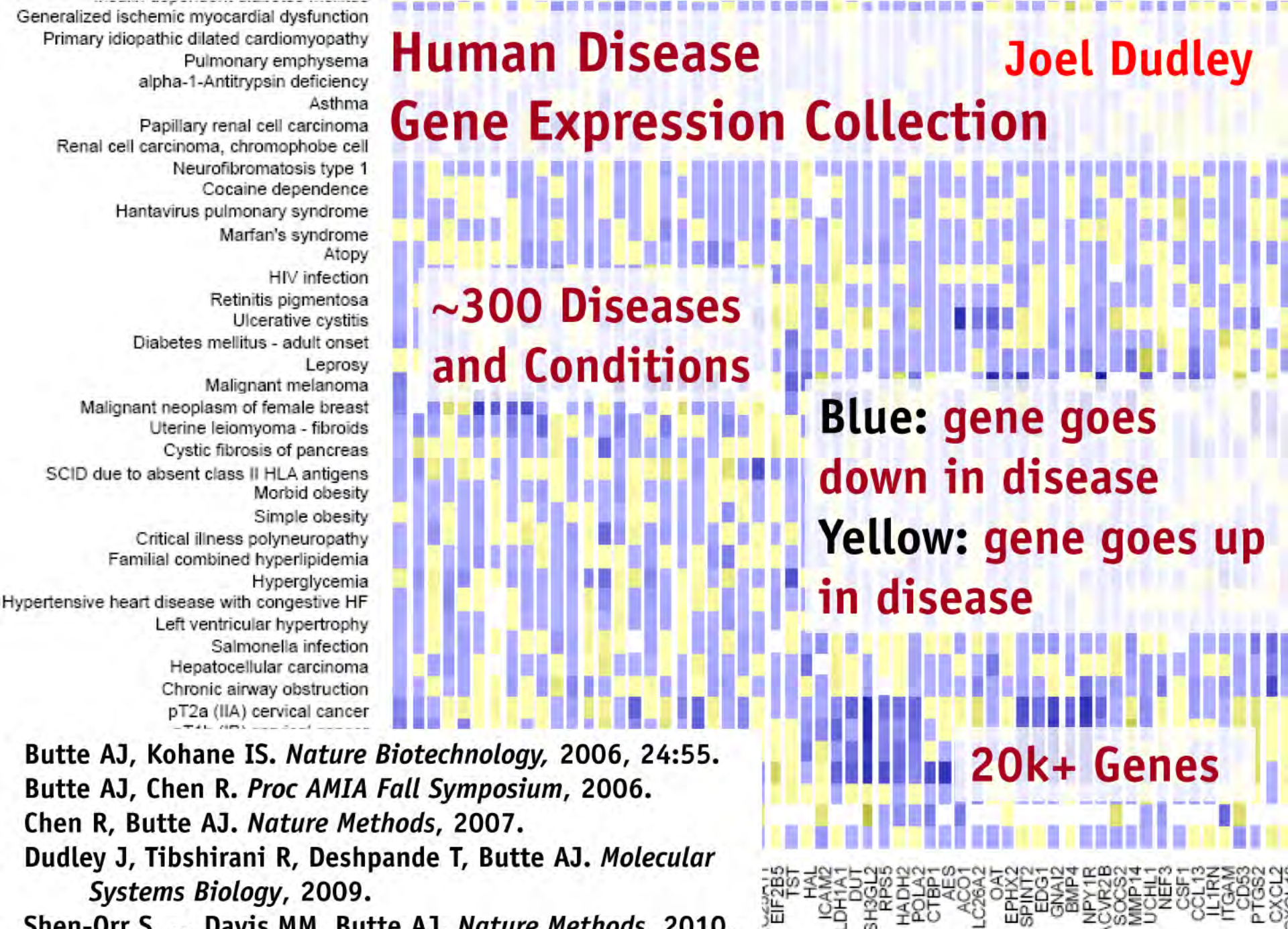
Pre-publication; embargoed for press. Kodama K, ..., Butte AJ. In revision, 2012.

Agenda

- Integrative genomics to find causal factors for complex disorders Link
- Genomic nosology and drug/diagnostic discovery Link
- Personalized disease-risk prediction and prevention Link

Human Disease Gene Expression Collection

Joel Dudley



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Chen R, Butte AJ. *Nature Methods*, 2007.

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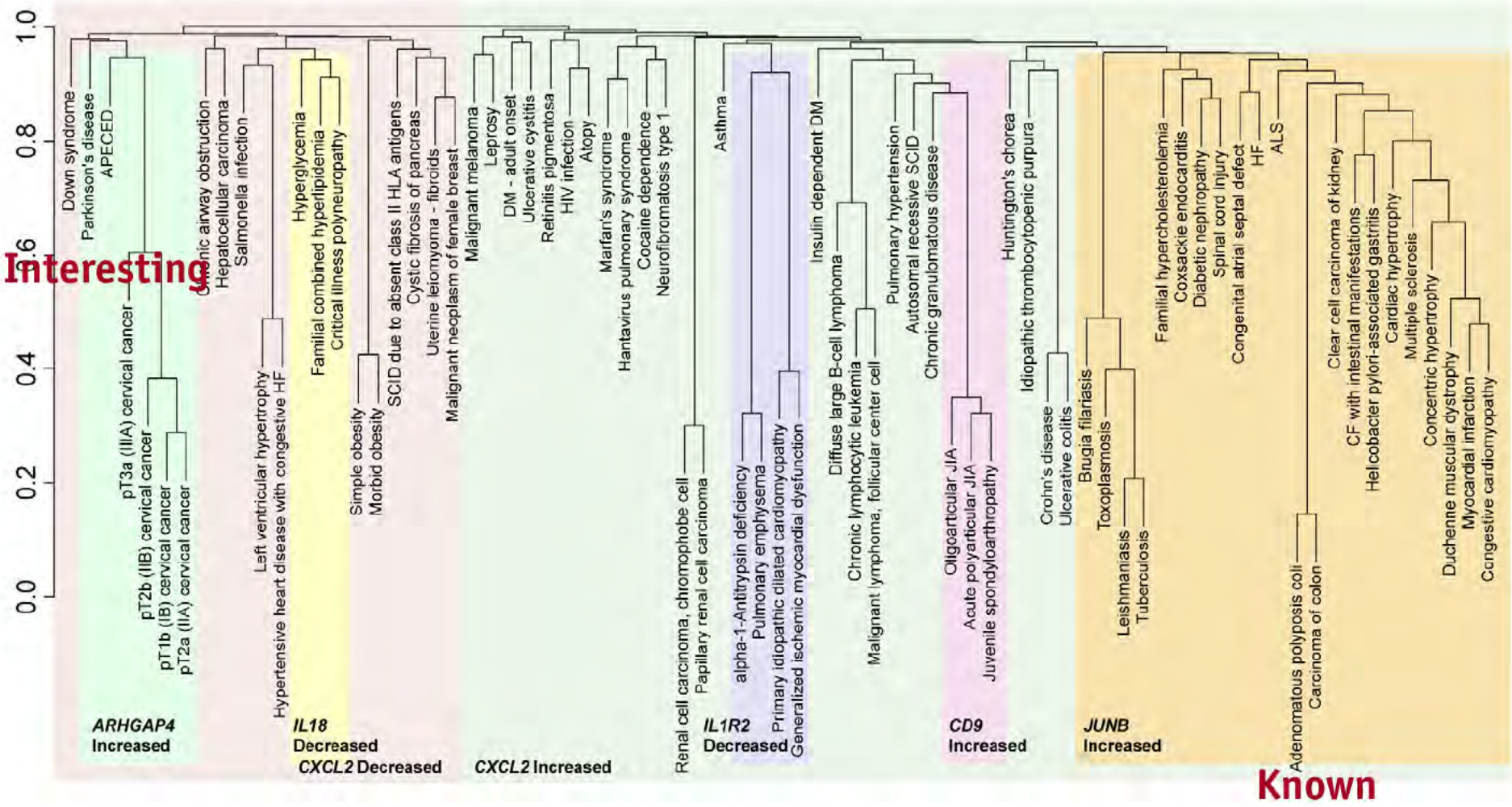

- **The Gene-expression Nosology of Medicine (GNOMED): across all disciplines**

Dudley J, Butte AJ. *Pacific Symposium on Biocomputing*, 2008.
Dudley J, Butte AJ. *Pacific Symposium on Biocomputing*, 2009.
Dudley J, Tibshirani R, Deshpande T, Butte AJ. *Molecular Systems Biology*, 2009.
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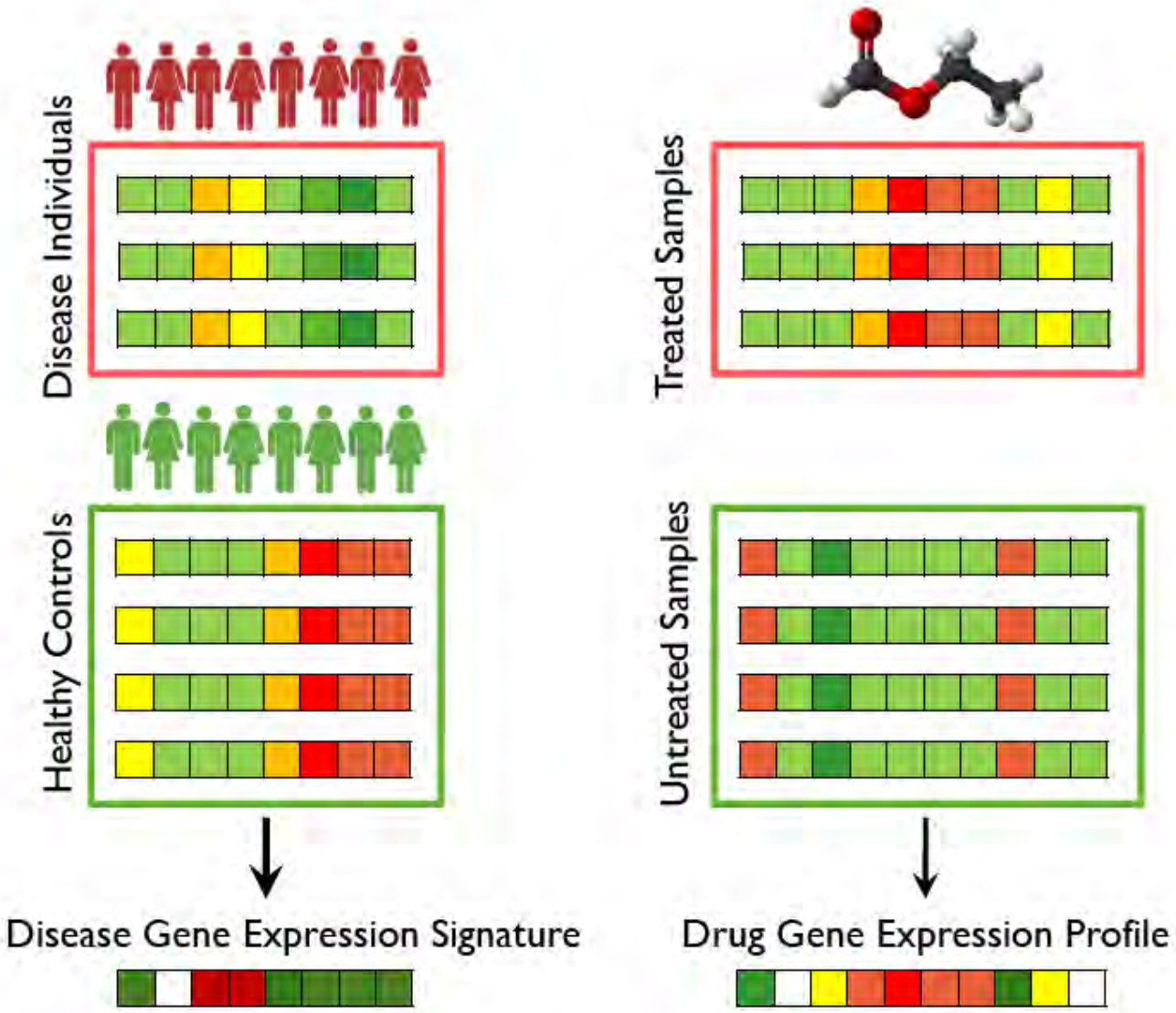
Suthram S, et al. *PLoS Computational Biology*, 2010.



Marina Sirota
Joel Dudley

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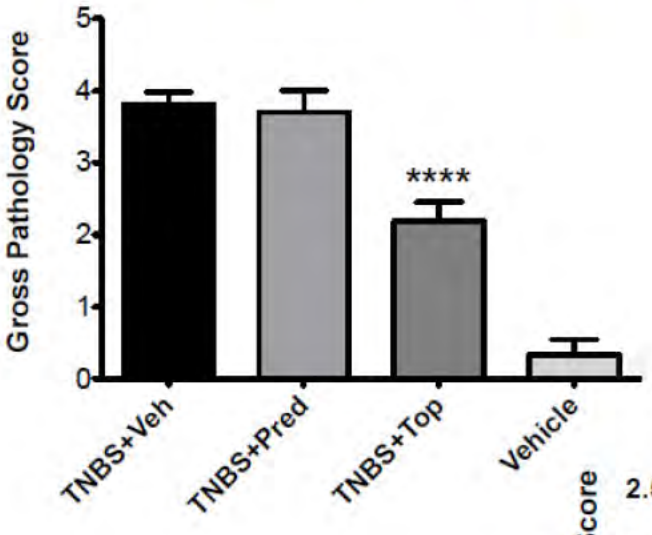
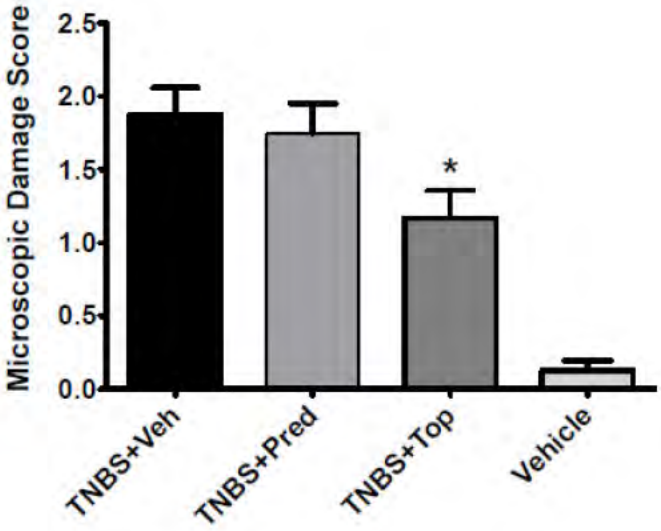
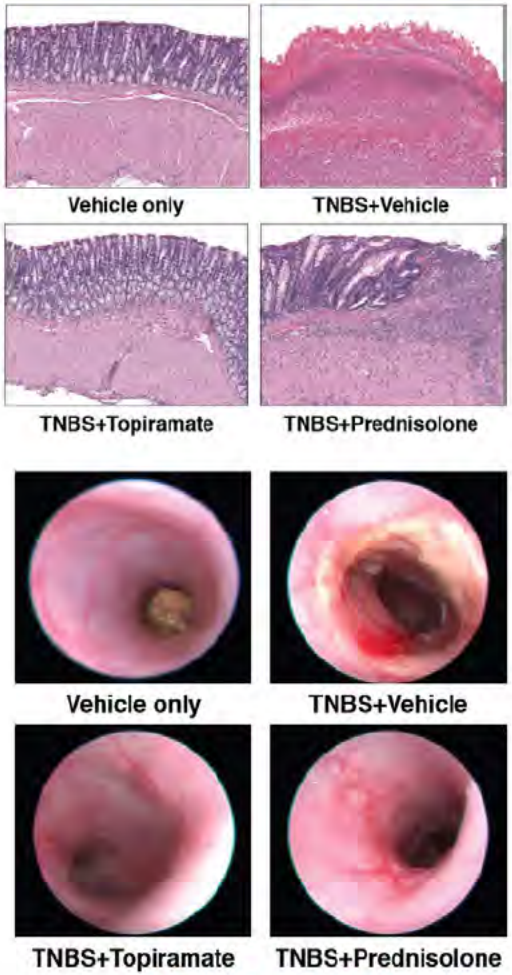
Sirota M, Dudley JT, ..., Sweet-Cordero A, Sage J, Butte AJ. *Science Translational Medicine*, 2011.

Anti-seizure drug works against a rat model of inflammatory bowel disease





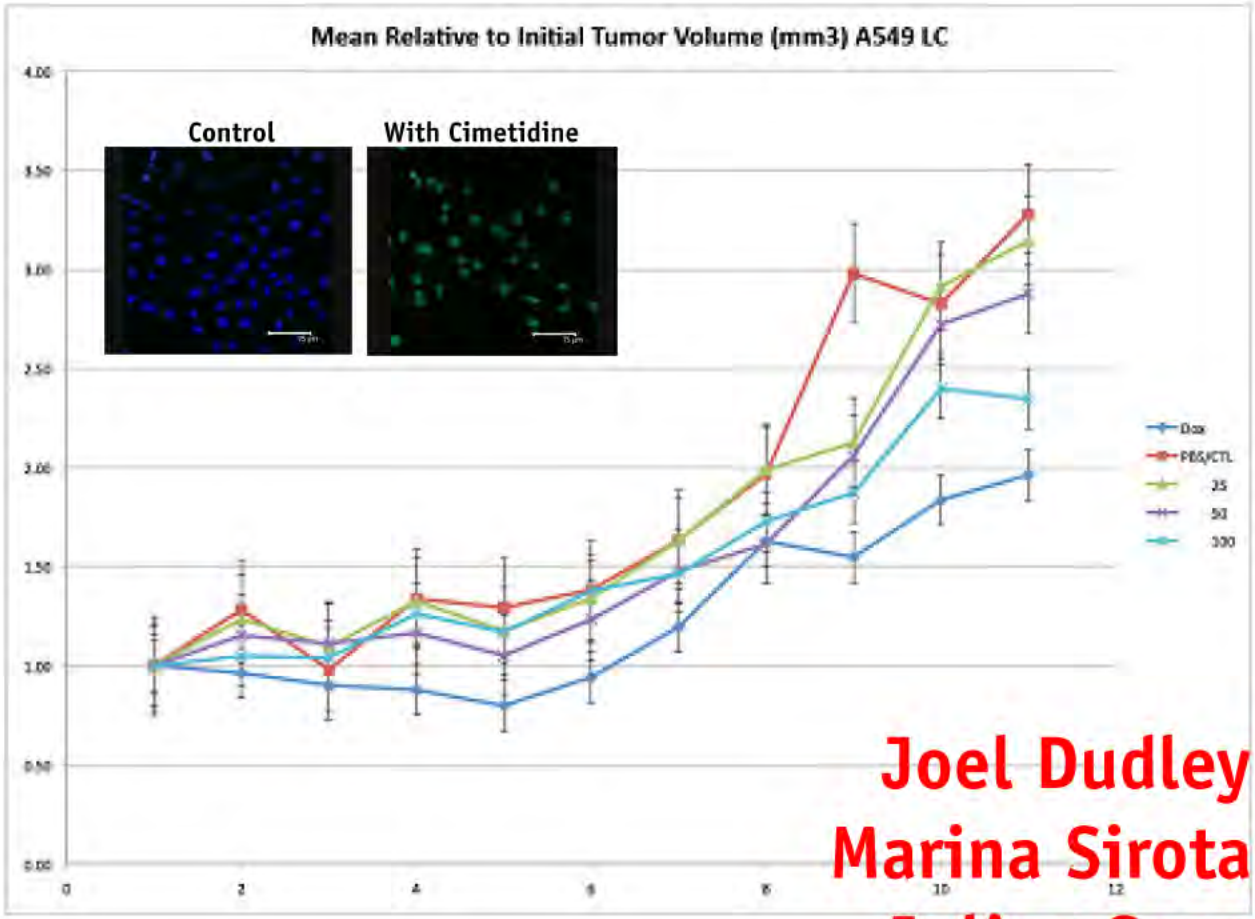


Marina Sirota
Joel Dudley
Mohan M Shenoy
Jay Pasricha

Dudley JT, Sirota M, ..., Pasricha J, Butte AJ. *Science Translational Medicine*, 2011.

Anti-ulcer drug works for lung adenocarcinoma

- Human lung adenocarcinoma cell lines explanted into mouse models
- Followed growth over 11 days
- Positive-control dose of doxorubicin grew to 2x original volume
- Tumors in mice treated with vehicle grew to 3.25x original volume
- Not only did our compound work statistically better than control, it worked in a dose-dependent manner
- Tumors in mice treated with 50 mg/kg/day grew 2.8x
- Those treated with 100 mg/kg/day grew only 2.3x.

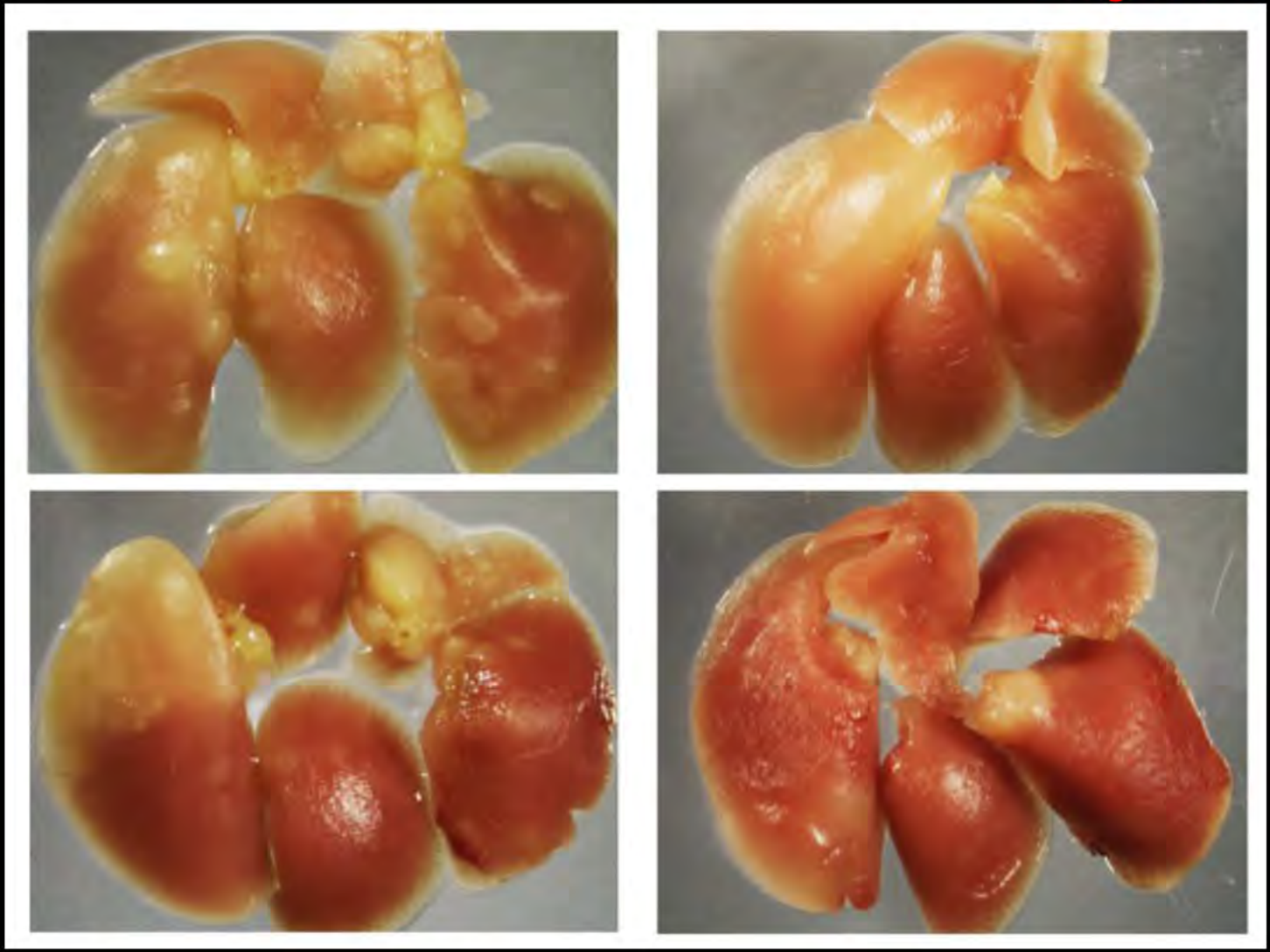


Joel Dudley
Marina Sirota
Julien Sage

Sirota M, Dudley JT,..., Sage J, Butte AJ. ***Science Translational Medicine*****, 2011,**

Drug X Shows Significant Activity Against Small Cell Lung Cancer

Joel Dudley
Alejandro Sweet-Cordero
Julien Sage
NuMedii



Vehicle control

Drug X

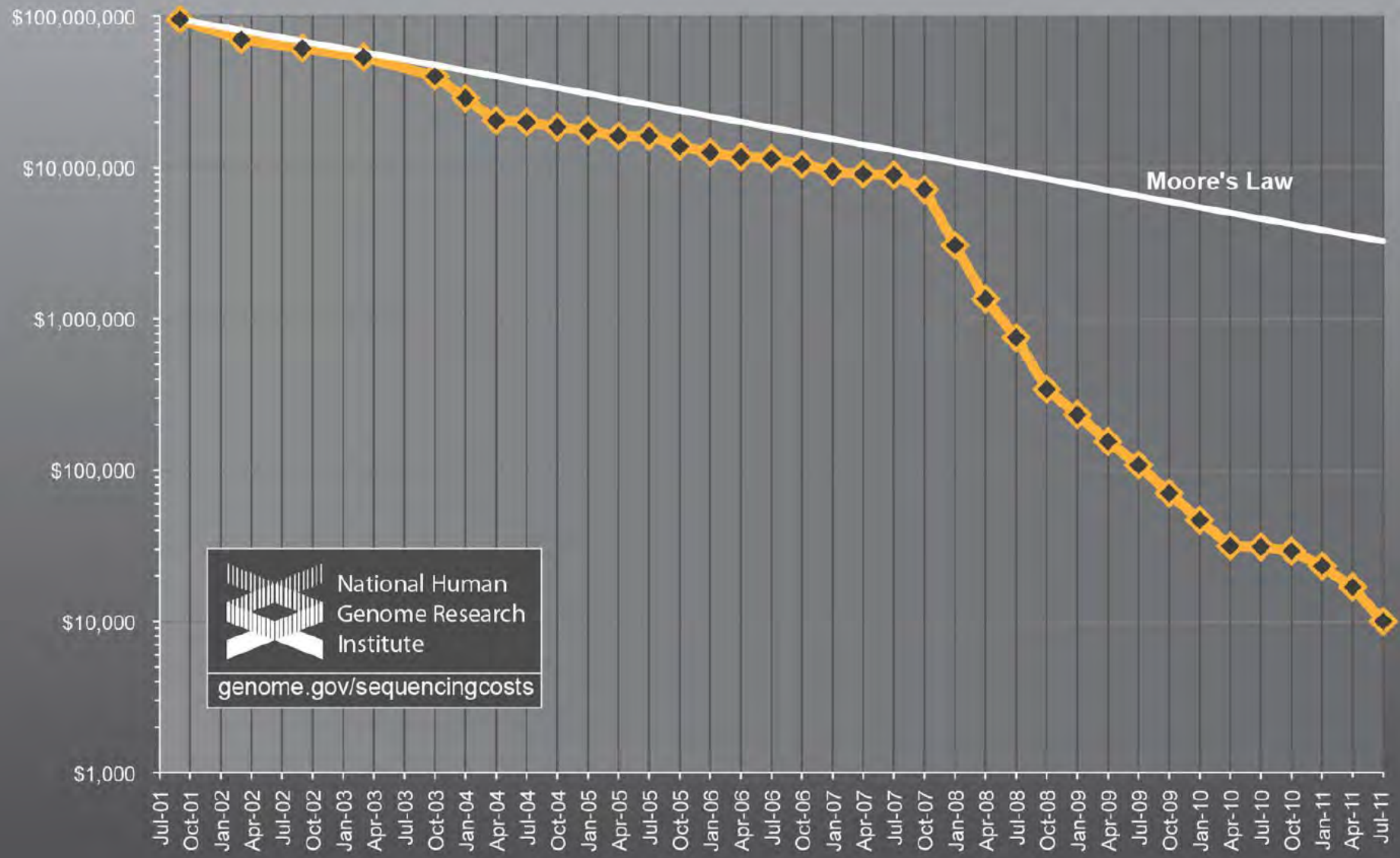
P53/Rb/p130 triple knockout model of SCLC

Mice dosed after tumor formation

Agenda

- Integrative genomics to find causal factors for complex disorders Link
- Genomic nosology and drug/diagnostic discovery Link
- Personalized disease-risk prediction and prevention Link

Cost per Genome



nature biotechnology

LETTERS

Published online August 10, 2009

Single-molecule sequencing of an individual human genome

Dmitry Pushkarev[1,2], Norma F Neff[1,2] & Stephen R Quake[1]

Recent advances in high-throughput DNA sequencing technologies have enabled order-of-magnitude improvements in both cost and throughput. Here we report the use of single-molecule methods to sequence an individual human genome. We aligned billions of 24- to 70-bp reads (32 bp average) to ~90% of the National Center for Biotechnology Information (NCBI) reference genome, with 28× average coverage. Our results were obtained on one sequencing instrument by a single operator with four data collection runs. Single-molecule sequencing enabled analysis of human genomic information without the need for cloning, amplification or ligation. We determined ~2.8 million single nucleotide polymorphisms (SNPs) with a false-positive rate of less than 1% as validated by Sanger sequencing and 99.8% concordance with SNP genotyping arrays. We identified 752 regions of copy number variation by analyzing coverage depth alone and validated 27 of these using digital PCR. This milestone should allow widespread application of genome sequencing to many aspects of genetics and human health, including personal genomics.

on a surface can be extended asynchronously, thereby allowing substantial flexibility in the kinetics of sequencing chemistry. Previous reports of single-molecule sequencing have been proofs of principle[11–13], and their sequencing throughput has not been competitive with alternative approaches. Generally, read lengths have been relatively short and error rates have been dominated by deletions; it has not been clear whether the resulting sequence quality is suitable for human genome sequencing applications.

The Heliscope Single Molecule Sequencer (Helicos Biosciences) is the first commercial release of a single-molecule sequencing instrument. It allows one to follow ~1 billion individual molecules as they are sequenced over the course of a week—a throughput that is practical for human genome sequencing. There have been several technical improvements to the platform since the reported sequencing of a viral genome[12], including more than a 1,000-fold improvement in parallelism, a new generation of sequencing reagents that allows digital measurement of homopolymer sequences, and a new software algorithm, IndexDP, for performing alignments to the entire human genome.

We used two of the instrument's 50 flow-cell channels to resequence

Clinical assessment incorporating a personal genome

Euan A Ashley, Atul J Butte, Matthew T Wheeler, Rong Chen, Teri E Klein, Frederick E Dewey, Joel T Dudley, Kelly E Ormond, Aleksandra Pavlovic, Alexander A Morgan, Dmitry Pushkarev, Norma F Neff, Louanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreiya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Wait Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

Summary

Background The cost of genomic information has fallen steeply, but the clinical translation of genetic risk estimates remains unclear. We aimed to undertake an integrated analysis of a complete human genome in a clinical context.

Methods We assessed a patient with a family history of vascular disease and early sudden death. Clinical assessment included analysis of this patient's full genome sequence, risk prediction for coronary artery disease, screening for causes of sudden cardiac death, and genetic counselling. Genetic analysis included the development of novel methods for the integration of whole genome and clinical risk. Disease and risk analysis focused on prediction of genetic risk of variants associated with mendelian disease, recognised drug responses, and pathogenicity for novel variants. We queried disease-specific mutation databases and pharmacogenomics databases to identify genes and mutations with known associations with disease and drug response. We estimated post-test probabilities of disease by applying likelihood ratios derived from integration of multiple common variants to age-appropriate and sex-appropriate pre-test probabilities. We also accounted for gene-environment interactions and conditionally dependent risks.

Lancet, May 1, 2010.

Patient zero

40 year old male in good health presents to his doctor with his whole genome

No symptoms

Exercises regularly

Takes no medications

Family history of aortic aneurysm

Family history of sudden death

Presents with 2.8 million SNPs

752 copy number variants

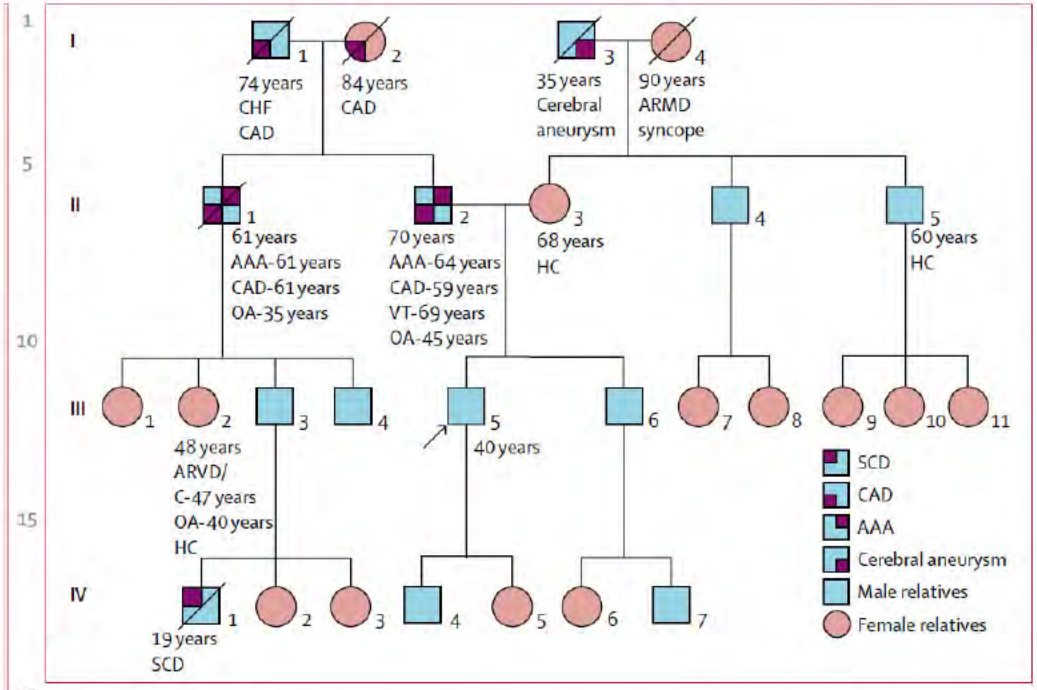


Figure 2: **Patient pedigree**
The arrow shows the patient. Diagonal lines show relatives who are deceased. Years are age at death or diagnosis. AAA=abdominal aortic aneurysm. ARMD=age-related macular degeneration. ARVD/C=arrhythmogenic right-ventricular dysplasia or cardiomyopathy. CAD=coronary artery disease. CHF=congestive heart failure. HC=hypercholesterolaemia. HTN=hypertension. OA=osteoarthritis. SCD=sudden cardiac death (presumed). VT=paroxysmal ventricular tachycardia.

STANFORD
SCHOOL OF MEDICINE

Variants predisposing to cardiac risk

	Amino-acid substitution	Gene name	Chromosome number	Position	SNP location	Reference base*	Patient genotype	Associated disease†	Mutation databases‡	Functional prediction§	Mode of disease-gene inheritance
Previously described rare variants in genes associated with common disease											
LPA[15,16]	I4399M¶	Apolipoprotein A precursor, lipoprotein(a)	6	160881127	rs3798220	T	C/T	Coronary artery disease	Associated with high lipoprotein(a) concentrations	Benign	NA
FRZB[17]	R200W	Frizzled-related protein	2	183411581	rs288326	G	A/G	Osteoarthritis	Possibly associated with osteoarthritis‖	Damaging	NA
Previously described rare variants in genes associated with rare disease											
HFE	H63D	Hereditary haemochromatosis protein precursor	6	26199158	rs1799945	C	C/G	Haemochromatosis	Previously described, disease-associated	Damaging	Recessive, incomplete penetrance
BTD[20]	D444H	Biotinidase precursor	3	15661697	rs13078881	G	C/G	Biotinidase deficiency	Previously described, intermediate phenotype	Damaging	Recessive
SLC26A2[21]	R492W	Solute carrier family 26 (sulphate transporter), member 2	5	149340823	None	C	C/T	Diastrophic dysplasia	Disease-associated	Damaging	Recessive
LAMB3[22]	R635X	Laminin, β3	1	207865689	None	G	A/G	Epidermolysis bullosa, junctional	Disease-associated, most common mutation	Truncated protein	Recessive
SLC3A1[23]	M467T	Solute carrier family 3 (cystine, dibasic, and neutral aminoacid transporters), member 1	2	44393296	None	T	C/T	Cystinuria	Disease-associated, most common mutation	Damaging	Recessive
Previously described variants of unknown importance in disease-associated genes											
TMEM43[24]	M41V	Transmembrane protein 43	3	14146021	None	A	A/G	ARVD/C	Reported in one of 150 probands with ARVD/C	Benign	Dominant, incomplete penetrance
MYBPC3[25]	R326Q	Myosin-binding protein C, cardiac-type	11	47324447	rs34580776	C	C/T	Familial hypertrophic cardiomyopathy	Variant of unknown importance	Intermediate	Dominant, incomplete penetrance
Novel variants potentially associated with rare disease											
DSP[26]	R1838H	Desmoplakin	6	7528007	Novel	G	A/G	ARVD/C	Not found	Damaging	Dominant, incomplete penetrance
CDC73[26]	Q430X	Parafibromin	1	191468879	Novel	C	C/T	Hyperparathyroidism, jaw tumour	Not found	Truncated protein	Dominant, loss of heterozygosity
CFTR[27]	G458R	Cystic fibrosis transmembrane conductance regulator	7	116976093	Novel	G	A/G	Cystic fibrosis	Not found	Damaging	Recessive
HFE2	H174Y	Haemojuvelin precursor	1	144127058	Novel	C	C/T	Haemochromatosis, juvenile	Not found	Damaging	Recessive

- **Rare variants in 3 genes clinically associated with sudden cardiac death: *TMEM43*, *DSP*, and *MYBPC3***
- **Variant in *LPA* consistent with a family history of coronary artery disease**

Euan Ashley and team

Ashley et al (2010), *Lancet* 375:1525

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- Rare variants in 3 genes clinically associated with sudden cardiac death: *TMEM43*, *DSP*, and *MYBPC3*
- Variant in *LPA* consistent with a family history of coronary artery disease

Euan Ashley and team

Ashley et al (2010), *Lancet* 375:1525

Pharmacogenomics predictions

- Heterozygous null mutation in *CYP2C19* → clopidogrel resistance?
- Variants associated with positive response to lipid-lowering therapy
- *CYP4F2* and *VKORC1* variants → low initial warfarin dose

	Gene name	SNP location	Patient genotype	Drug(s) affected	Summary of effects	Level of evidence
SLCO1B1	Solute carrier organic anion transporter family, member 1B1	rs4149056	T/T	HMG-CoA reductase inhibitors (statins)	No increased risk of myopathy	High[32-34]
CYP2C19	Cytochrome P450, family 2, subfamily C, polypeptide 19	rs4244285	A/G	Clopidogrel and CYP2C19 substrates	CYP2C19 poor metaboliser; many drugs might need adjustment	High[35]
VKORC1	Vitamin K epoxide reductase complex, subunit 1	rs9923231	C/T	Warfarin	Reduced dose needed	High[36]
CYP4F2	Cytochrome P450, family 4, subfamily F, polypeptide 2	rs2108622	C/C	Warfarin	Reduced dose needed	High[37]
ADRB1	β1 adrenergic receptor	rs1801252	A/A	Atenolol, metoprolol	Might be preferable to calcium-channel blockers	High[38,39]
SLCO1B1	Solute carrier organic anion transporter family, member 1B1	rs11045819	A/C	Fluvastatin	Good response	Medium[40]
HMGCR	HMG-CoA reductase	rs17238540	T/T	Pravastatin	Patient might have good response	Medium
HMGCR	HMG-CoA reductase	rs17244841	A/A	Pravastatin, simvastatin	No reduced efficacy	Medium
ADRB2	β2 adrenergic receptor, surface	rs1042713	A/G	β blockers	Other treatment options might be preferable	Medium[41]
ADRB2	β2 adrenergic receptor, surface	rs1042714	C/C	β blockers	Other treatment options might be preferable	Medium[41,42]
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6	rs3892097 rs1800716	C/C	Metoprolol and other CYP2D6 substrates	Normal CYP2D6 metaboliser	Medium[43]
CDKN2A/B	Cyclin-dependent kinase inhibitor 2A/2B	rs10811661	T/T	Metformin	Reduced likelihood of response	Medium[44]
CDKN2A/B	Cyclin-dependent kinase inhibitor 2A/2B	rs10811661	T/T	Troglitazone	Reduced likelihood of response	Medium[44]

SNP=single nucleotide polymorphism. HMG-CoA=3-hydroxy-3-methylglutaryl-coenzyme A.

Table 3: **Pharmacogenomic variants with summary of effects and level of evidence**

Russ Altman and team

Ashley EA*, Butte AJ*, Wheeler MT, Chen R, Klein TE, Dewey FE, Dudley JT, Ormond KE, Pavlovic A, Hudgins L, Gong L, Hodges LM, Berlin DS, Thorn CF, Sangkuhl K, Hebert JM, Woon M, Sagreiya H, Whaley R, Morgan AA, Pushkarev D, Neff NF, Knowles W, Chou M, Thakuria J, Rosenbaum A, Zaranek AW, Church G, Greely HT*, Quake SR*, Altman RB*. Clinical evaluation incorporating a personal genome. *Lancet*, 2010.

Existing SNP-disease databases are too limited for application to a human genome

Genome-wide association studies

- NHGRI GWAS Catalog
  - 1032 papers → 5050 SNPs for 557 diseases (6280 records), but 26% without OR, 33% without risk/protective alleles

Individual candidate-gene associations

- NIH Genetic Association Database
  - 56,000 papers, 130,000 records, ~2000 genes, only 4% with dbSNP ids, 1706 with alleles, none with risk/protective
- Online Mendelian Inheritance in Man
  - no dbSNP ids, monogenic
- Human Genome Mutation Database
  - 113247 mutations, most Mendelian disease, few SNPs, no genotypes, or odds ratios

ORIGINAL ARTICLE

Association of *IL23R*, *TNFRSF1A*, and HLA-DRB1*0103 Allele Variants with Inflammatory Bowel Disease Phenotypes in the Finnish Population

Maarit Lappalainen, MSc,[*,†] *Leena Halme, MD, PhD,*[‡] *Ulla Turunen, MD,*[§] *Päivi Saavalainen, PhD,*[*,‖] *Elisabet Einarsdottir, PhD,*[*,‖] *Martti Färkkilä, MD, PhD,*[§] *Kimmo Kontula, MD, PhD,*[*,†] *and Paulina Paavola-Sakki, MD, PhD*[†,§]

Background: Crohn's disease (CD) and ulcerative colitis (UC), 2 major forms of inflammatory bowel disease (IBD), are complex disorders with significant genetic predisposition. The first CD-associated gene, *CARD15/NOD2*, was recently identified and since then several reports on novel IBD candidate genes have emerged. We investigated disease phenotype association to genetic variations in *IL23R*, *ATG16L1*, *DLG5*, *ABCB1/MDR1*, *TLR4*, *TNFRSF1A*, chromosome 5 risk haplotype including *SLC22A4* and *SLC22A5*, and HLA-DRB1*0103 allele among Finnish IBD patients.

Methods: A total of 699 IBD patients were genotyped for disease-associated variants by polymerase chain reaction (PCR) and restriction enzyme digestion or Sequenom iPLEX method.

Results: Five markers spanning the *IL23R* gene were associated with CD. The SNP (single nucleotide polymorphism) rs2201841 gave the strongest association ($P = 0.002$). The rare HLA-DRB1*0103 allele was found to associate with UC ($P = 0.008$), and the *TNFRSF1A* A36G variant was associated with familial UC ($P = 0.007$). Upon phenotypic analysis we detected association between familial UC and rare *TNFRSF1A* alleles 36G and IVS6+10G ($P = 0.001$ and $P = 0.042$, respectively). In addition, *IL23R* markers were associated with stricturing CD ($P = 0.010–0.017$), and ileocolonic CD was more prevalent in the carriers of the same 2 *TNFRSF1A* variants ($P = 0.021$ and $P = 0.028$, respectively). Less significant genotype–phenotype associations were observed for the *TLR4* and HLA variants.

Conclusions: We were able to replicate the association of the *IL23R* variants with CD as well as HLA-DRB1*0103 with UC; confirmation of *TNFRSF1A* association with UC needs additional studies. Our findings also suggest that polymorphisms at *IL23R* and *TNFRSF1A*, and possibly HLA and *TLR4*, loci may account for phenotypic variation in IBD.

(*Inflamm Bowel Dis 2008;14:1118–1124*)

Key Words: Finnish, inflammatory bowel disease, HLA-DRB1*0103, IL23R, TNFRSF1A

Since the initial discovery of the association of *CARD15/NOD2* gene variants with Crohn's disease (CD),[1–3] several new susceptibility genes for inflammatory bowel disease (IBD) have been reported. In 2004 the positional cloning approach led to the identification of the associated variants in solute carrier family 22 (*SLC22A* members 4 and 5)[4] and the discs large homolog 5 (*DLG5*)[5] genes that are implicated in fatty acid oxidation and in maintaining epithelial integrity, respectively. It has not, however, been unequivocally proved that the *SLC22A* genes represent the actual disease genes.[6–13] Most of the studies have confirmed the association of CD with the *SLC22A* gene variants or with the chromosome 5 risk haplotype; however, a study of more than 981 Belgian IBD patients could not replicate the association with IBD, CD, or ulcerative colitis (UC).[14] A recent study by Silverberg et al[15] using a large cohort of IBD trios excluded the *SLC22A5* gene variant as the potential causal variant. The association of genetic variations in the *DLG5* gene with IBD and CD was initially described in 2 large European study samples.[5] The haplotype A, tagged by SNP DLG5_e26 ins/delA, was significantly undertransmitted in IBD and CD, whereas haplotype D, tagged by the SNP G113A (R30Q), was significantly overtransmitted in both IBD and CD. Several groups have not been able to replicate the association since the original report.[13,14,16] However, in 1 case gender-specific analysis revealed an association.[17]

The association of IBD with genetic variation in the Toll-like receptor 4 (*TLR4*) gene has been investigated by many groups but the results have been controversial, which

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From the *Research Program for Molecular Medicine, Biomedicum Helsinki, Finland, †Department of Medicine, University of Helsinki, Helsinki, Finland, ‡Department of Transplantation and Liver Surgery, Helsinki University Hospital, Helsinki, Finland, §Department of Gastroenterology, Helsinki University Hospital, Helsinki, Finland, ‖Department of Medical Genetics, Biomedicum Helsinki, Finland.

Supported by a grant from the Special State Funds of the Helsinki University Central Hospital (EVO), University of Helsinki, the Finnish Academy, and the EU commission (MEXT-CT-2005-025270).

Reprints: Kimmo Kontula, Department of Medicine, University of Helsinki, Haartmaninkatu 4, FIN-00290 Helsinki, Finland (e-mail: kimmo.kontula@hus.fi).

DOI 10.1002/ibd.20431
Published online 13 March 2008 in Wiley InterScience (www.interscience.wiley.com).

Rong Chen
Optra Systems

- Study published in 2008 in *Inflammatory Bowel Disease*
- Crohn's Disease and Ulcerative Colitis
- Investigated 9 loci in 700 Finnish IBD patients
- We record 100+ items
  - GWAS, non-GWAS papers
  - Disease, Phenotype
  - Population, Gender
  - Alleles and Genotypes
  - p-value (and confidence)
  - Odds ratio (and confidence)
  - Technology, Study design
  - Genetic model
- Mapped to UMLS concepts

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- Investigated 9 loci in 700 Finnish IBD patients
- We record 100+ items
  - GWAS, non-GWAS papers

TABLE 1. Case-control Analysis of the *IL23R* Gene Including 8 SNPs

dbSNP ID	Allele	Location	Controls $n = 292$	IBD $n = 697$	P value	CD $n = 238$	P value	UC $n = 459$	P value
rs1004819	C	Intron 5	0.751	0.704	**0.037**	0.671	**0.005**	0.721	0.215
	T		0.249	0.296		0.329		0.279	

sinki, Haartmaninkatu 4, FIN-00290 Helsinki, Finland (e-mail: kimmo.kontula@hus.fi).

DOI 10.1002/ibd.20431

Published online13 March 2008 in Wiley InterScience (www.interscience.wiley.com).

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  - Genetic model
- Mapped to UMLS concepts

- Study published in 2009 in *Rheumatology*
- Ankylosing spondylitis
- Investigated 8 SNPs in IL23R in 2000 UK case-control patients

Rheumatology 2009;48:386–389
Advance Access publication 2 February 2009

Concise Report

Association between the interleukin 23 receptor a spondylitis is confirmed by a new UK case–contr meta-analysis of published series

Tugce Karaderi[1], David Harvey[1], Claire Farrar[1], Louise H. Appleton[1], M Roger D. Sturrock[3], Matthew A. Brown[4], Paul Wordsworth[1] and Jennife

Objectives. It has been shown previously that *IL-23R* variants are associated with AS. We con population and a meta-analysis with the previously published studies, in order to refine these *IL-23*
Methods. The UK case–control study included 730 new cases and 1331 healthy controls. In th combined with 1088 published cases. Allelic associations were analysed using contingency tables 3150 controls from four different published studies and the new UK cases were combined. DerSi random effects pooled odds ratios (ORs).
Results. In the UK case–control study with new cases, four of the eight SNPs showed significan UK study, seven of the eight *IL-23R* SNPs showed significant associations ($P < 0.05$) with AS, maxi when cases with IBD and/or psoriasis were excluded. The meta-analysis showed significant assoc associations were again seen not only with rs11209032 ($P = 4.06 \times 10^{-9}$, OR ~1.2) but also with
Conclusions. *IL-23R* polymorphisms are clearly associated with AS, but the primary causal associa polymorphisms could contribute either increased or decreased susceptibility to AS; functional studie Additionally, observed stronger associations with SNPs rs11209026 and rs11465804 upon exclu represent an independent association with AS.

Key words: IL-23 receptor, AS, Polymorphism, SpA, Genetic association.

Introduction

The heritability of AS estimated from twin studies in the United Kingdom and elsewhere is in excess of 90% [1]. The best known component of this arises from the HLA-B27 immune response gene that contributes 20–30% of the total genetic risk [2]. Substantial progress has now been made in identifying non-MHC genes causing susceptibility to AS; *IL-23R*, encoding one component of the interleukin 23 receptor, is one of these genes identified by genome-wide association studies [3]. IL-23R, a member of haemopoietin receptor superfamily, is the IL-23R-specific component of the heterodimeric receptor for the cytokine IL-23. The other subunit, IL-12Rβ1, is also a component of the IL-12 receptor (together with the IL-12Rβ2 subunit). Cells expressing the IL-23R subunit respond to IL-23 rather than IL-12 [4]. The IL-23 receptor is important in CD4 T-cell differentiation into the T_H17 lymphocyte subset that mediates inflammation in several animal models of autoimmunity [5, 6]. In various experimental models, T_H17 cells producing IL-17 have been shown to cause tissue damage in the brain, joints, heart, lungs and intestines [7]. *IL-23R* variants have also been implicated in susceptibility to human a riasis and multiple sclero common susceptibility loc associated with the serone

In a previous study, w is strongly associated wit tion has been supported b Spain [13]. We present her study, an extended UK stu series, strengthening the e *IL-23R*.

Methods

Study population

All patients were seen by AS, as defined by the m recruited from those atten (Oxford, UK) and the Ro Disease (Bath, UK) AS appeals and by referral fro gave informed written con was carried out with releva 98/5/23).

New UK case–control s association between IL-

In this study, 730 new AS healthy controls from the U design. None of the new U reports. New cases were (MassArray, Sequenom, S

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IL-23R and AS

Study I | Study II

	Minor Allele	MAF cases	MAF controls	Chi-square	*P*-value	OR	95% CI	MAF cases	MAF controls	Chi-square	*P*-value	OR	95% CI
Case–control study: A. Including all new AS cases only (730)								Extended study: C. Including all new AS cases (730) and WTCCC cases (1088)					
819	A	0.33	0.3	3.12	0.077	1.13	0.99, 1.30	0.33	0.3	9.83	0.0017	1.19	1.07, 1.32
9629	G	0.43	0.45	2.41	0.12	0.9	0.79, 1.03	0.43	0.45	4.08	0.043	0.9	0.81, 1.00
5804	C	0.04	0.06	6.45	0.011	0.68	0.50, 0.92	0.04	0.06	11.12	0.0009	0.68	0.54, 0.85
9026	A	0.05	0.06	5.41	0.02	0.71	0.53, 0.95	0.05	0.06	12.74	0.0004	0.67	0.53, 0.83
151	A	0.32	0.34	1.7	0.19	0.91	0.79, 1.05	0.32	0.34	6.05	0.014	0.87	0.79, 0.97
9677	A	0.36	0.31	7.86	0.0051	1.21	1.06, 1.39	0.36	0.31	12.91	0.0003	1.22	1.09, 1.35
9032	A	0.37	0.32	10.78	0.001	1.25	1.09, 1.43	0.37	0.32	22.22	$<10^{-5}$	1.29	1.16, 1.43
965	G	0.47	0.44	3.33	0.068	1.13	0.99, 1.29	0.47	0.44	9.19	0.0024	1.17	1.06, 1.29

. Results of the new and extended UK case–control study, combining UK WTCCC cases and new UK cases

- Tables can be rotated
- NLP is hard

- Study published in 2009 in *Rheumatology*

Rheumatology 2009;48:386–389
Advance Access publication 2 February 2009
doi:10.1093/rheumatology/ken501

Concise Report

Association between the interleukin 23 receptor and ankylosing spondylitis is confirmed by a new UK case–control study and meta-analysis of published series

TABLE 1. Results of the new and extended UK case–control study, combining UK WTCCC cases and new UK cases

		Study I						
SNP	Minor Allele	MAF cases	MAF controls	Chi-square	*P*-value	OR	95% CI	MAF cases
	Case–control study: A. Including all new AS cases only (730)							Extended study: C
rs1004819	A	0.33	0.3	3.12	0.077	1.13	0.99, 1.30	0.33
rs10489629	G	0.43	0.45	2.41	0.12	0.9	0.79, 1.03	0.43
rs11465804	C	0.04	0.06	6.45	0.011	0.68	0.50, 0.92	0.04
rs11209026	A	0.05	0.06	5.41	0.02	0.71	0.53, 0.95	0.05
rs1343151	A	0.32	0.34	1.7	0.19	0.91	0.79, 1.05	0.32
rs10889677	A	0.36	0.31	7.86	0.0051	1.21	1.06, 1.39	0.36
rs11209032	A	0.37	0.32	10.78	0.001	1.25	1.09, 1.43	0.37
rs1495965	G	0.47	0.44	3.33	0.068	1.13	0.99, 1.29	0.47

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was carried out with relevant ethical approval (MREC project No. 98/5/23).

New UK case–control study and extended UK study of association between IL-23R and AS

In this study, 730 new AS cases, 1088 published cases and 1331 healthy controls from the UK were compared using a case–control design. None of the new UK cases has been included in previous reports. New cases were genotyped using iPLEX technology (MassArray, Sequenom, San Diego, CA, USA) except for SNP

- Tables can be rotated
- NLP is hard

TABLE 1. Case-control Analysis of the *IL23R* Gene Including 8 SNPs

dbSNP ID	Allele	Location	Controls $n = 292$	IBD $n = 697$	P value	CD $n = 238$	P value
rs1004819	C	Intron 5	0.751	0.704	**0.037**	0.671	**0.005**
	T		0.249	0.296		0.329	

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What are the alleles for rs1004819?

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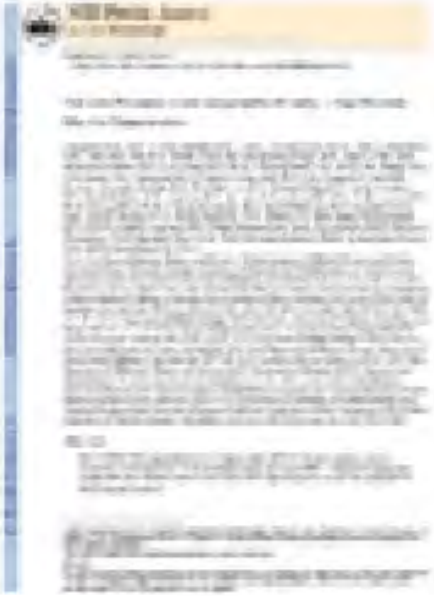
rs11209026	A	0.05	0.06	5.41	0.02	0.71	0.53, 0.95	0.05

Alleles for rs1004819 are C and T

Population Diversity

	Sample Ascertainment				Genotype Detail NEW				Alleles	
ss#	Population	Individual Group	Chrom. Sample Cnt.	Source	C/C	C/T	T/T	HWP	C	T
ss120253447	ENSEMBL_Venter		2	IG	1.000				1.000	
ss137986136	ENSEMBL_Watson		2	IG		1.000			0.500	0.500
ss143546670	ENSEMBL_Venter		2	IG		1.000			0.500	0.500
	ENSEMBL_celera		4	IG	0.500		0.500		0.500	0.500
ss1466382	CEPH		184	AF					0.730	0.270
	HapMap-CEU	European	226	IG	0.513	0.398	0.088	1.000	0.712	0.288
	HapMap-HCB	Asian	86	IG	0.116	0.512	0.372	0.584	0.372	0.628
	HapMap-JPT	Asian	172	IG	0.221	0.442	0.337	0.343	0.442	0.558
	HapMap-YRI	Sub-Saharan African	226	IG	0.416	0.496	0.088	0.251	0.664	0.336
	HAPMAP-ASW		98	IG	0.469	0.510	0.020	0.100	0.724	0.276
	HAPMAP-CHB	Asian	82	IG	0.268	0.488	0.244	1.000	0.512	0.488
	HAPMAP-CHD		170	IG	0.141	0.482	0.376	1.000	0.382	0.618
	HAPMAP-GIH		176	IG	0.182	0.500	0.318	1.000	0.432	0.568
	HAPMAP-LWK		180	IG	0.556	0.389	0.056	0.752	0.750	0.250
	HAPMAP-MEX		100	IG	0.580	0.380	0.040	0.655	0.770	0.230

~11% of records reported genotypes in the negative strand



VARIMED: Variants Informing Medicine

Number of papers curated	Distinct SNPs	Diseases and phenotypes	Narrow phenotypes	Records
~7,300	~119,000	~2,200	~19,000	~330,000

Chen R, Davydov EV, Sirota M, Butte AJ.
PLoS One.
2010 October: 5(10): e13574.

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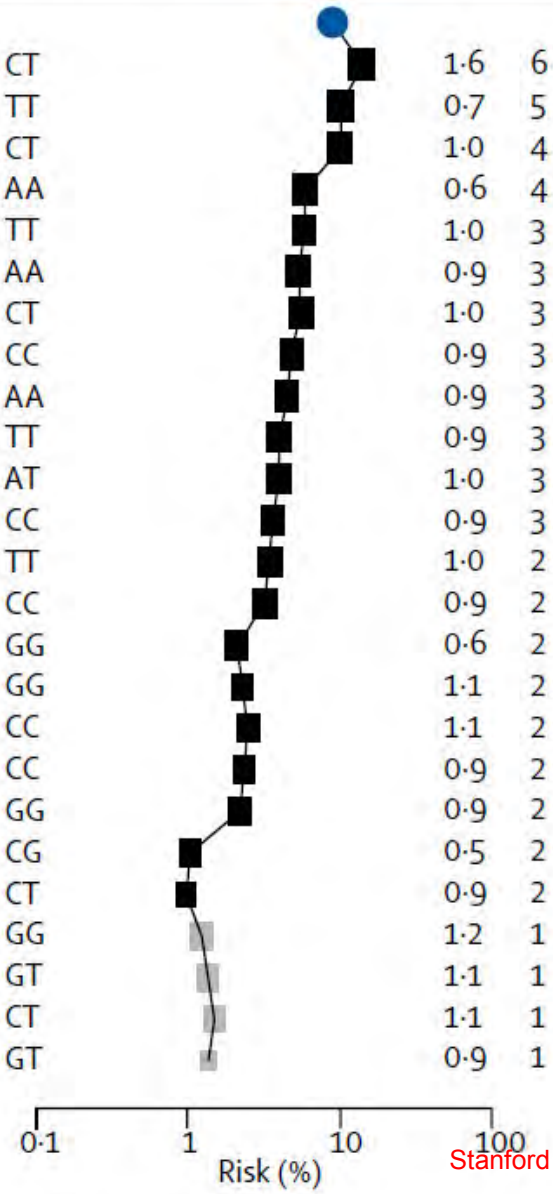
Optra Systems

45% of known published disease SNPs are outside exons

		SNPs	Diseases	SNP/Disease Associations
All	Exome	35,727	1,490	45,896
	Outside	31,581	740	35,031
p < 1E-6	Exome	4,820	403	5,782
	Outside	3,836	317	4,476
p < 5E-8	Exome	3,889	332	4,641
	Outside	2,911	262	3,402

D Alzheimer's disease

Gene*	SNP location	Patient genotype	LR	Studies†	Samples‡	Post-test probability (%)
						9·0%
TOMM40	rs157581	CT	1·6	6	7740	13·90%
DAPK1	rs4878104	TT	0·7	5	10397	10·19%
TRAK2	rs13022344	CT	1·0	4	6512	10·12%
DAPK1	rs4877365	AA	0·6	4	4841	5·89%
E8F3	rs11016976	TT	1·0	3	5736	5·87%
TNK1	rs1554948	AA	0·9	3	5736	5·32%
MYH13	rs2074877	CT	1·0	3	5366	5·55%
GALP	rs3745833	CC	0·9	3	5366	4·82%
PCK1	rs8192708	AA	0·9	3	5366	4·47%
	rs1859849	TT	0·9	3	5304	4·02%
	rs11622883	AT	1·0	3	5248	3·97%
WWC1	rs17070145	CC	0·9	3	2545	3·65%
LMNA	rs505058	TT	1·0	2	4646	3·49%
ACAN	rs2882676	CC	0·9	2	4590	3·22%
PGBD1	rs3800324	GG	0·6	2	4590	2·11%
GOLM1	rs10868366	GG	1·1	2	2156	2·30%
GOLM1	rs7019241	CC	1·1	2	2156	2·49%
	rs9886784	CC	0·9	2	2156	2·36%
	rs10519262	GG	0·9	2	2156	2·22%
	rs463946	CG	0·5	2	1922	1·04%
PLAU	rs2227564	CT	0·9	2	956	0·98%
ADAM12	rs1278279	GG	1·2	1	2320	1·23%
SORL1	rs2070045	GT	1·1	1	2031	1·36%
ABCA1	rs2230806	CT	1·1	1	1691	1·50%
PSEN1	rs165932	GT	0·9	1	170	1·37%



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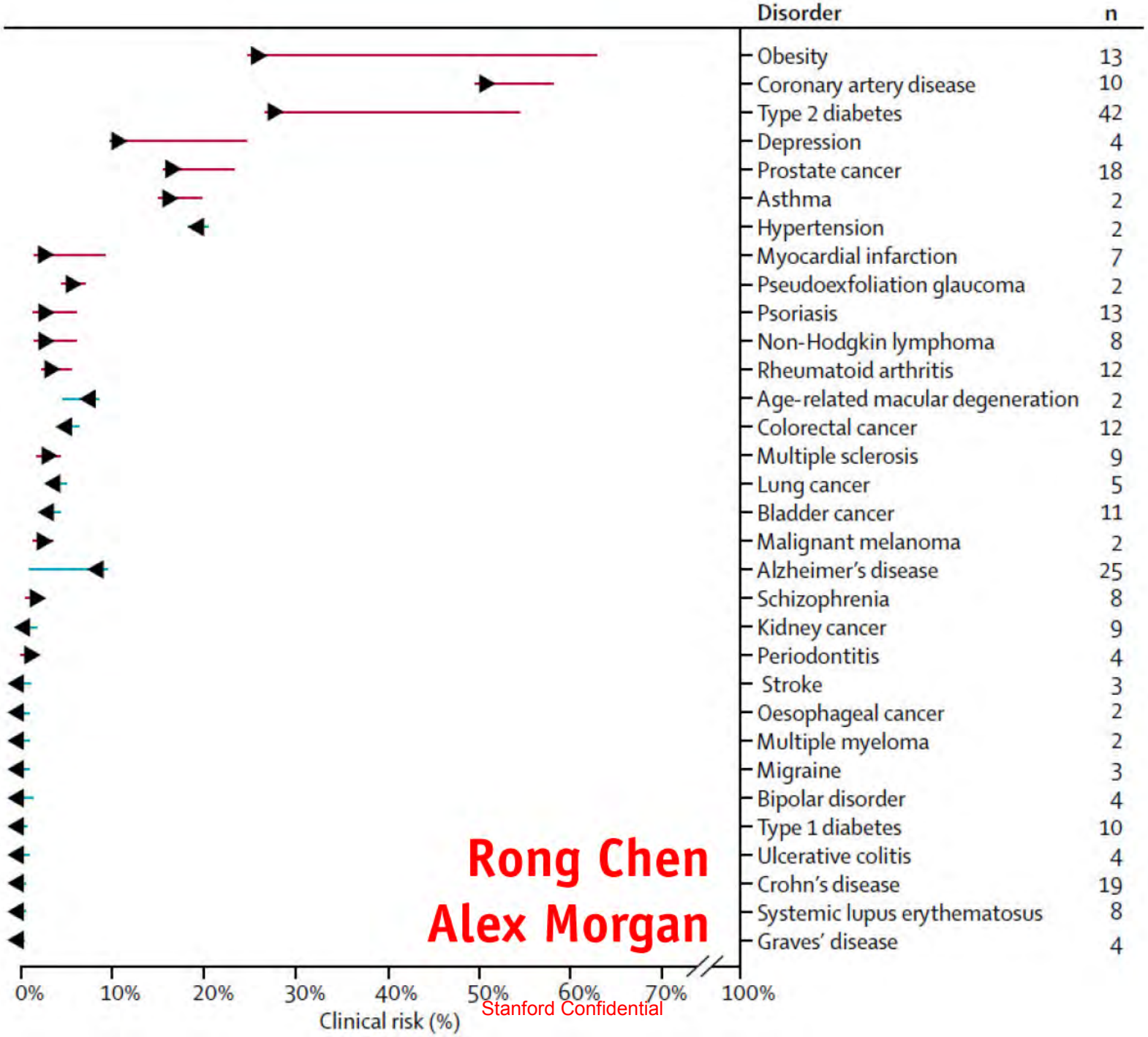
Alex Morgan

Ashley EA*, Butte AJ*, Wheeler MT, Chen R, Klein TE, Dewey FE, Dudley JT, Ormond KE, Pavlovic A, Hudgins L, Gong L, Hodges LM, Berlin DS, Thorn CF, Sangkuhl K, Hebert JM, Woon M, Sagreiya H, Whaley R, Morgan AA, Pushkarev D, Neff NF, Knowles W, Chou M, Thakuria J, Rosenbaum A, Zaranek AW, Church G, Greely HT*, Quake SR*, Altman RB*. Clinical evaluation incorporating a personal genome. *Lancet*, 2010.



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PLoS GENETICS

Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence

Frederick E. Dewey[1], Rong Chen[2], Sergio P. Cordero[3], Kelly E. Ormond[4,5], Colleen Caleshu[1], Konrad J. Karczewski[3,4], Michelle Whirl-Carrillo[4], Matthew T. Wheeler[1], Joel T. Dudley[2,3], Jake K. Byrnes[4], Omar E. Cornejo[4], Joshua W. Knowles[1], Mark Woon[4], Katrin Sangkuhl[4], Li Gong[4], Caroline F. Thorn[4], Joan M. Hebert[4], Emidio Capriotti[4], Sean P. David[4], Aleksandra Pavlovic[1], Anne West[6], Joseph V. Thakuria[7], Madeleine P. Ball[8], Alexander W. Zaranek[8], Heidi L. Rehm[9], George M. Church[8], John S. West[10], Carlos D. Bustamante[4], Michael Snyder[4], Russ B. Altman[4,11], Teri E. Klein[4], Atul J. Butte[2], Euan A. Ashley[1]*

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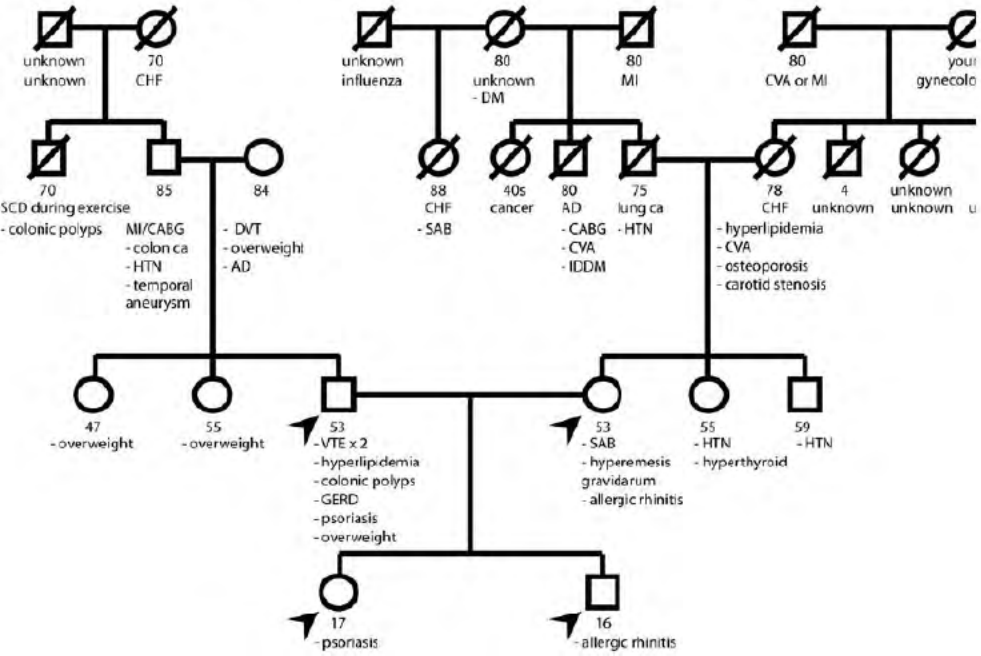
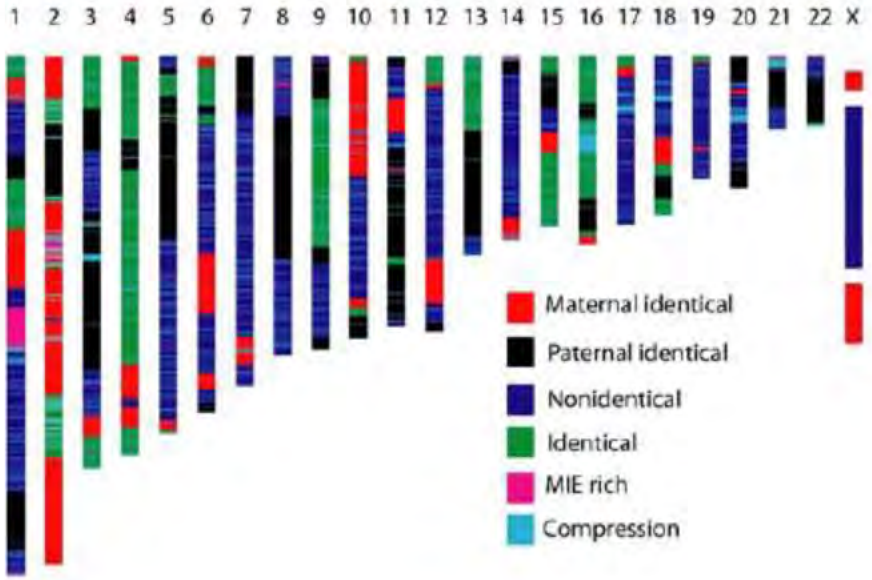
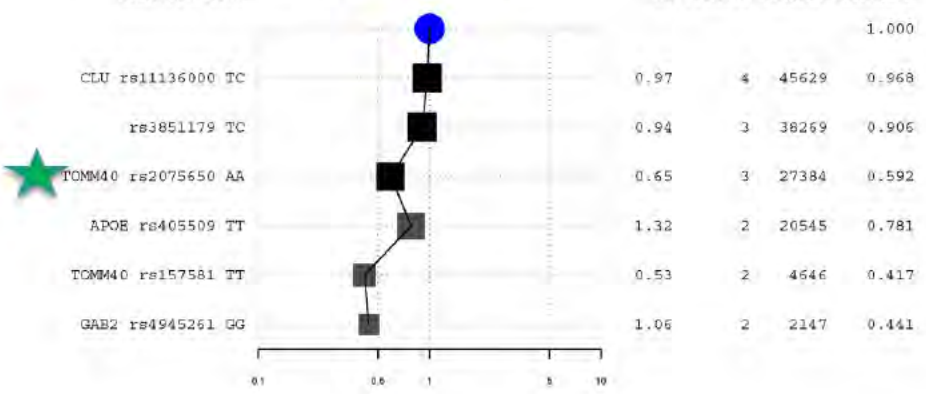




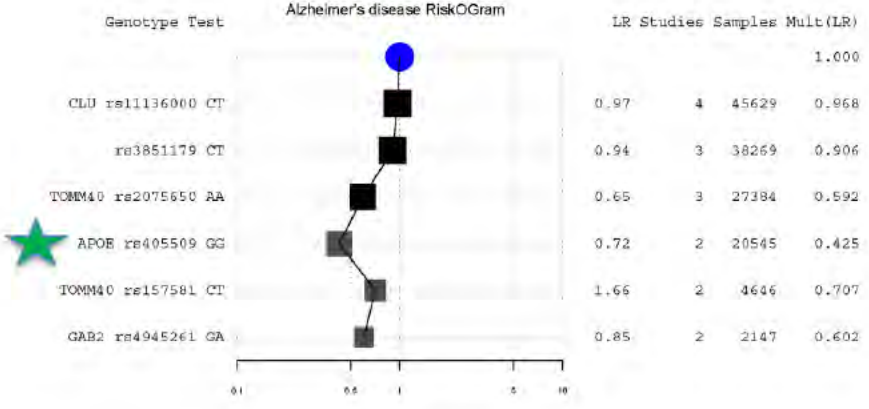
Alzheimer's Disease: All family members have protective SNPs, except the son

Rong Chen

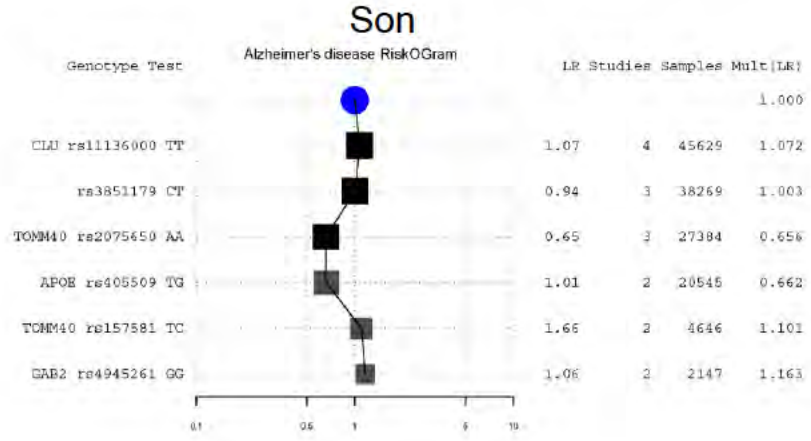
Father



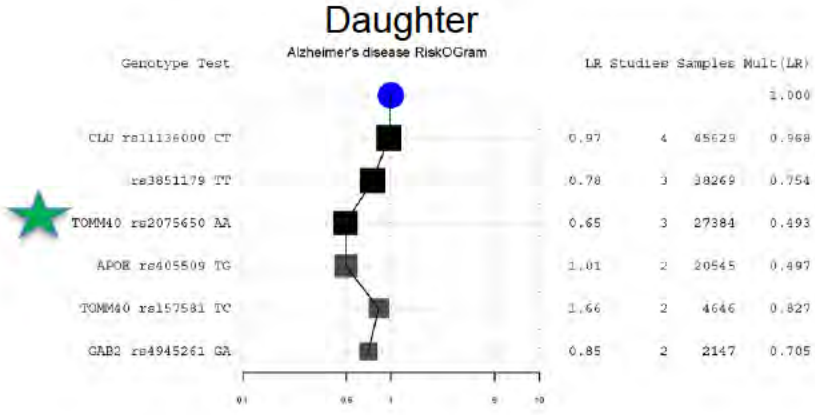
Mother



Son

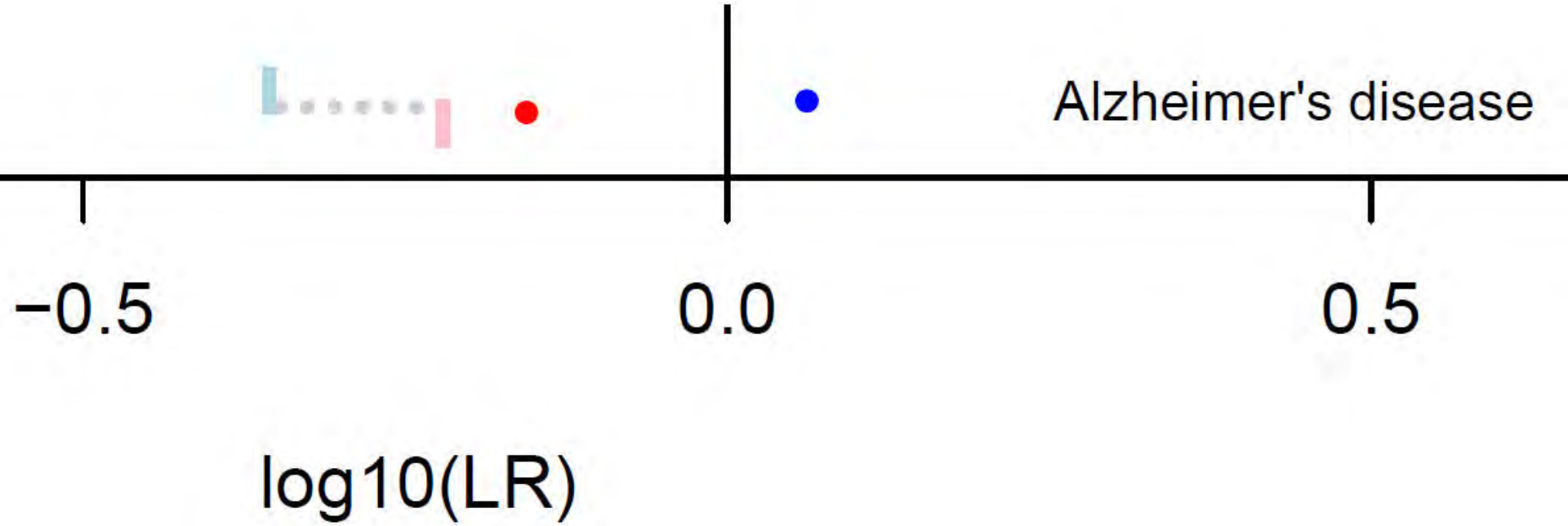


Daughter



PLoS Genetics, 2011.

Plotting family disease risk



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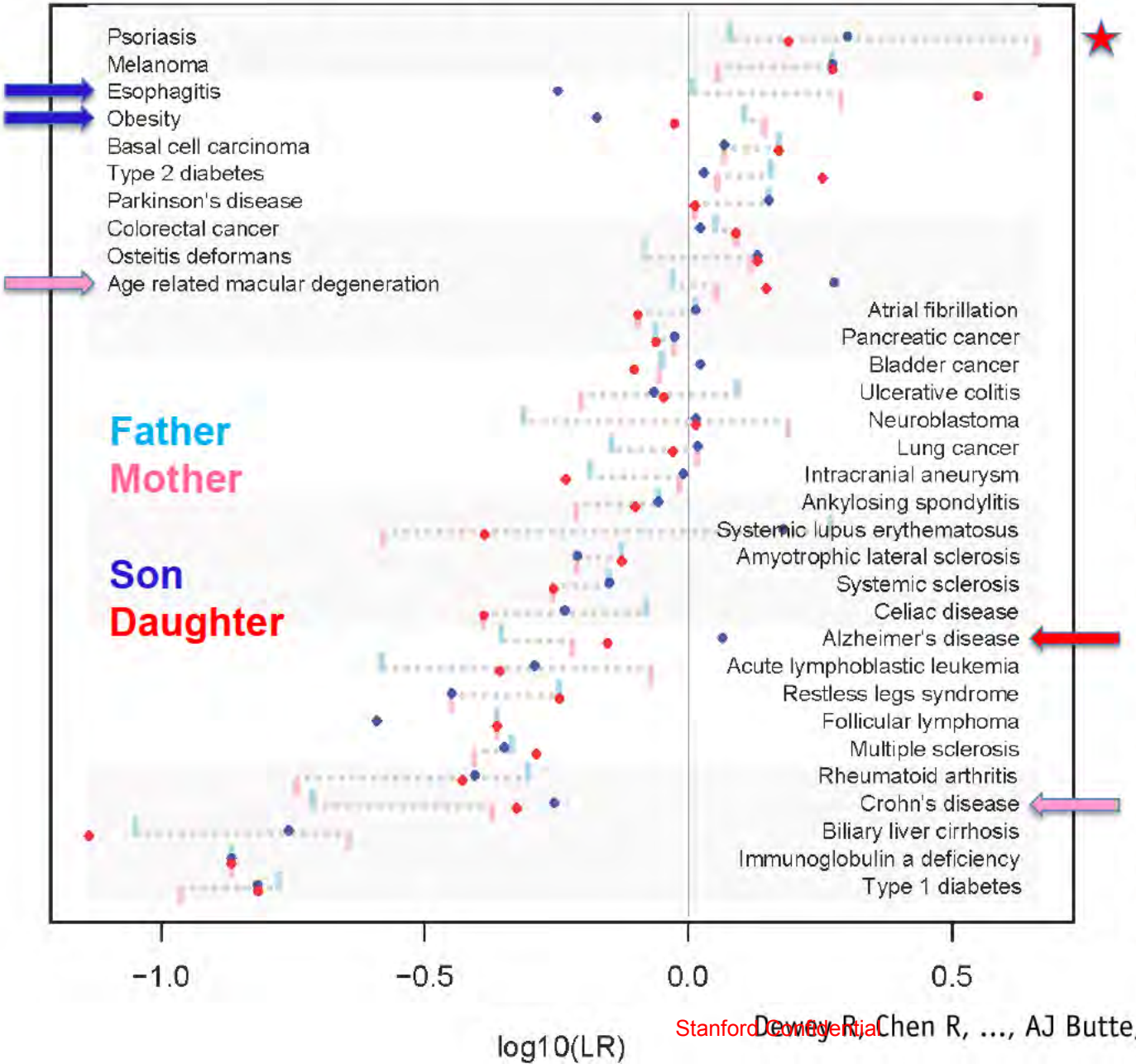
All in the family... Not.



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Both the son and daughter are protective from **obesity** while both parents are at risk.

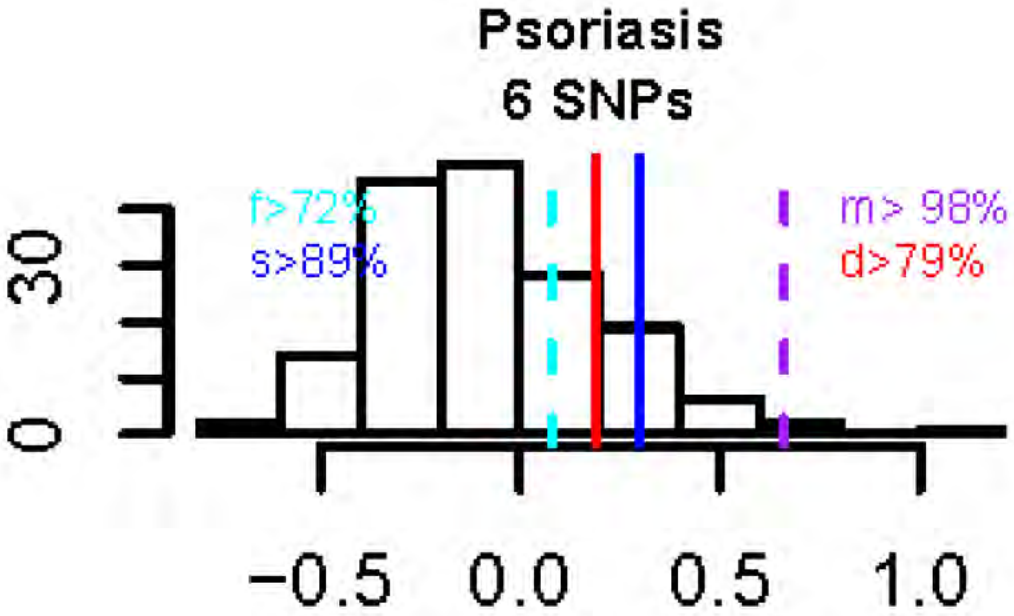
Both parents are at slight risk on **esophagitis**, and the daughter is at high risk and the son has protection.

Both parents are protective from **Alzheimer's disease**. The son is at high risk and the daughter is protective although less protective than the parents.

Both the son and the daughter have higher risk of **Crohn's disease** than the parents, but all family members are at the protective side.

Dewey, F, Chen R, ..., AJ Butte, E Ashley. *PLoS Genetics*, 2011.

Visualizing family psoriasis risk compared to background HapMap individuals



f Father > 72%ile
m Mother > 98%ile

s Son > 79%ile
d Daughter > 79%ile

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Dewey R, Chen R, ..., AJ Butte, E Ashley. *PLoS Genetics*, 2011.

Take Home Points

- Molecular, clinical, and epidemiological data and tools already exist → diagnostics, therapeutics, and disease mechanisms. Integration is enabling.

- Bioinformatics is not just about building tools. We know our tools; we should use them first.

- We need new investigators who can imagine basic questions to ask of these repositories of clinical and genomic measurements.

Translational Bioinformatics

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- Mike Snyder, Carlos Bustamante, Anne Brunet / Genetics
- Jay Pasricha / Gastroenterology
- Rob Tibshirani, Brad Efron / Statistics
- Hannah Valantine, Kiran Khush/ Cardiology
- Ken Weinberg / Pediatric Stem Cell Therapeutics
- Mark Musen, Nigam Shah / National Center for Biomedical Ontology
- Minnie Sarwal / Nephrology
- David Miklos / Oncology

Butte Lab

Systems Medicine • Stanford Pediatrics • Packard Children's Hospital

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