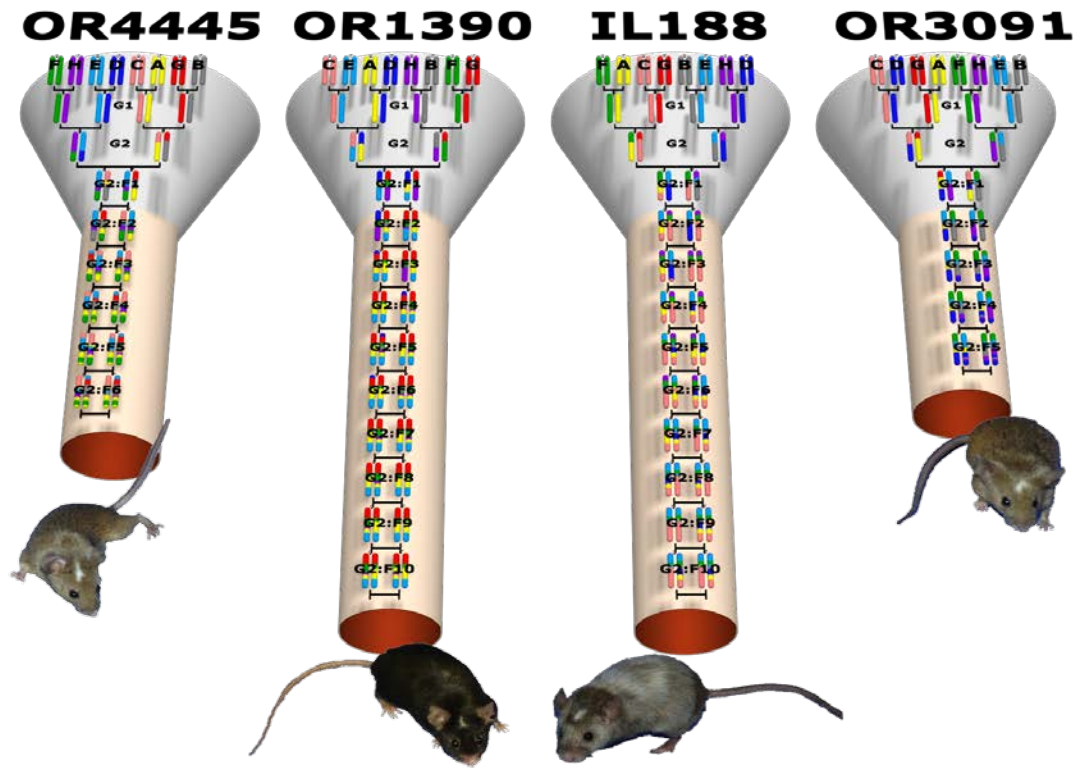


The Collaborative Cross: What We've Learned from Randomized, Structured Populations

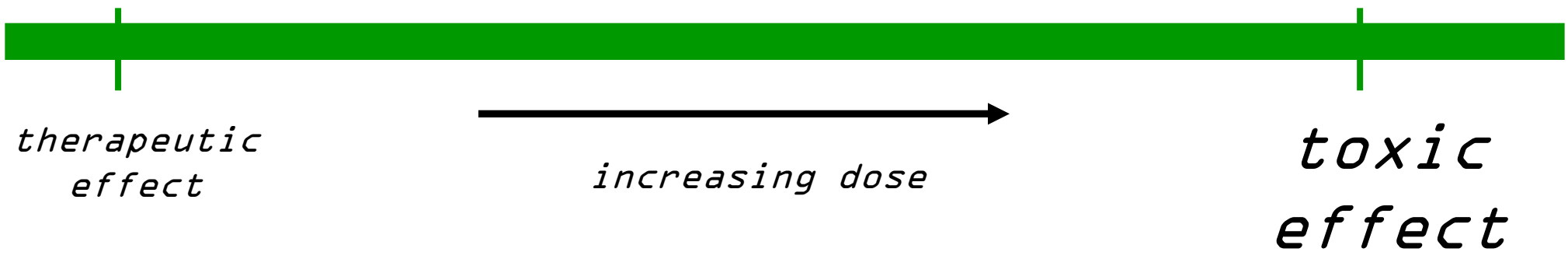
David Threadgill
Texas A&M University

Peracelsus

(Phillippus Aureolus Theophrastus Bombastus von Hohenheim)

1493-1541

Known as the ‘father of toxicology’. The saying “Dosis facit venenum” (The dose makes the poison) is attributed to him. His actual quote translates “All things are poisons, for there is nothing without poisonous qualities...it is only the dose which makes a thing poison.”

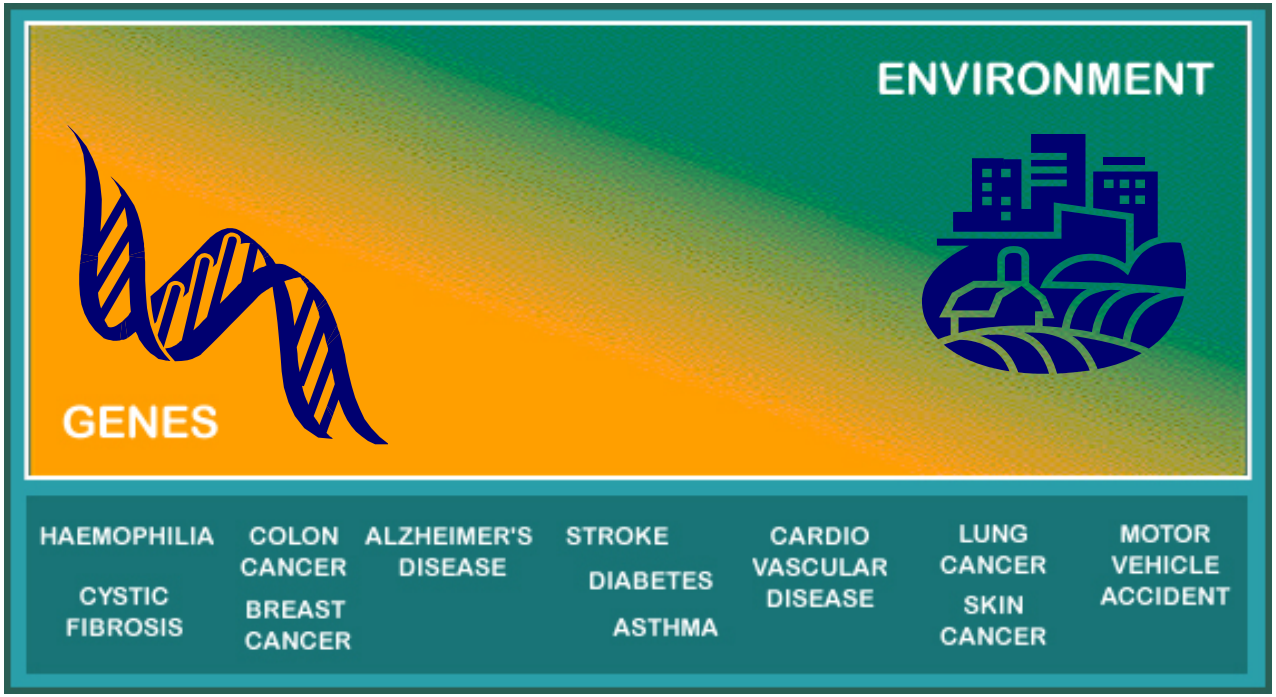


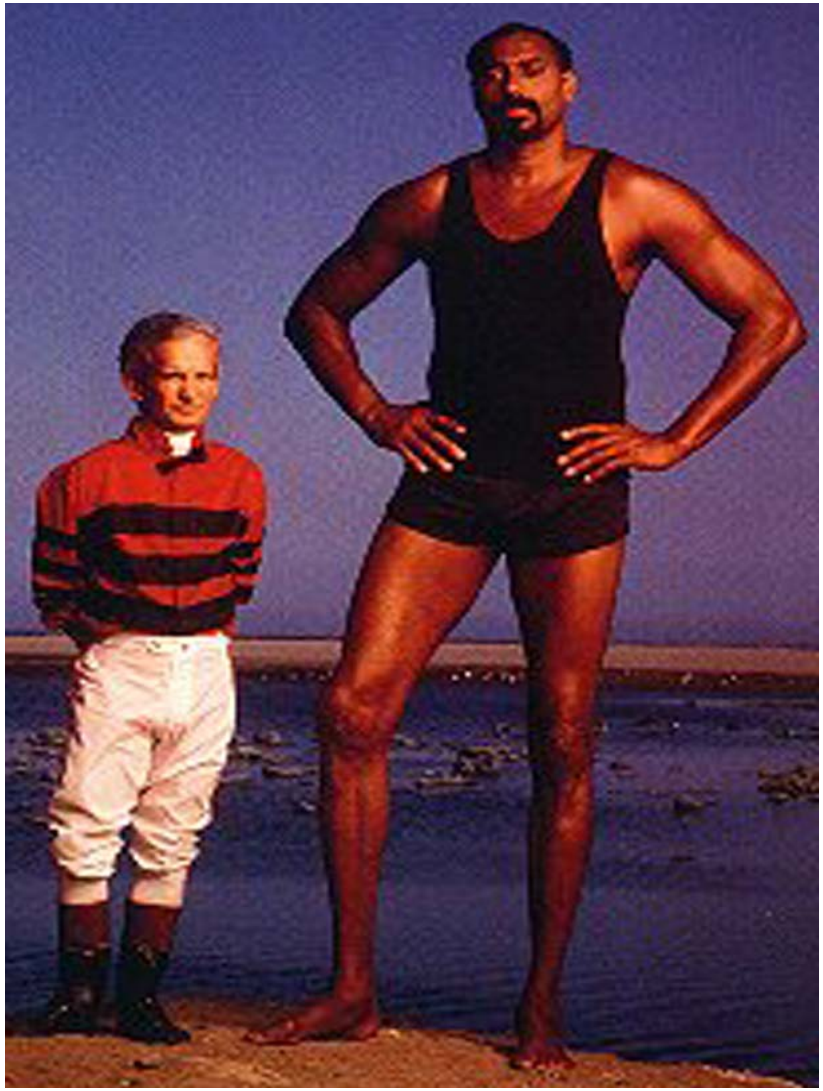
Claudius Galenus (Galen of Pergamum)

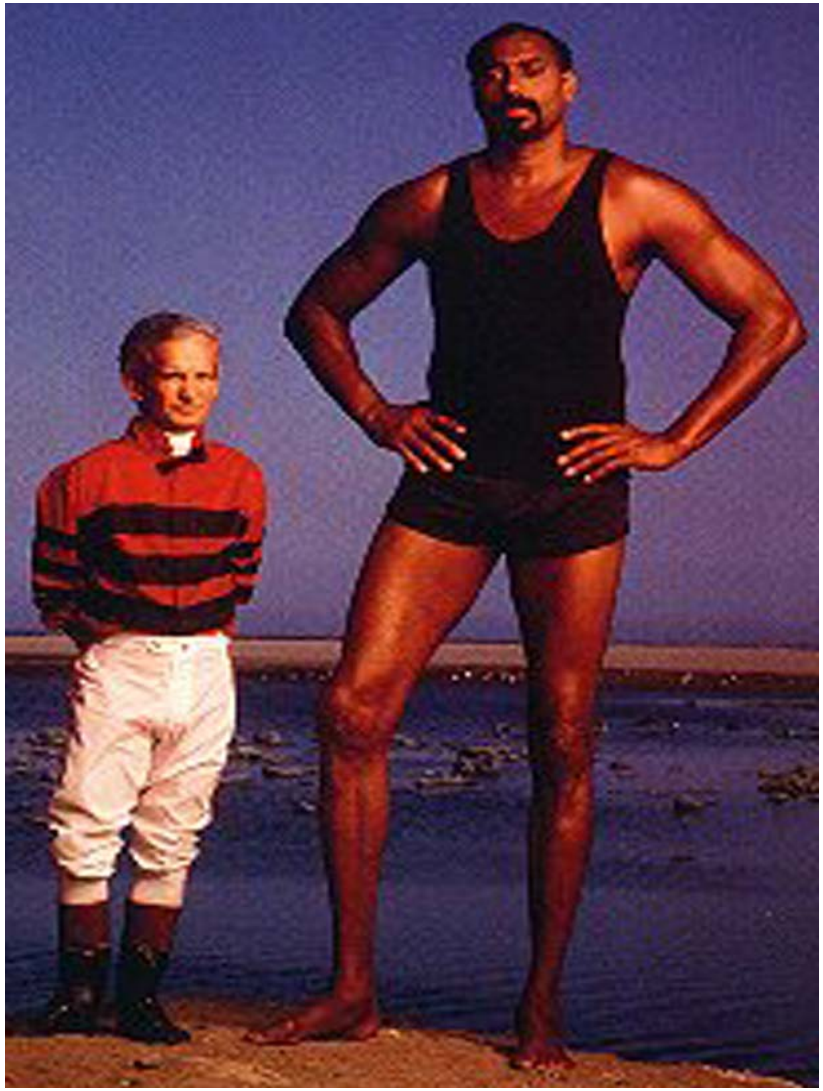
129-217 AD

"But remember throughout that no external cause is efficient without a predisposition of the body itself. Otherwise, external causes which affect one would affect all."

Library of Congress



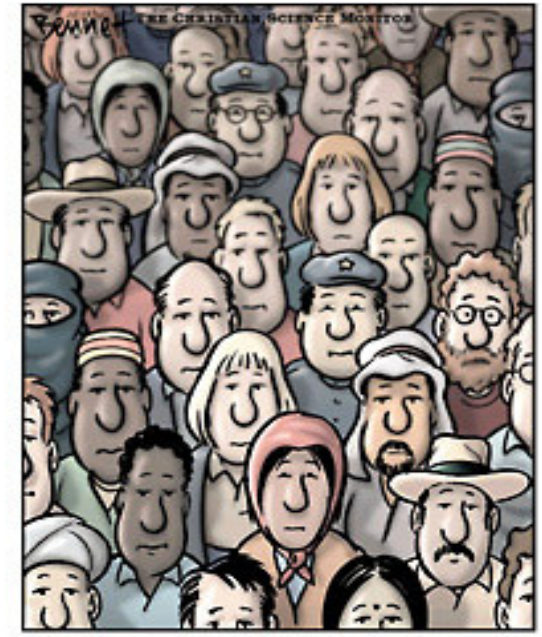




Classical Model

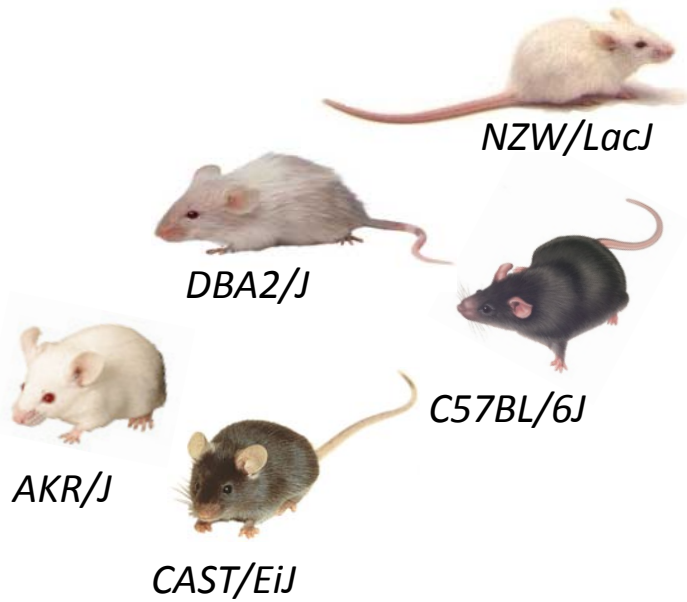
C57BL/6J

Single genome-based prediction



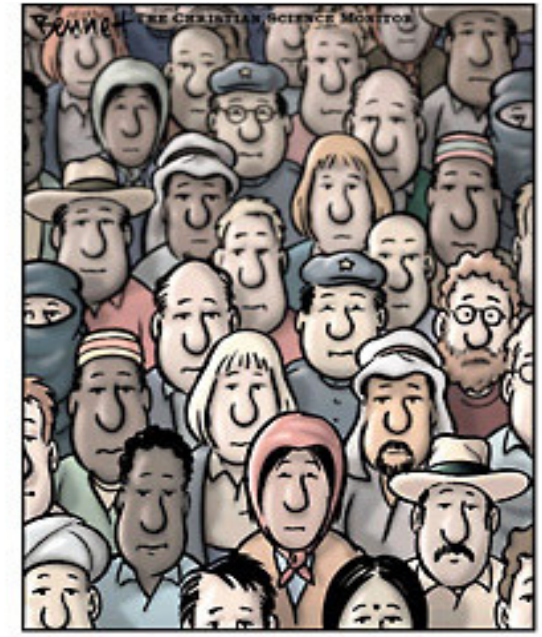
Genetically Diverse Human Population

Population Model



Population-based model

Single genome-based model



Genetically Diverse Human Population

Outline

Introduction to the Collaborative Cross

Generalized genetic characteristics

Example of ethanol metabolism

Genetic dissection of complex and quantitative traits: from fantasy to reality via a community effort

David W. Threadgill, Kent W. Hunter, Robert W. Williams

Multi-parental recombinant inbred panel

A second resource identified at the CTC organizational meeting is a second-generation recombinant inbred panel. The original RI lines were not developed with complex traits in mind (Bailey 1971). Rather, they were designed to efficiently localize Mendelian traits. With a 1,000-line advanced, multi-parental RI panel, single-gene resolution would be approached if each line archived 100 recombination sites. Such a purposely designed RI panel could serve as a new community mapping resource by combining diverse germ-plasms derived from a variety of inbred strains with the

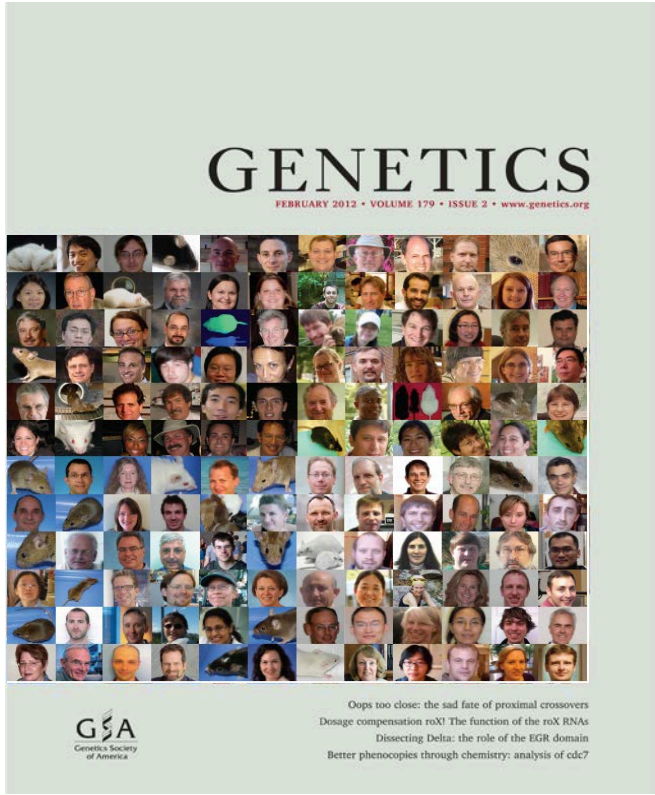
Mammalian Genome, 2002

Nature Genetics, 2004

COMMENTARY

Nature Genetics **36**, 1133 - 1137 (2004)
doi:10.1038/ng1104-1133

The Collaborative Cross, a community resource for the genetic analysis of complex traits



Genetics, 2012

Ten Years of the Collaborative Cross

David W. Threadgill*,[1] and Gary A. Churchill†

Characteristics of the Collaborative Cross Model

- *Genome-wide variation so that all components of systems are interrogated*
- *Randomization of genetic variation with no minor alleles so causative relationships can be identified*
- *Sufficiently large to power analysis of modest interactions*
- *Infinitely reproducible to support data integration and reproduction*

Factor Ramdomization

R. A. Fisher, Rothamsted Experimental Station (1919-1933)

1925, Statistical Methods for Research Workers
1935, The Design of Experiments

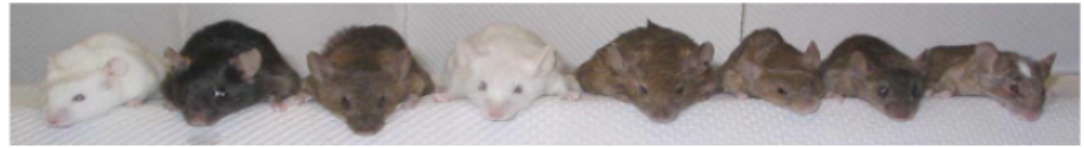
AJAX	K OF K	NITHSDALE	GREAT SCOTT	DUKE OF YORK	S C B
GREAT SCOTT	DUKE OF YORK	ARRAN COMRADE	IRON DUKE	EPICURE	S C B
IRON DUKE	EPICURE	AJAX	K OF K	NITHSDALE	S C B
K OF K	NITHSDALE	GREAT SCOTT	DUKE OF YORK	ARRAN COMRADE	S C B
	UP TO DATE	KERR's PINK	UP TO DATE	BRITISH QUEEN	S C B
	BRITISH QUEEN	TINWALD PERFECTION	EPICURE	KERR's PINK	S C B
	KERRS PINK	UP TO DATE	IRON DUKE	AJAX	S C B
	TINWALD PERFECTION	ARRAN COMRADE	BRITISH QUEEN	TINWALD PERFECTION	S C B

S = SULPHATE ROW C = CHLORIDE ROW
B = BASAL ROW

Diagram 1. Plan of experiment. Farmyard manure series.

Fisher and MacKenzie, "Studies in Crop Variation. II. The Manural Response of Different Potato Varieties," Journal of Agricultural Science 13 (1923): 311-320.

Collaborative Cross



Founder Inbred Strains

A C57BL/6 129S1 NOD NZO PWK CAST WSB

F1

G1

G2

G2:F1

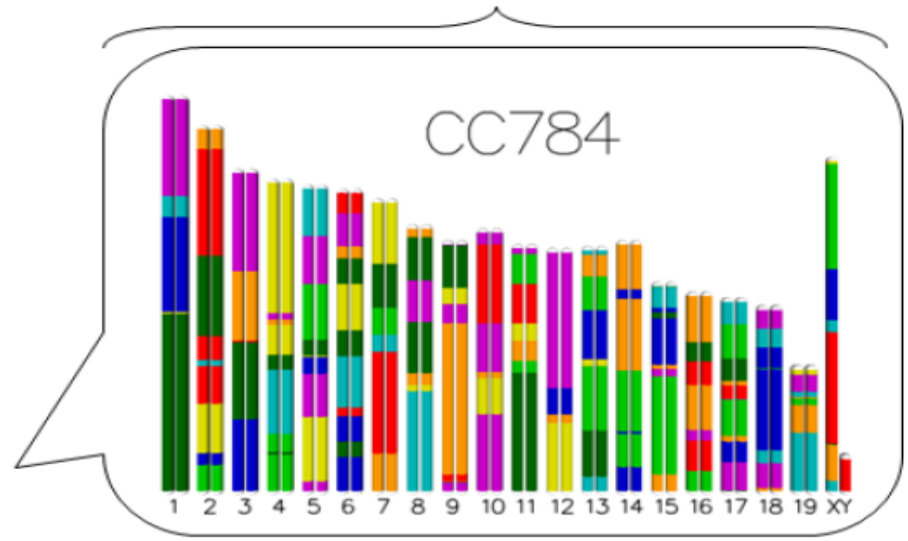
G2:F2

G2:F20

One Representative Chromosome

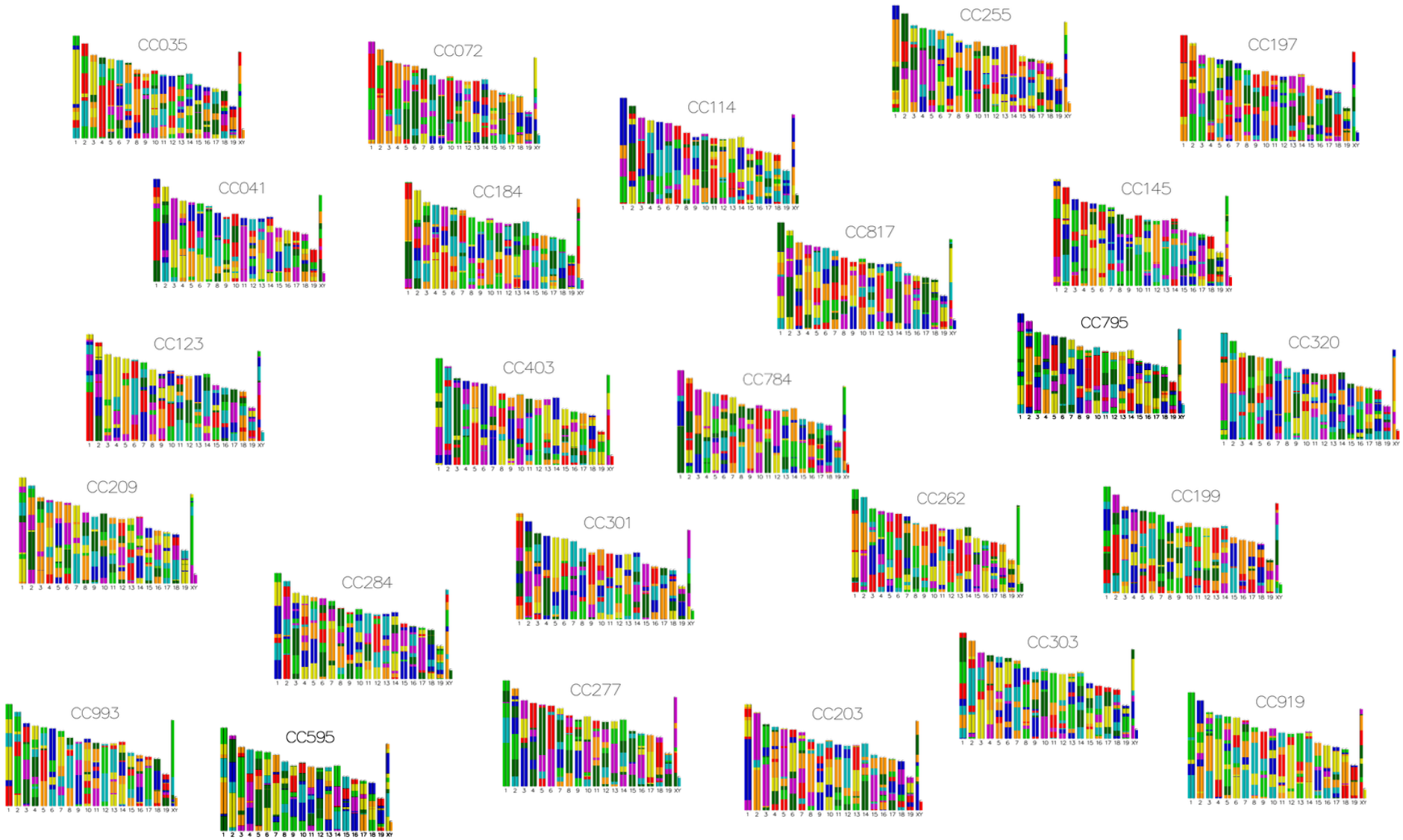
> 40M SNPs

One of ~250 Independent Collaborative Cross Lines

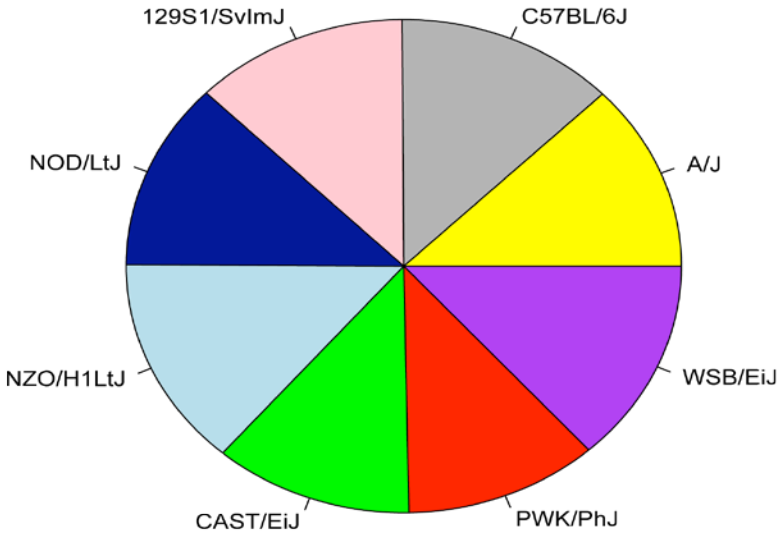


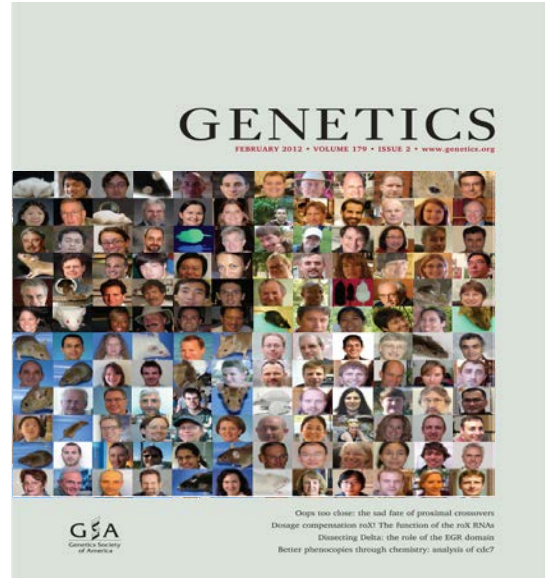
Nature Genetics, 2004

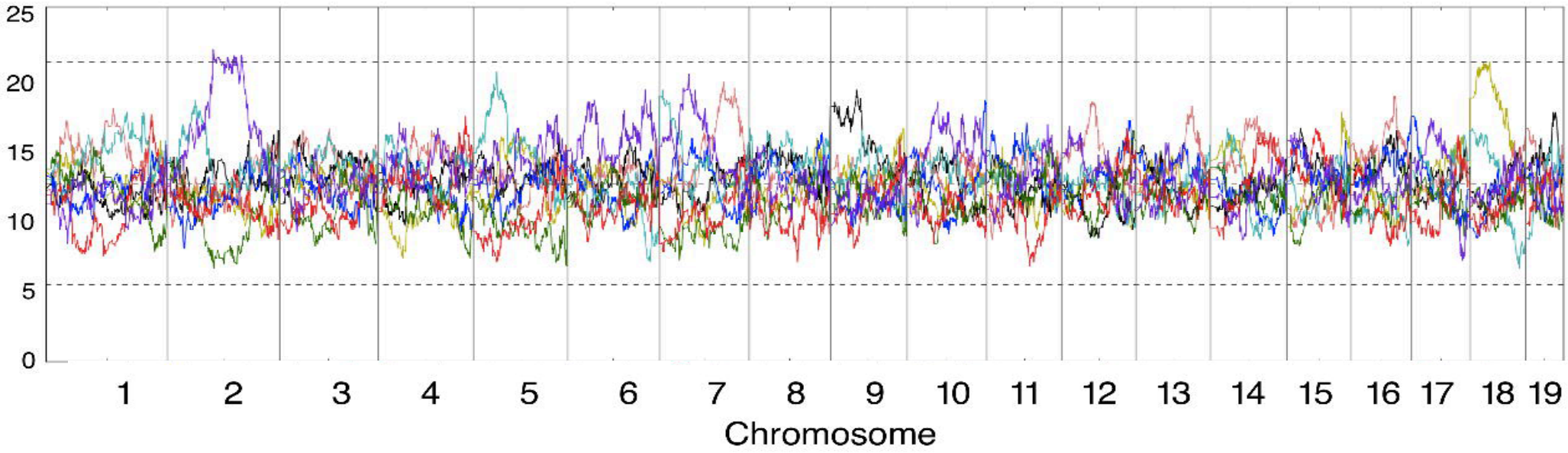
Power in Numbers



72 lines have been released to public



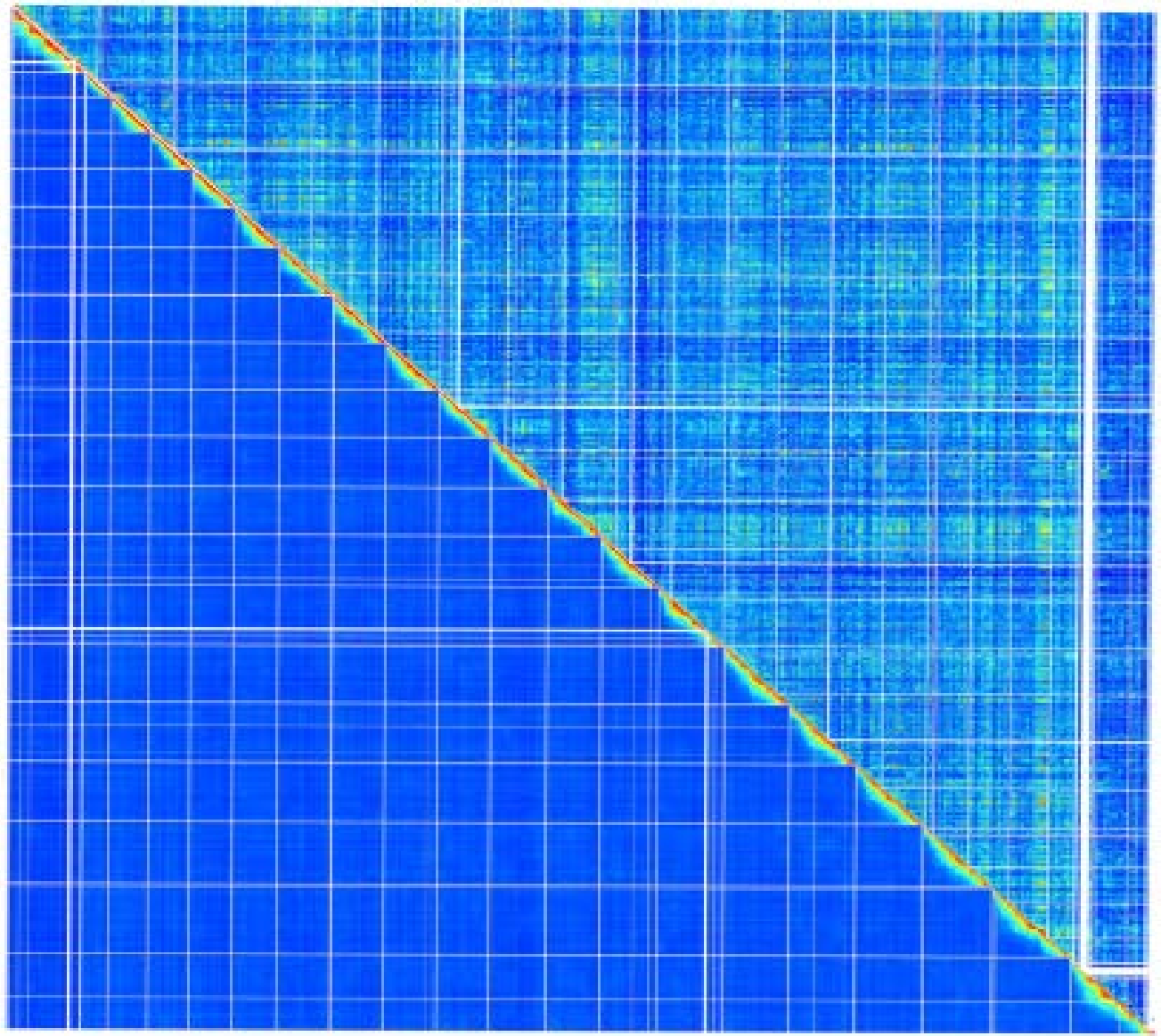




Genome Research, 2011; Genetics, 2012; BMC Genomics 2014

Comparison of LD Structures

Chr 1



Extant inbred strains

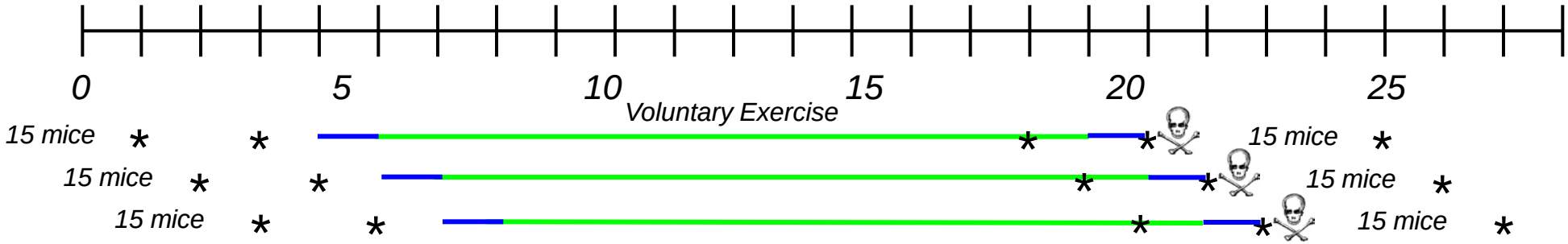
CC

Chr 19

Genetics, 2012


Chips

Initial Proof-of-Concept Experiment



Day 0

45 males from ORNL

Day 1

EtOH metabolism

Day 3

ECG

Urine collection

Blood collection

Feces

MRI

Day 4

Calorimeter

Day 5

Open running wheels

Day 16

ECG

MRI

Day 17

Calorimeter

Day 18

Social novelty

Blood collection

Feces

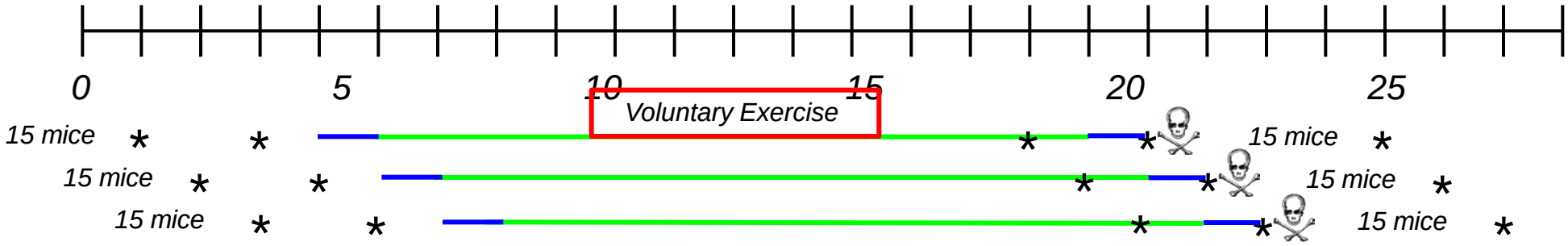
Tissue collection

DEXA

Influenza susceptibility
Dust mite allergy susceptibility

AJP - Endocrinology and Metabolism, 2011

Initial Proof-of-Concept Experiment



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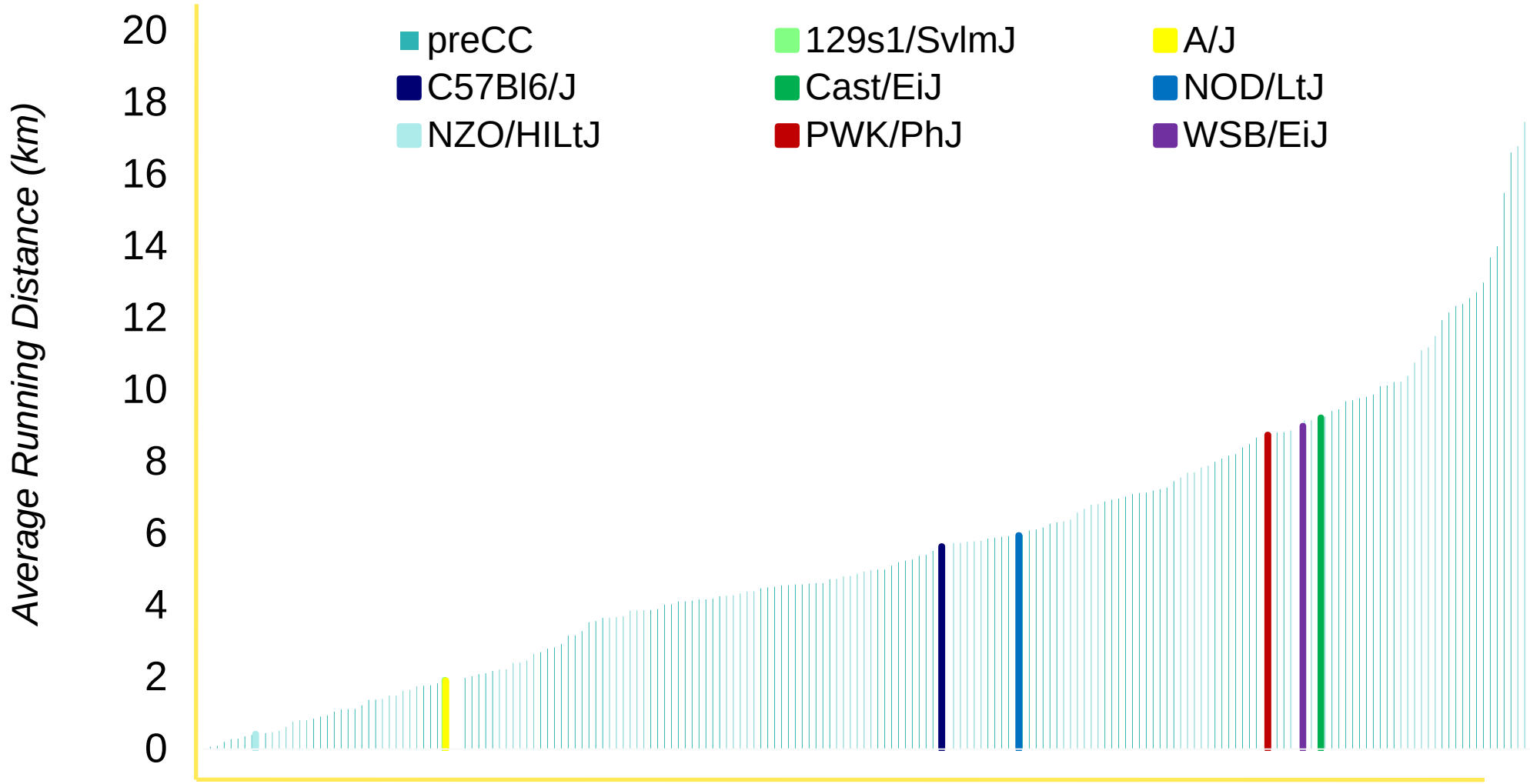
AJP - Endocrinology and Metabolism, 2011

Video has been removed for posting

OBSERVATION 1: Extreme Transgressive Variation

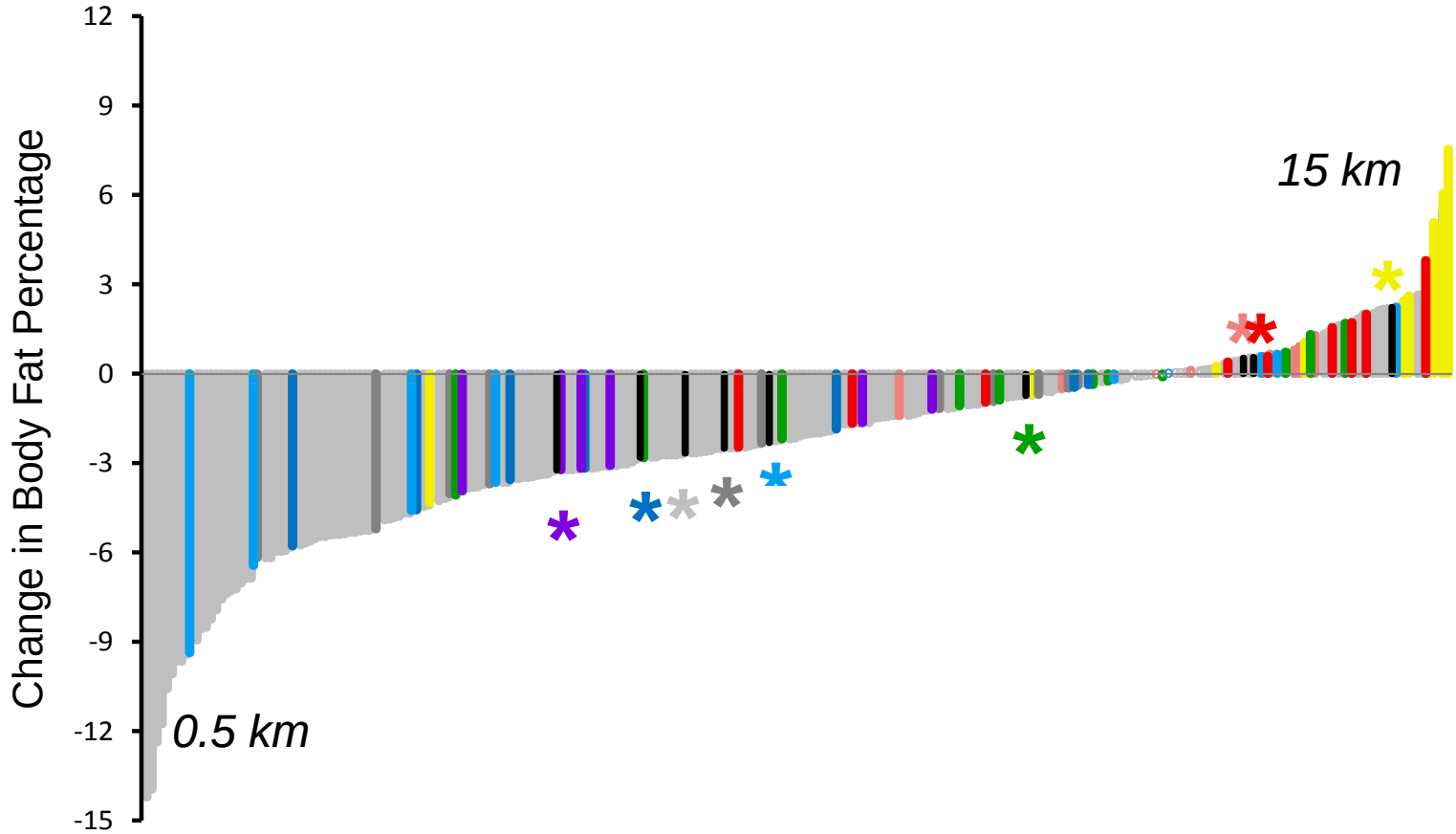
Average Daily Running Distance



AJP - Endocrinology and Metabolism, 2011

OBSERVATION 2: Disruption of Correlated Traits

Change in Body Fat Composition



AJP - Endocrinology and Metabolism, 2011

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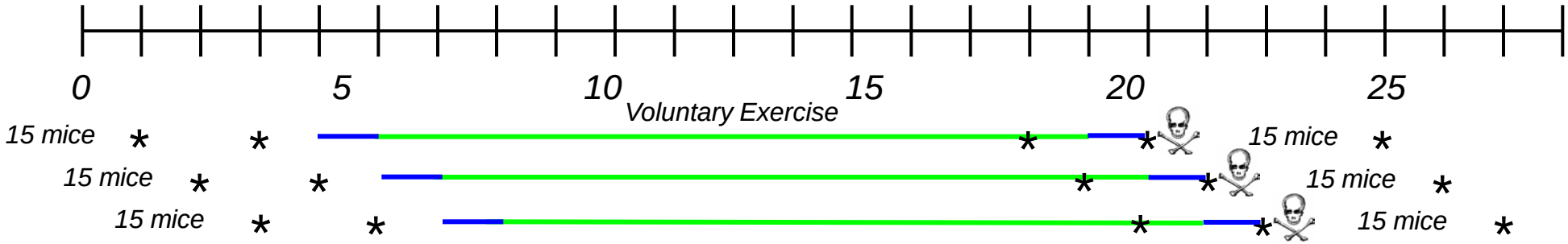

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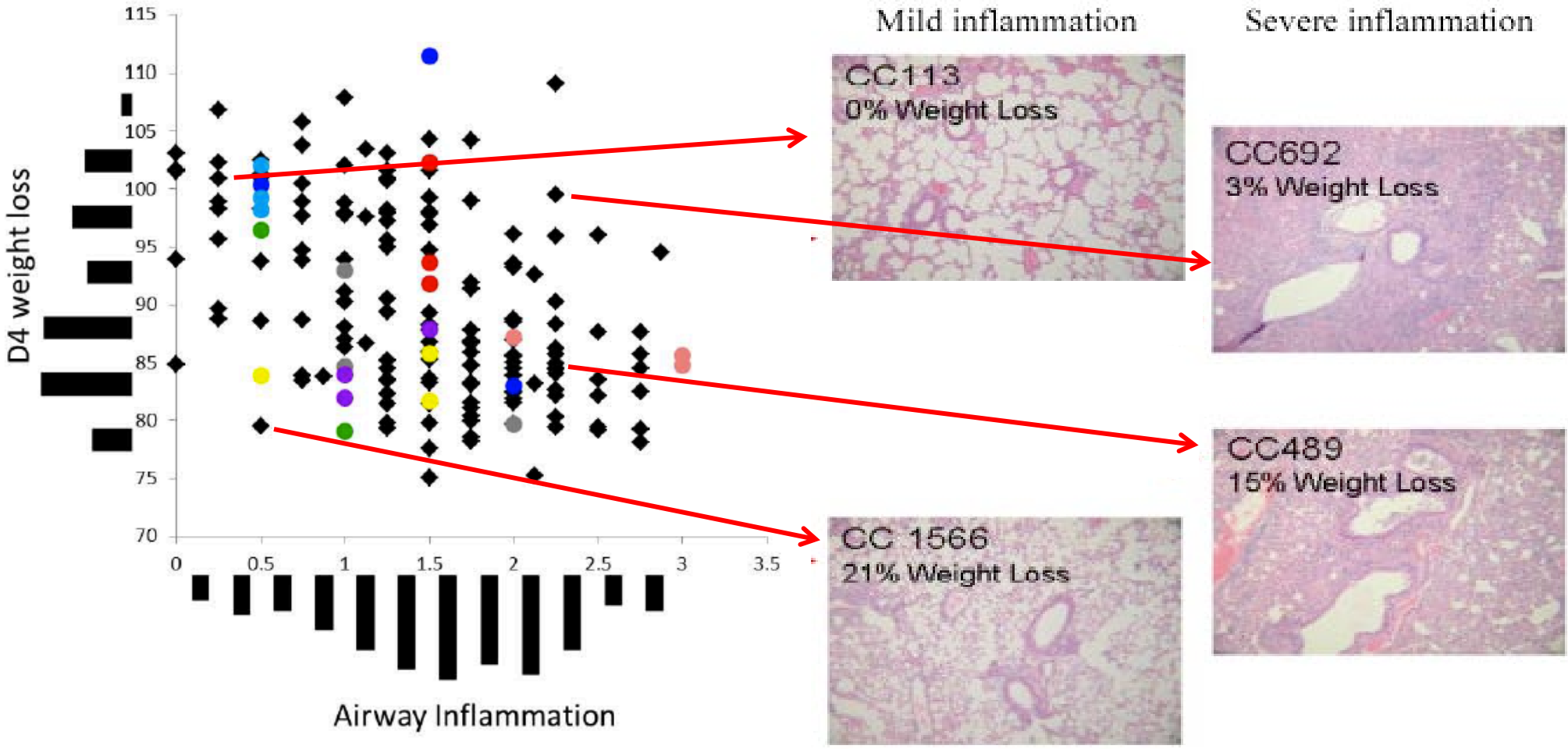
AJP - Endocrinology and Metabolism, 2011

OBSERVATION 2: Disruption of Correlated Traits

Influenza Infection (A/PR/8)



PLoS Pathogens, 2013

OBSERVATION 3: Emergent Properties

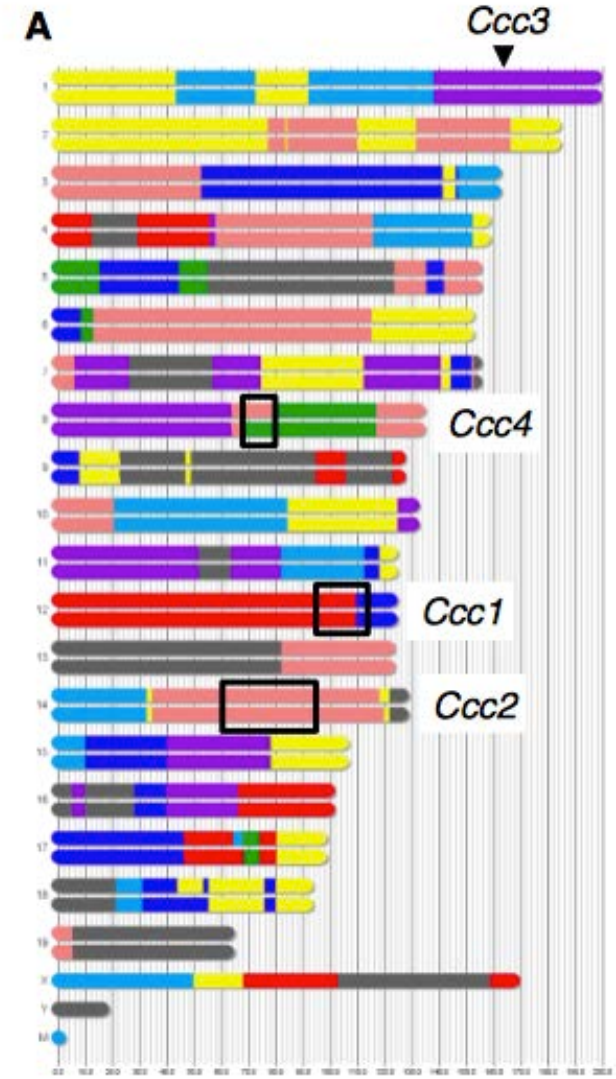
Spontaneous Colitis

Mammalian Genome
Genes, Phenotypes and Systems

The Collaborative Cross as a Resource for Modeling Human Disease: CC011/Unc, a New Mouse Model for Spontaneous Colitis

Allison R. Rogala · Andrew P. Morgan · Alexis M. Christensen · Terry J. Gooch · Timothy A. Bell · Darla R. Miller · Virginia L. Godfrey · Fernando Pardo-Manuel de Villena

Mammalian Genome 25: 95-108, 2014



OBSERVATION 4: Models Human Phenotypic Distribution

Ebola Infection

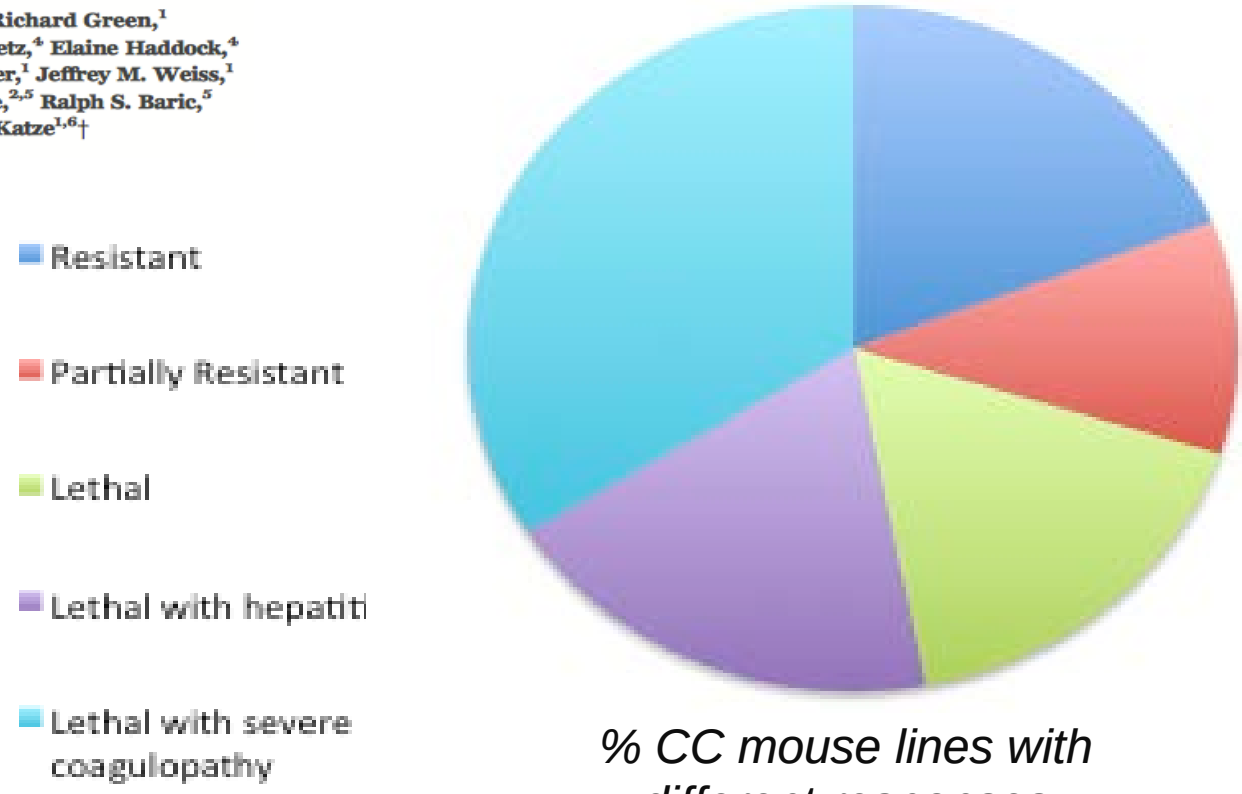
Science

EBOLA MOUSE MODEL

Host genetic diversity enables Ebola hemorrhagic fever pathogenesis and resistance

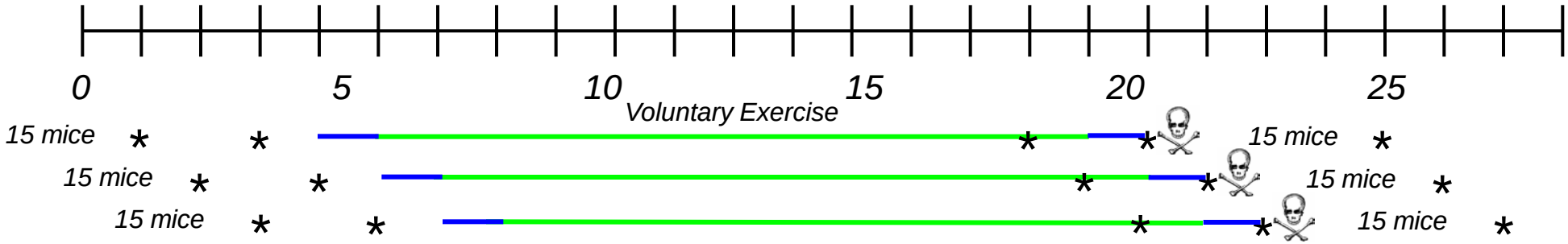
Angela L. Rasmussen,[*1] Atsushi Okumura,[*1,4] Martin T. Ferris,[2] Richard Green,[1] Friederike Feldmann,[3] Sara M. Kelly,[1] Dana P. Scott,[3] David Safronetz,[4] Elaine Haddock,[4] Rachel LaCasse,[3] Matthew J. Thomas,[1] Pavel Sova,[1] Victoria S. Carter,[1] Jeffrey M. Weiss,[1] Darla R. Miller,[2] Ginger D. Shaw,[2] Marcus J. Korth,[1] Mark T. Heise,[2,5] Ralph S. Baric,[5] Fernando Pardo-Manuel de Villena,[2] Heinz Feldmann,[4] Michael G. Katze[1,6]†

Science 346: 987-991, 2014



% CC mouse lines with different responses

Initial Proof-of-Concept Experiment



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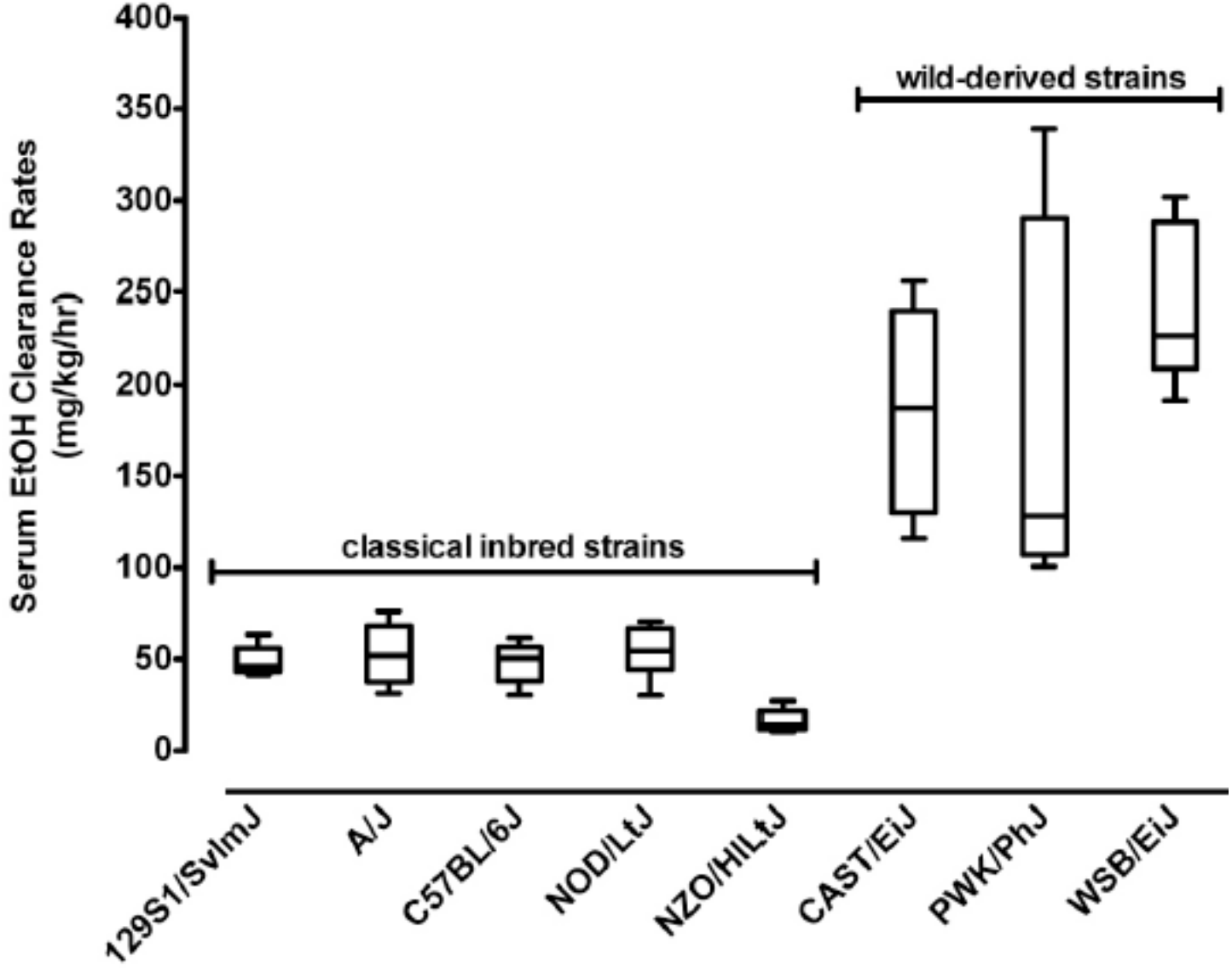
AJP - Endocrinology and Metabolism, 2011

EtOH Clearance Rate



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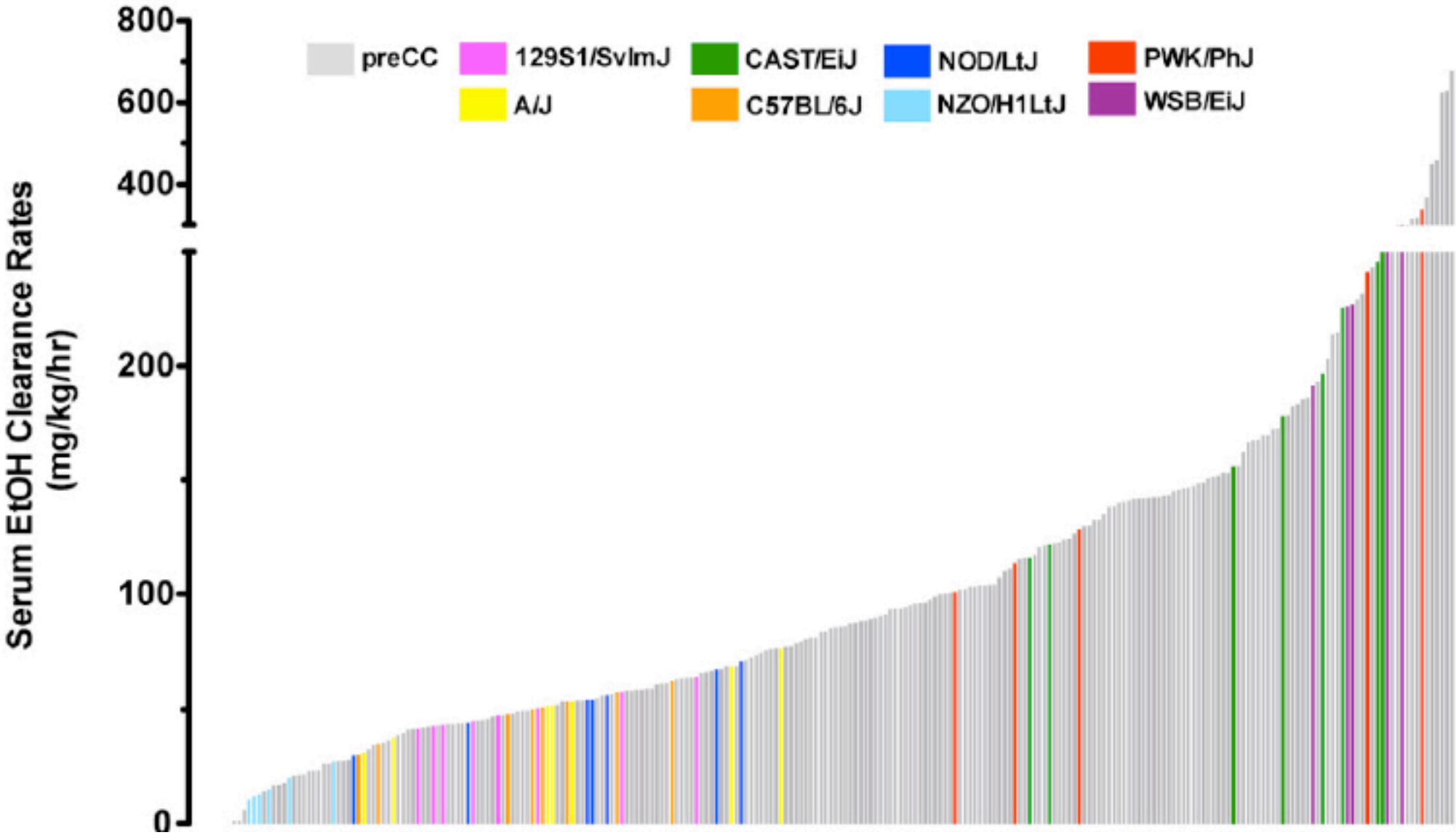
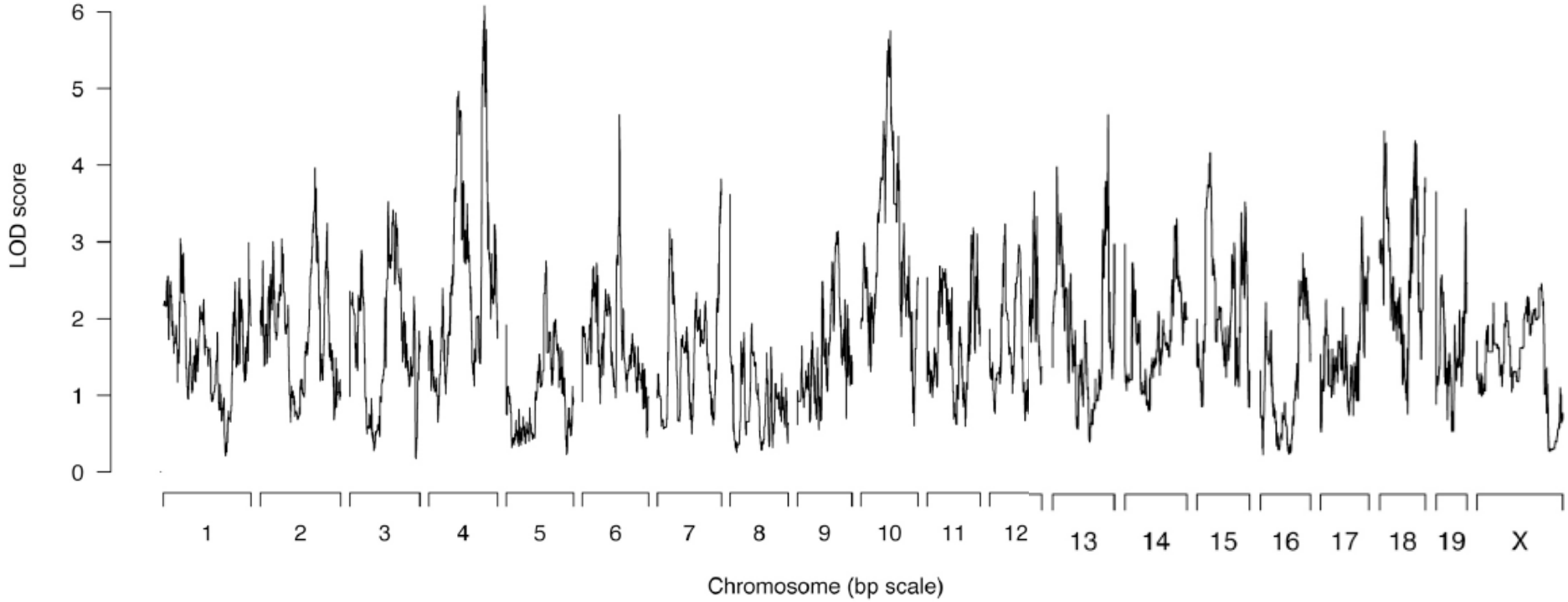


Genetic Analysis of EtOH Clearance Rate

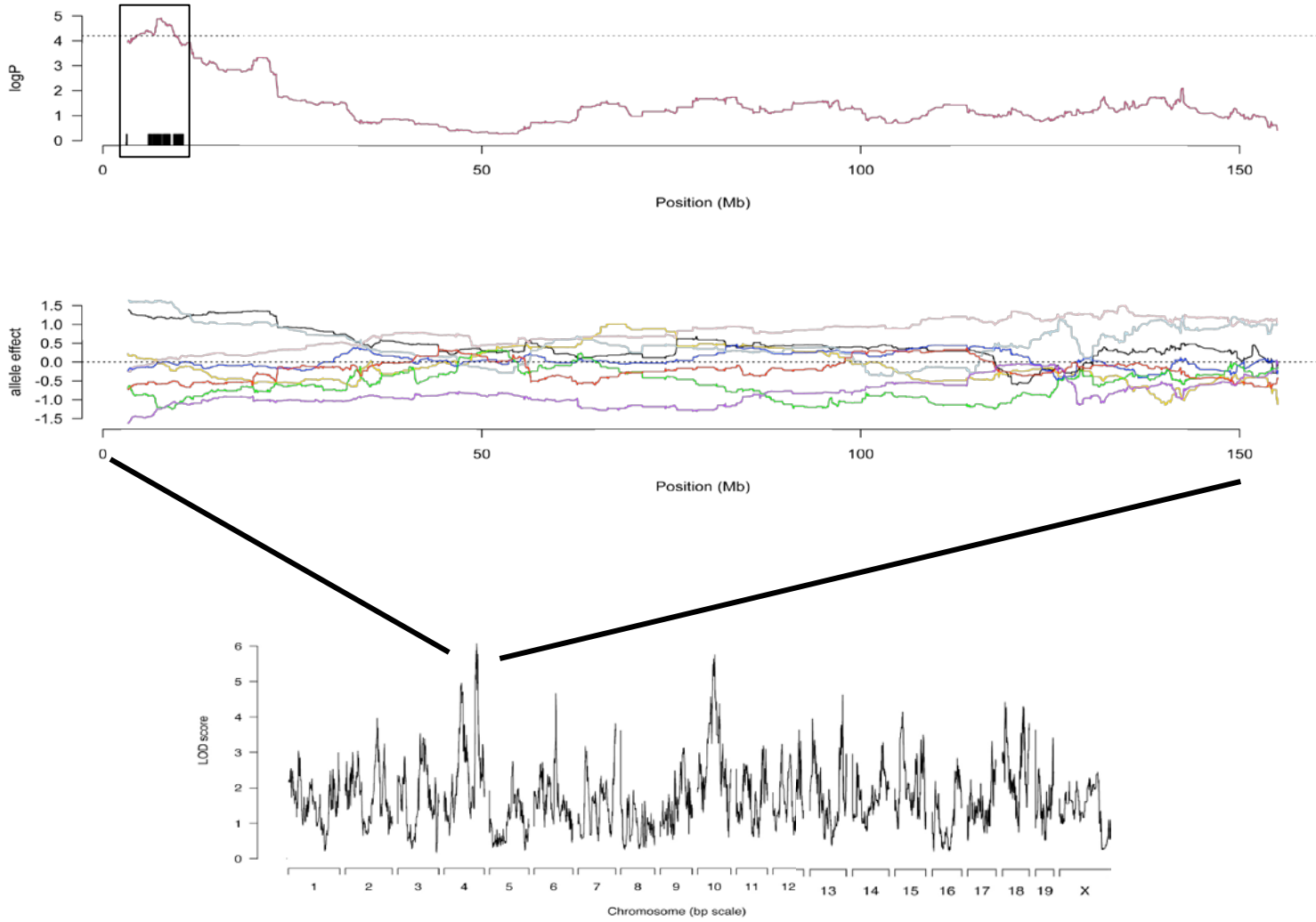


Genetic Analysis of EtOH Clearance Rate

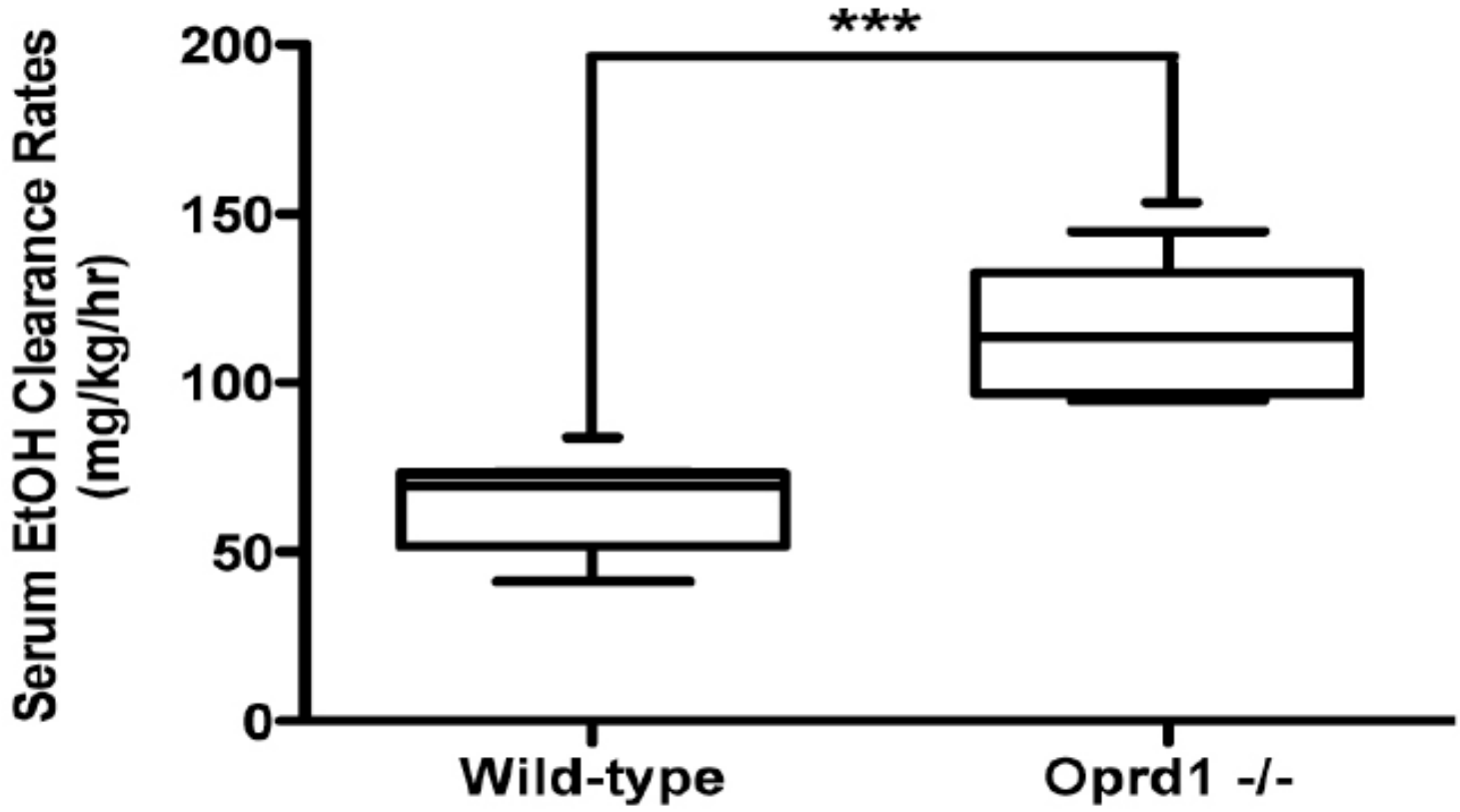
Increasing Resolution with Allele Effect Plots

Oprd1

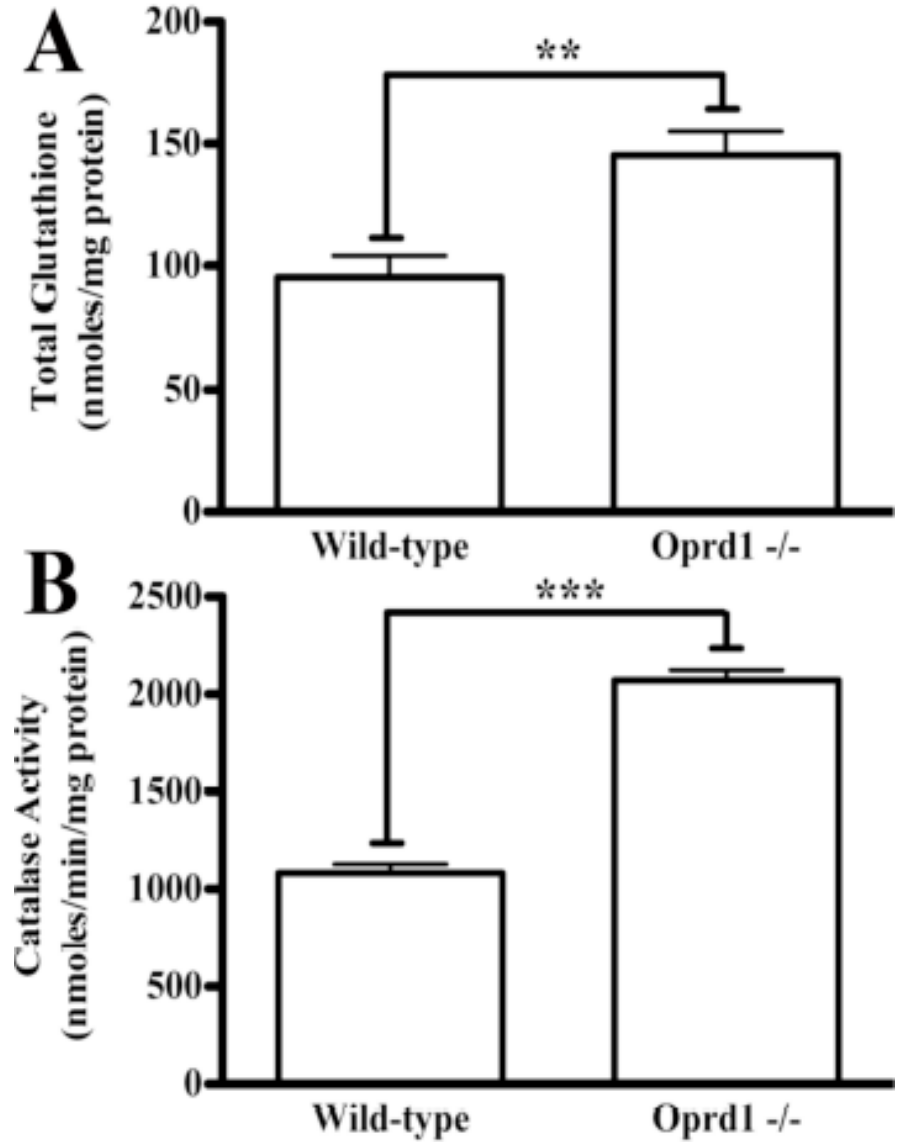
opioid receptor, delta 1



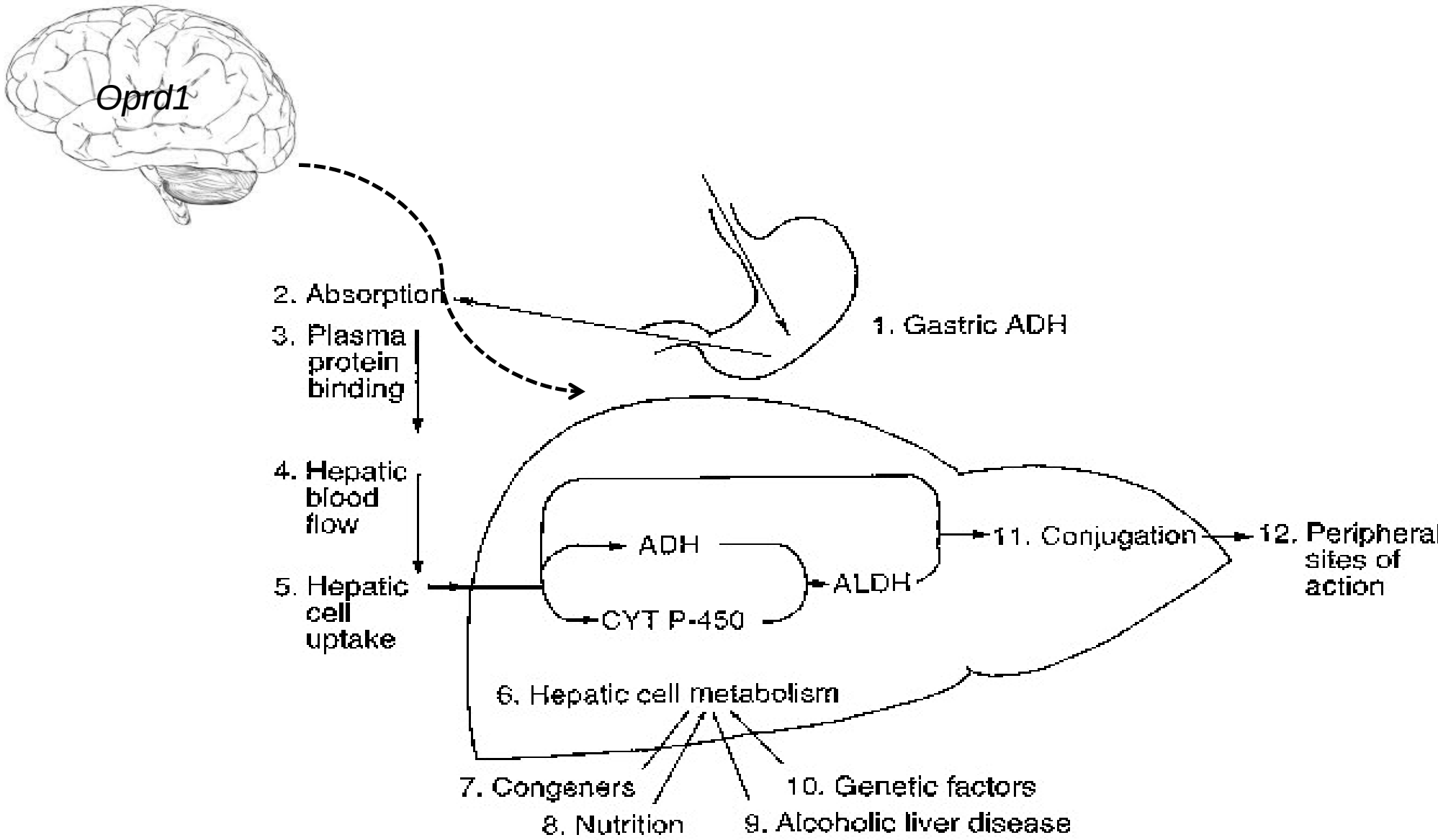
Confirmation of *Oprd1* with Naltrindole



Effect of *Oprd1* on Liver Activity



CNS Control of Ethanol Clearance?



from Clinics in Liver Disease 2, 673 (2005)

Summary: Novel Models

Extreme transgressive variation

Disruption of correlated phenotypes

Emergent disease models

Models human phenotypic distribution

Why Are Population Models Important for Toxicology?

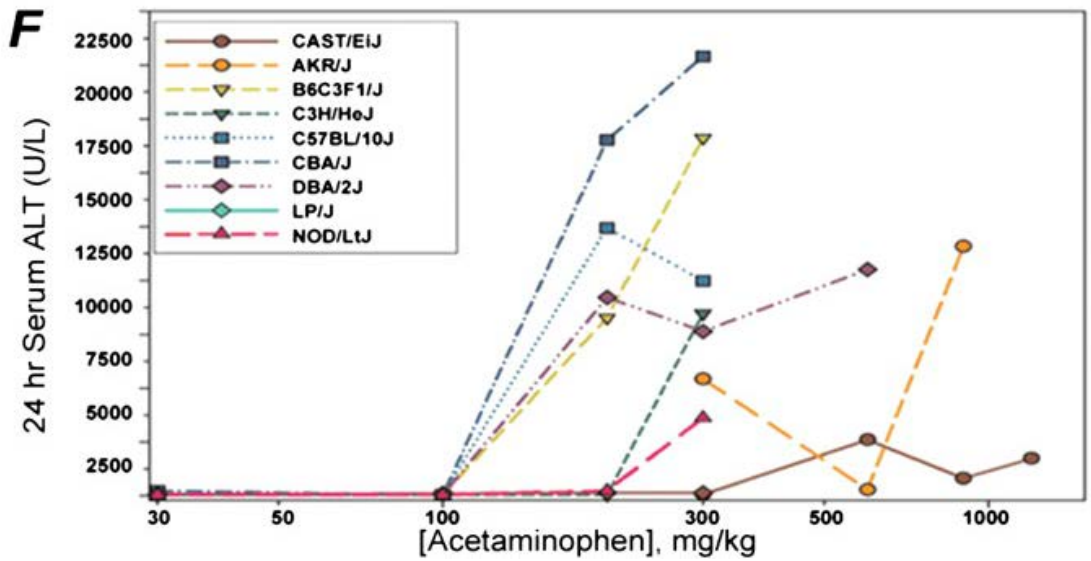
Variation in dose-response curves

GENOME RESEARCH

Mouse population-guided resequencing reveals that variants in *CD44* contribute to acetaminophen-induced liver injury in humans

Alison H. Harrill[1,2,12], Paul B. Watkins[3,12], Stephen Su[6], Pamela K. Ross[2], David E. Harbourt[5], Ioannis M. Stylianou[7], Gary A. Boorman[8], Mark W. Russo[3], Richard S. Sackler[9], Stephen C. Harris[11], Philip C. Smith[5], Raymond Tennant[8], Molly Bogue[7], Kenneth Paigen[7], Christopher Harris[9,10], Tanupriya Contractor[9], Timothy Wiltshire[5], Ivan Rusyn[1,2,14] and David W. Threadgill[1,4,13,14,15]

Genome Research 19: 1507-1515, 2009

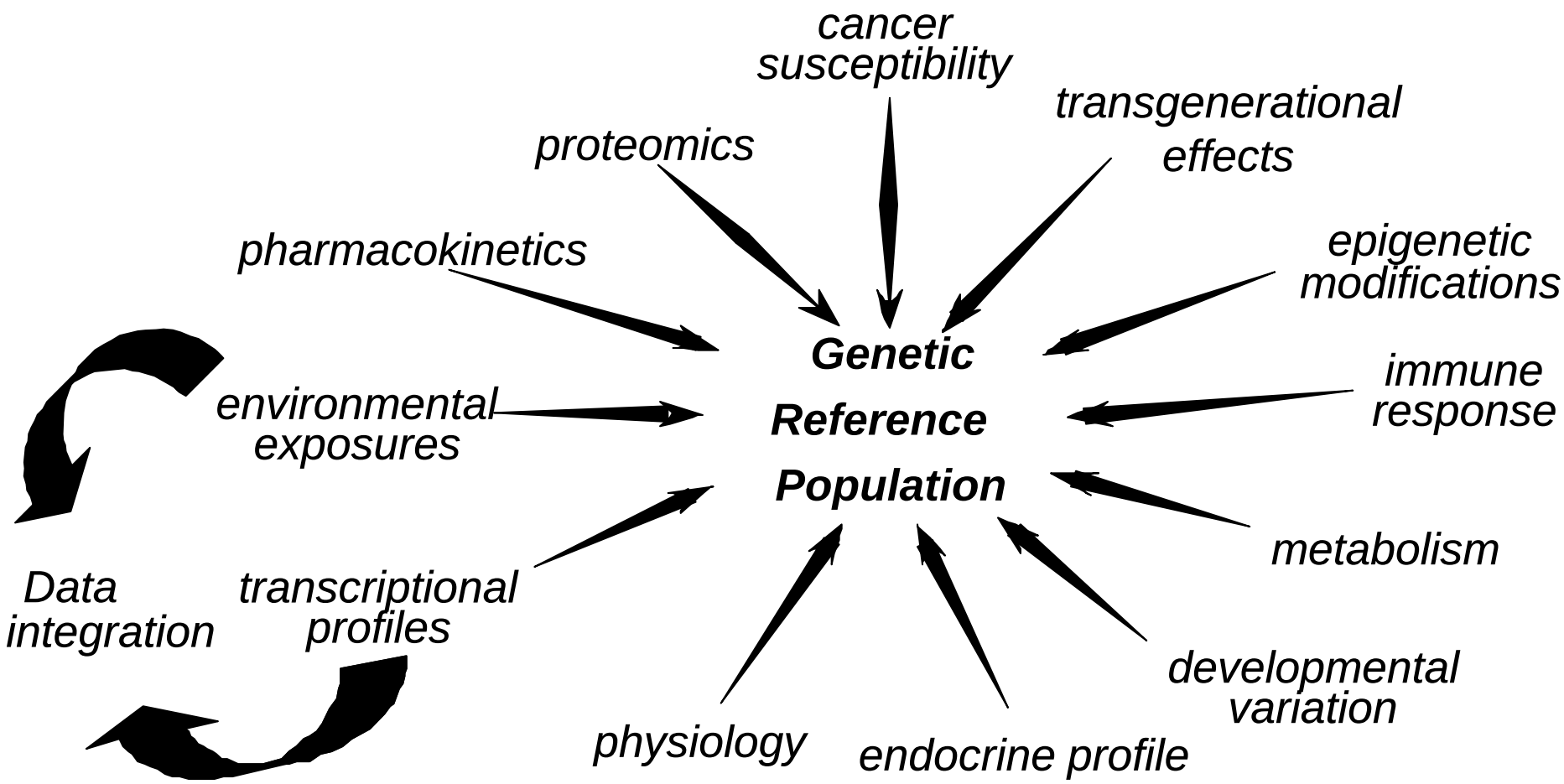


Expanding Uses of the CC

QTL mapping: when combined with Diversity Outbred (DO) model derived from CC, fine mapping is now possible at close to single gene resolution. Question of power for highly polygenic traits is still open. Likley only appropriate for oligogenic traits.

Functional validation/context analysis: reverse translation of GWAS or other findings to understand function and context.

Systems integration: interrogation across phenotypes (molecular and physiological) to understand biological wiring. Requires far fewer lines than QTL mapping since causative drivers of systems are not the goal. More appropriate for polygenic traits.



Data integration over SPACE and TIME by anchoring to a genetic reference population

Acknowledgements

Key Collaborative Cross Participants
Fernando Pardo-Manuel, UNC
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Fuad Iraqi, TAU
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Grant Morahan, UWA
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Elissa Chesler, JAX

Proof-of-Concept Experiments
Daniel Pomp, UNC
Wendy Foulds-Mathies, UNC
Mark Heise, UNC
Ralph Baric, UNC
Marty Ferris, UNC
Christine Powell, TAMU

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Lineberger Cancer Center/UNC