The Knockout Mouse Phenotyping Program (KOMP2)

Building the first comprehensive catalogue of mammalian gene function

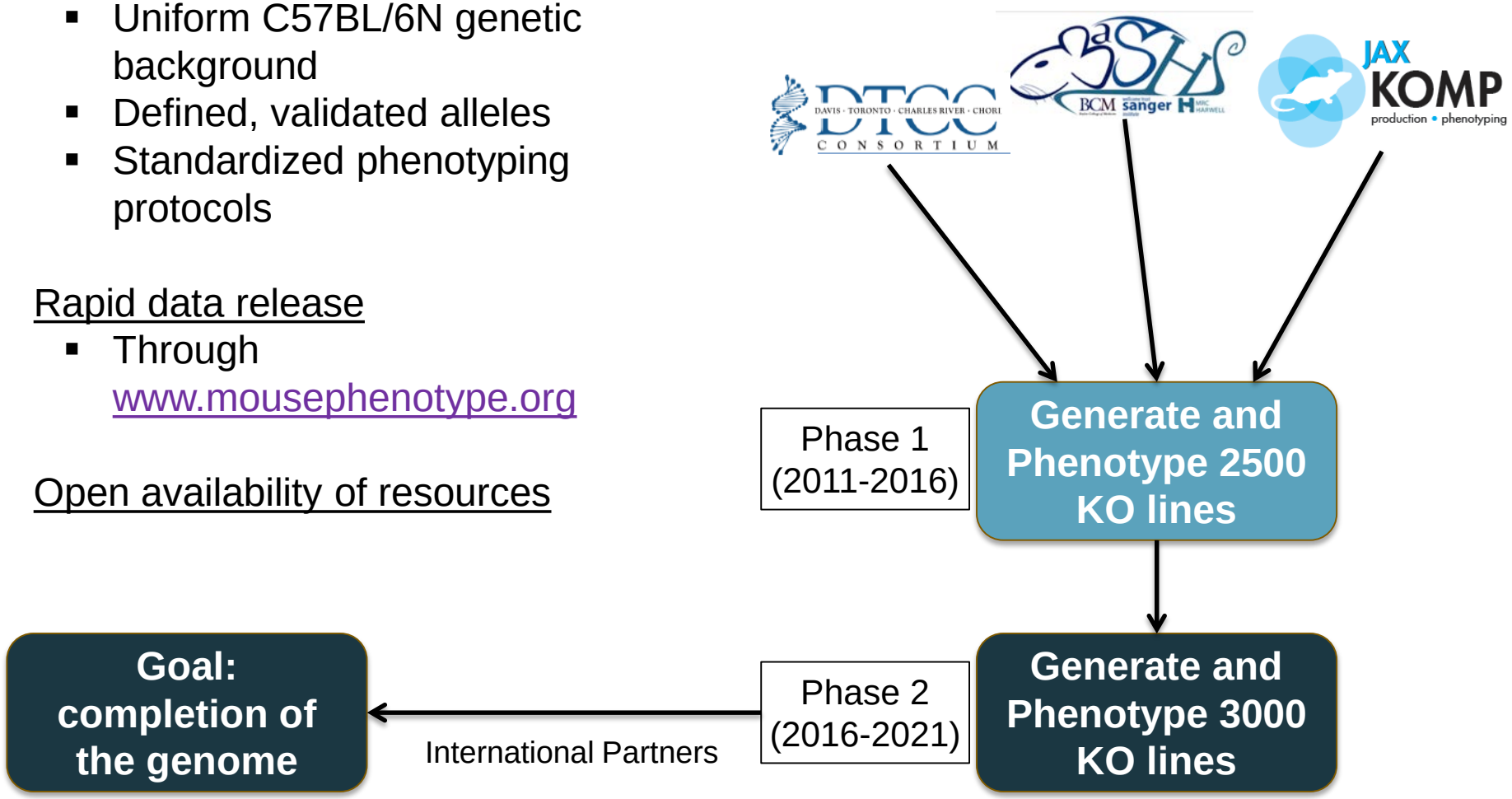
The context and challenge

- Much of the mammalian genome is “dark”** - the function of the majority of genes in the mouse and human genomes is unknown
- The functional consequences of human genetic variation are poorly understood
- The functional analysis of the various elements of the non-coding genome has been limited
- The number of variants of unknown significance is increasing rapidly, but is not met by a commensurate analysis of function
- The mouse is critical to dissect and understand the importance of genetic variation

**Oprea et al. and IDG, *Nature Reviews Drug Discovery*, Unexplored therapeutic opportunities In the human genome, May 2018.

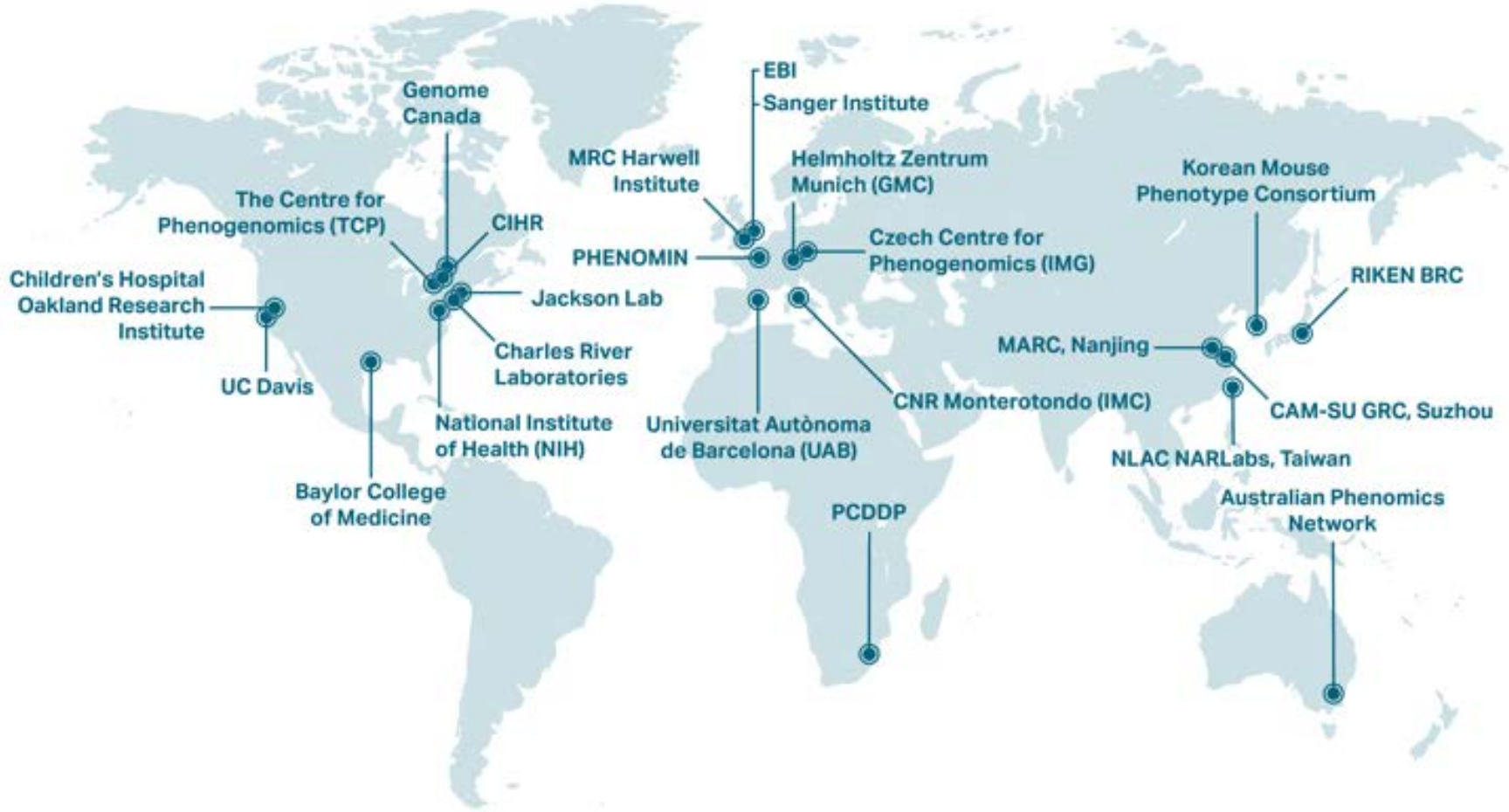
Knockout Mouse Phenotyping Program (KOMP^2)

- Standardization…Reproducibility
  - Uniform C57BL/6N genetic background
  - Defined, validated alleles
  - Standardized phenotyping protocols
- Rapid data release
  - Through www.mousephenotype.org
- Open availability of resources



IMPC

International Mouse Phenotyping Consortium



www.mousephenotype.org

KOMP2/IMPC Goals and Impact

- Generate a mouse null mutant for every protein-coding gene in the mouse genome
- Comprehensively phenotype each mouse mutant to determine developmental, physiological, and biochemical parameters
- Provide an important baseline for exploring gene function
- Develop a more profound understanding of the genome landscape and genetic mechanisms
- Enhance the interpretation of human genetic data, from rare to complex diseases, and the analysis of large population datasets
- **The functional annotation of human genetic variation**

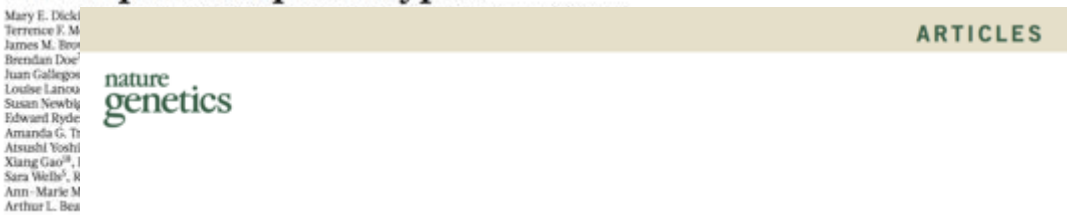
Evolution and Impact


ARTICLE

doi:10.1038/nature19356

High-throughput discovery of novel developmental phenotypes

Nature, 2016


ARTICLES

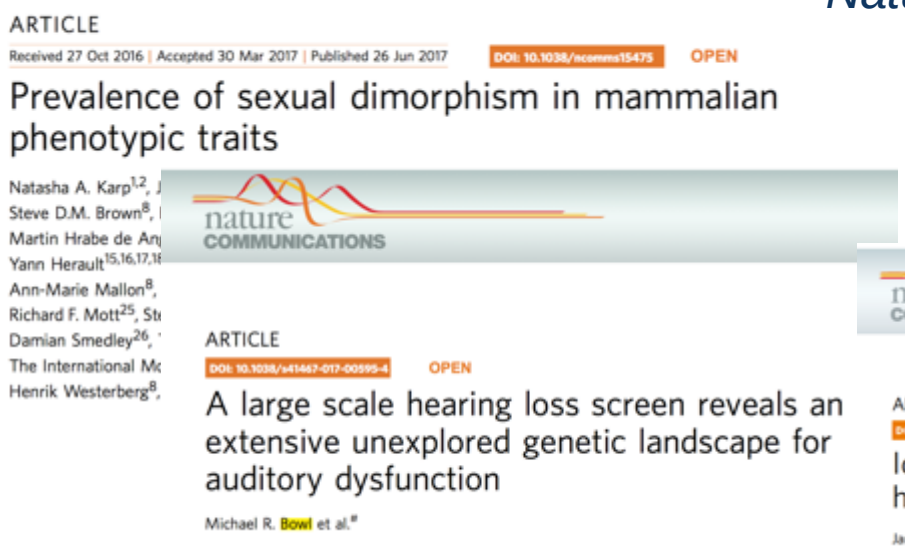
nature genetics

Nature Genetics, 2017

Disease model discovery from 3,328 gene knockouts by The International Mouse Phenotyping Consortium


nature COMMUNICATIONS

Nature Comms, 2017


ARTICLE

Received 27 Oct 2016 | Accepted 30 Mar 2017 | Published 26 Jun 2017

DOI: 10.1038/ncomms15475 OPEN

Prevalence of sexual dimorphism in mammalian phenotypic traits

Nature Comms, 2017

nature COMMUNICATIONS

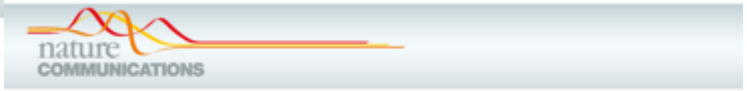
ARTICLE

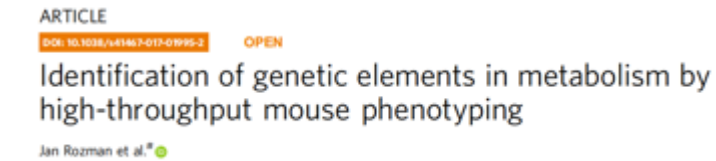
DOI: 10.1038/s41467-017-00595-4 OPEN

A large scale hearing loss screen reveals an extensive unexplored genetic landscape for auditory dysfunction

Michael R. Bowl et al.

Nature Comms, 2018


nature COMMUNICATIONS


ARTICLE

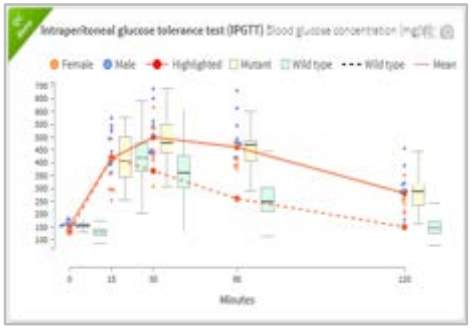
DOI: 10.1038/s41467-017-01995-2 OPEN

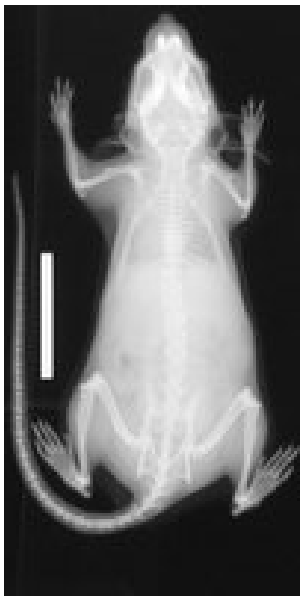
Identification of genetic elements in metabolism by high-throughput mouse phenotyping

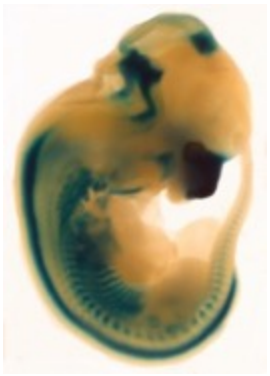
Jan Rozman et al.

Program Update

- 12,391 microinjections
- 7,548 genotype confirmed lines (>2000 CRISPR)
- 5,870 lines phenotyped
- Data Release (8.0) for 5,505 lines
- 61.7 million data points
- Approx. 369k images





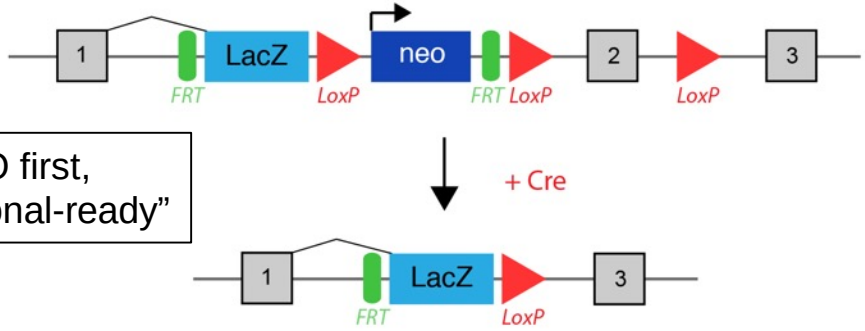


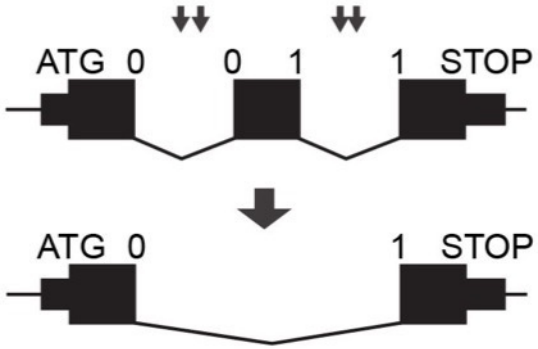
Knockout alleles

Phase 1: IKMC ES cell resources

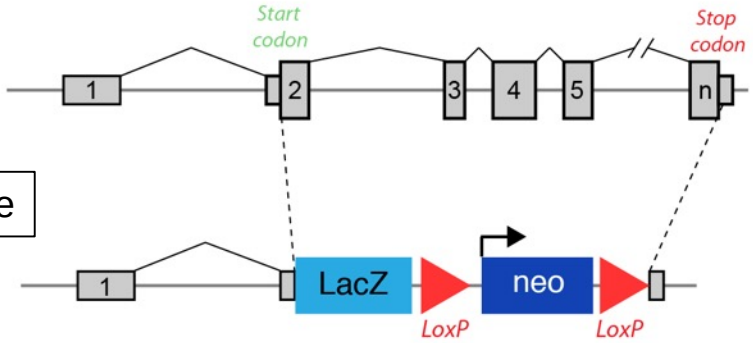
Phase 2: CRISPR-mediated exon deletion

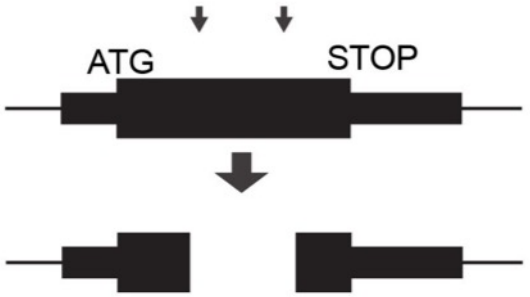
”KO first, conditional-ready”



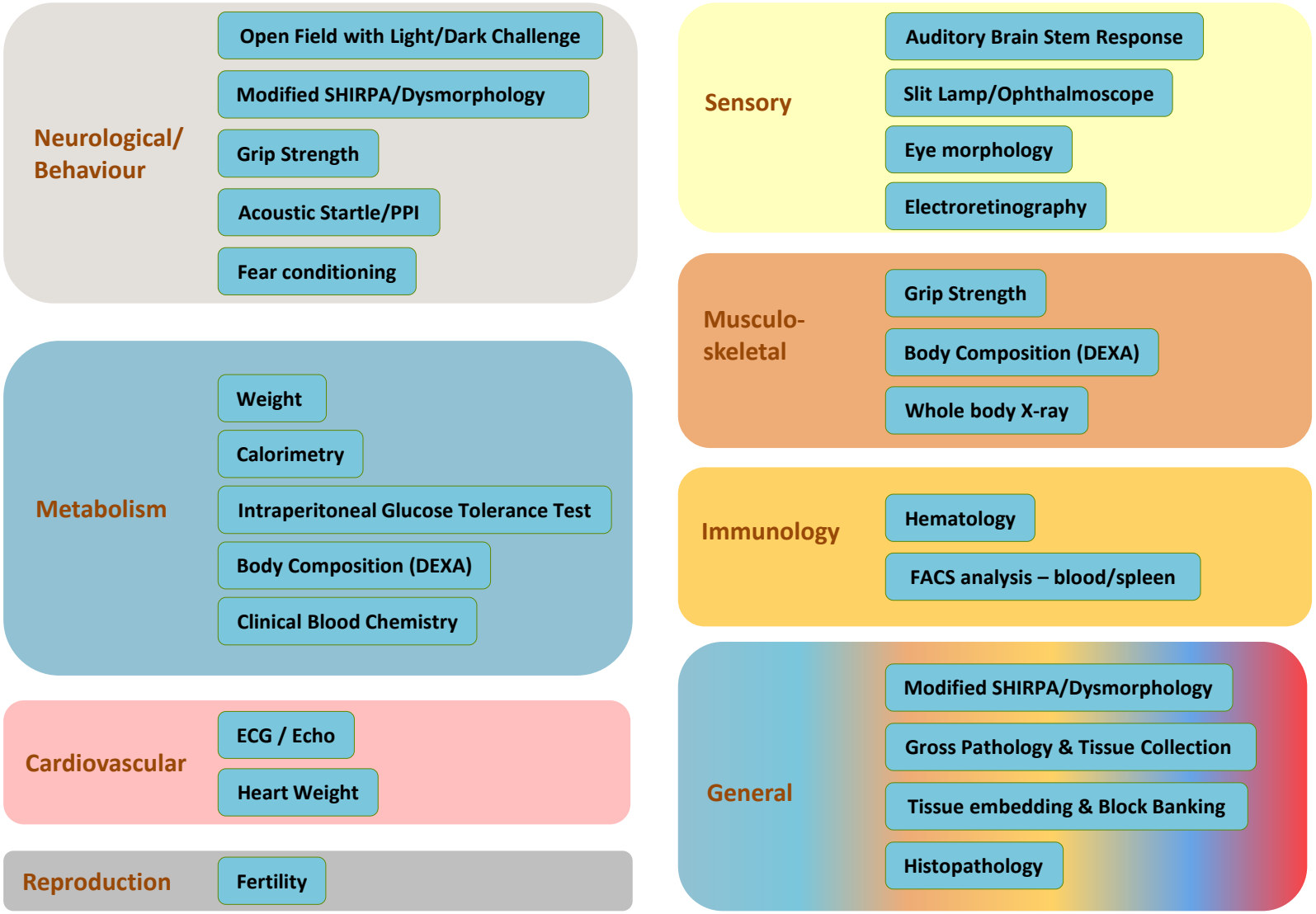


Velocigene

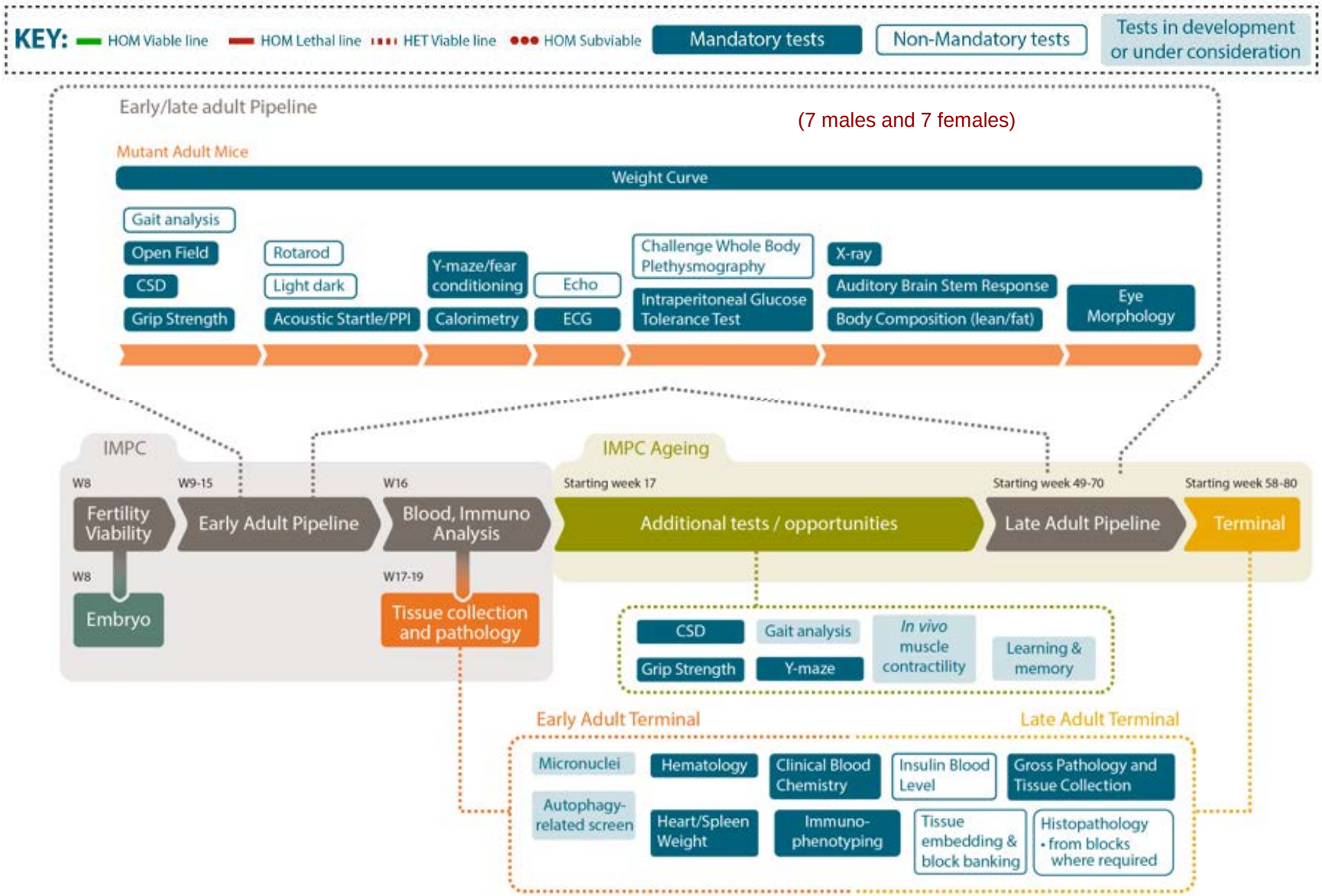




Phenotyping examines multiple systems



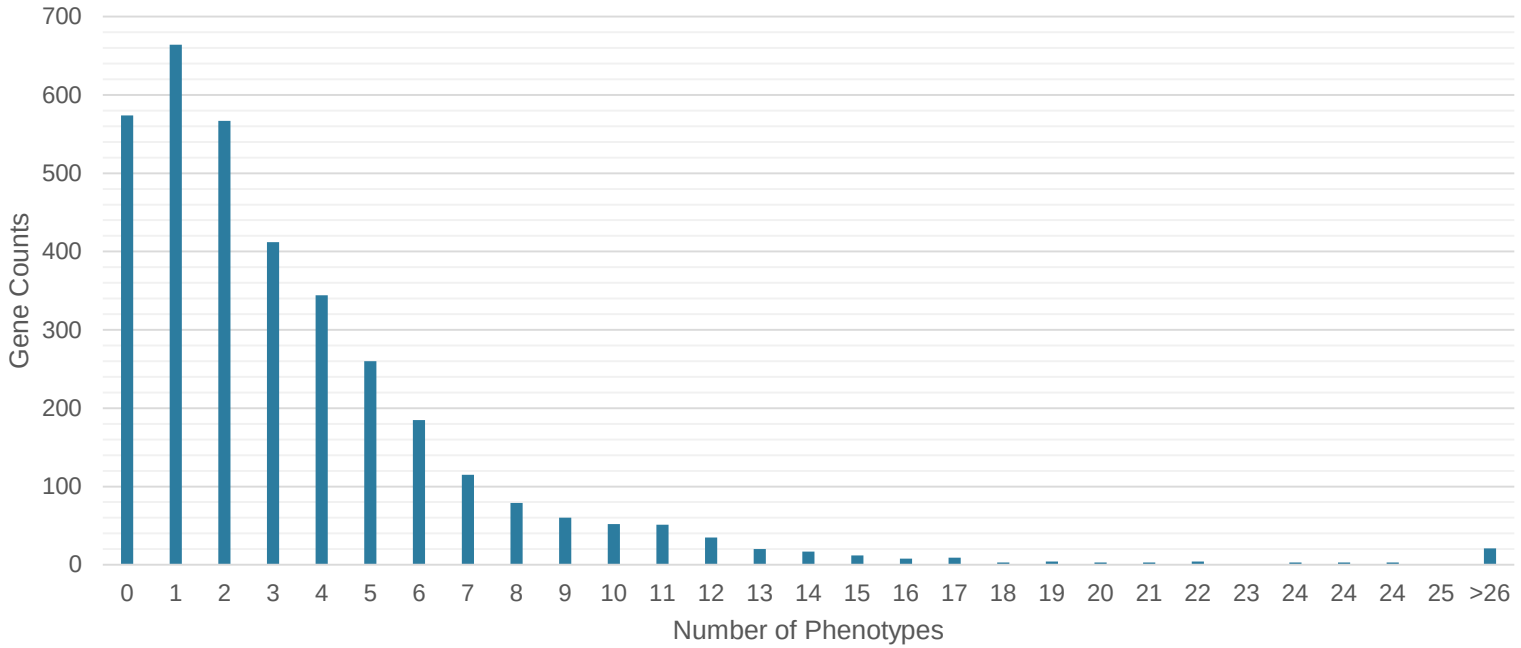
IMPC Standardized Adult Phenotyping Pipeline



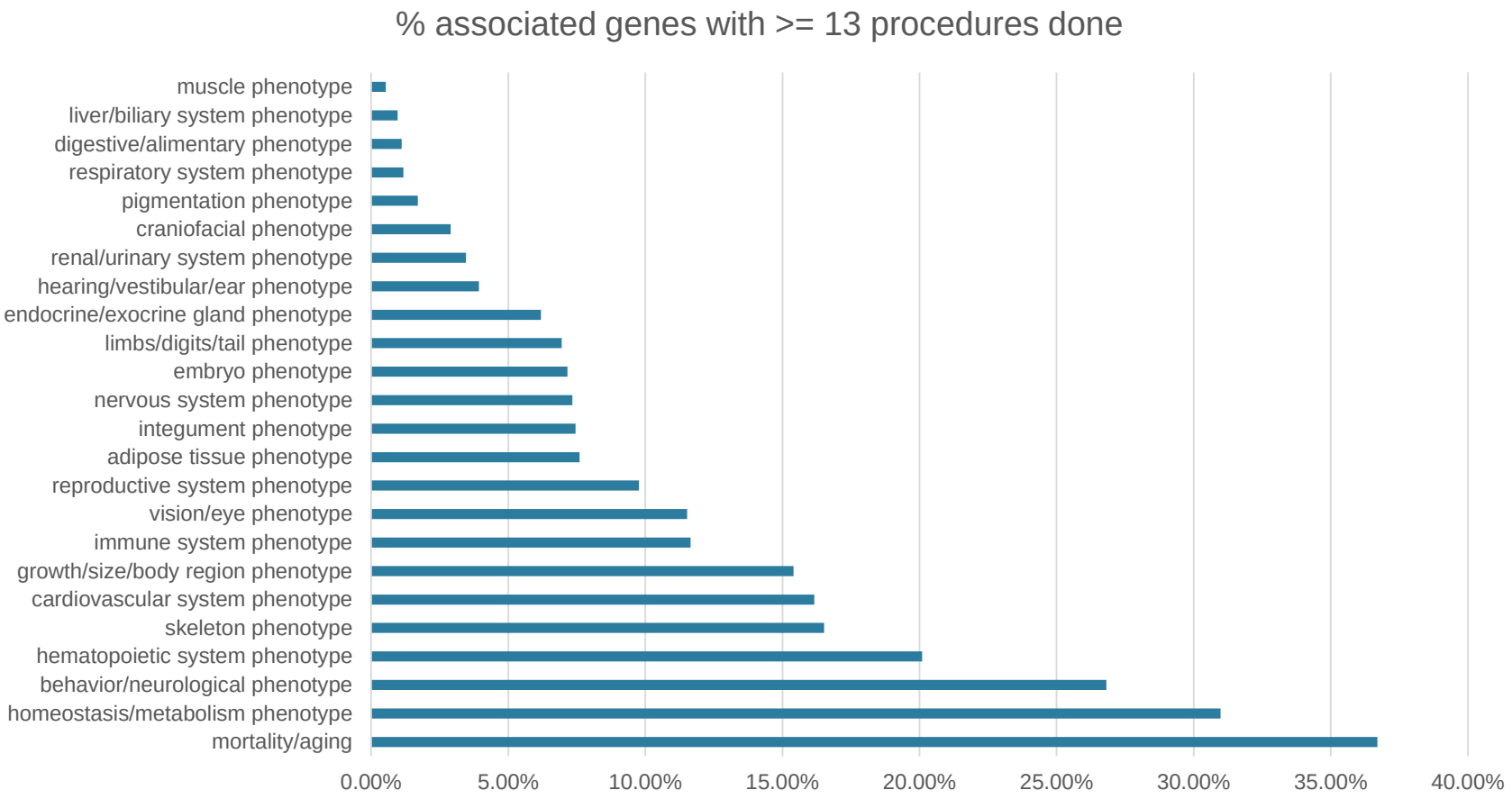
High hit rate, Extensive pleiotropy

- IMPC data: Of 3,513 gene KOs with sufficient phenotyping complete*, 2,929 (83.7)% show at least one phenotype.
- MGI data: Of 9,351** gene KOs, 8,389 (89.7%) report at least on phenotype.

* >= 13 Phenotyping parameters complete
** Includes some, but not all, IMPC data

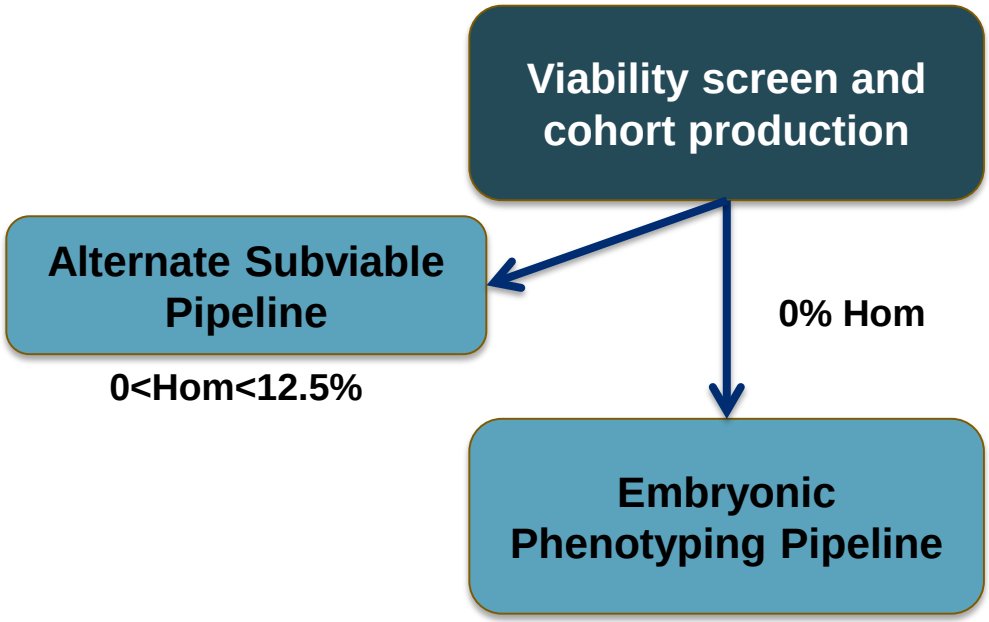


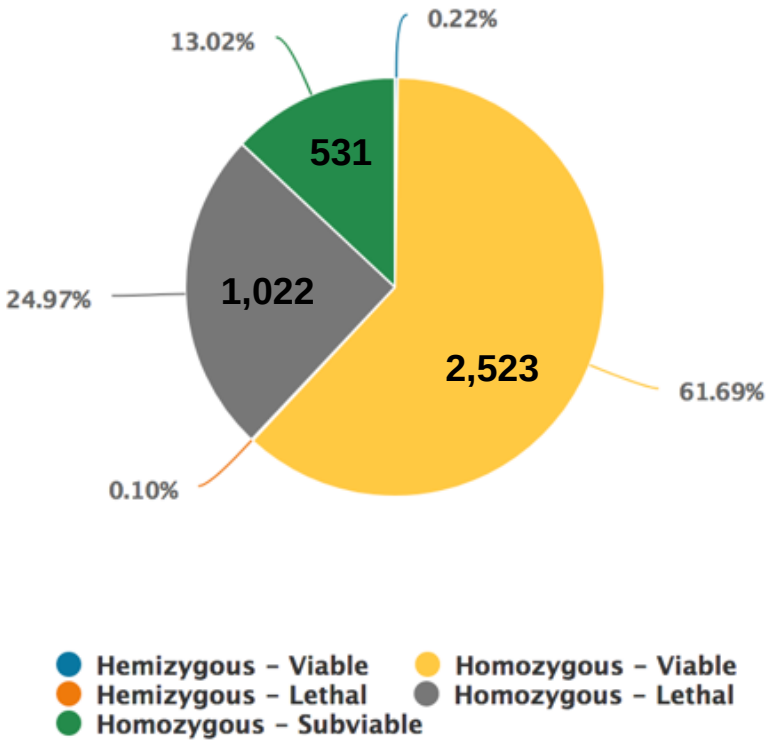
Hit rate varies by system



38% of all KO alleles show partial or complete embryonic lethality

KOMP2: Embryonic Lethality



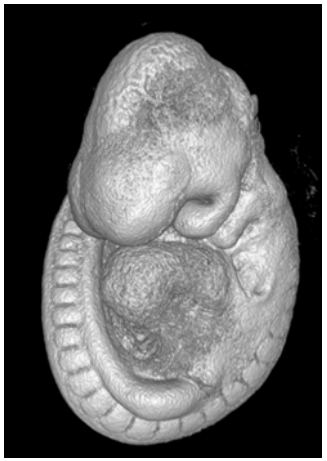
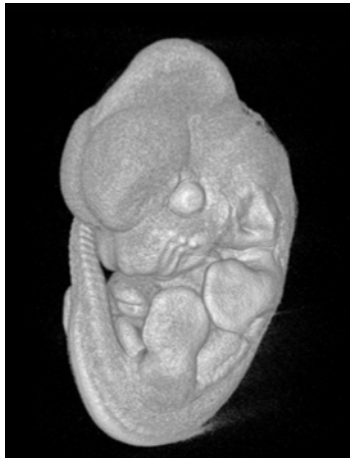
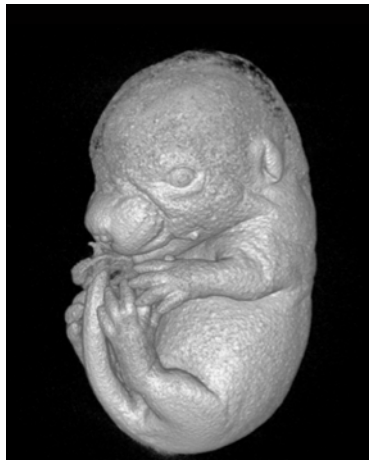


Chih-We Hsu, Ph.D.
Mary Dickinson, Ph.D

Embryonic Phenotyping Pipeline

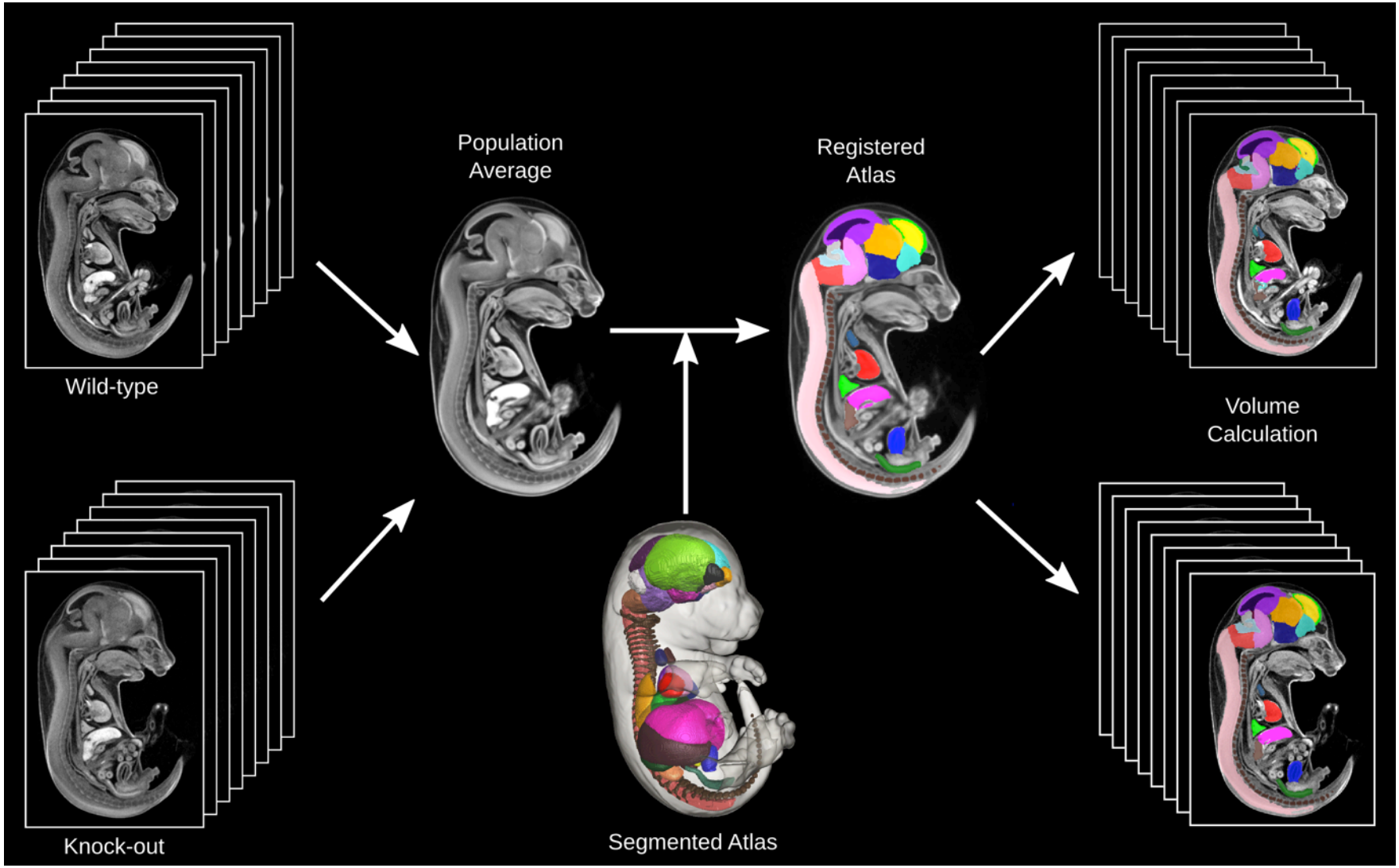
Lethal and subviable

Pattern formation (E9.5)	Mid-gestation (E12.5)	Organogenesis(E14.5/15.5)	Perinatal (E18.5/P0)
Genotype ratios	Genotype ratios	Genotype ratios	Genotype ratios
Gross Morphology	Gross Morphology	Gross Morphology	Gross Morphology


Chih-We Hsu, Ph.D.
Mary Dickinson, Ph.D.

Automated analysis pipeline for discovery of embryonic phenotypes



Michael Wong, Mark Henkelman

IMPC web portal

www.mousephenotype.org

Rare Disease Models

Produce and phenotype knockout mouse lines for 20,000 genes

Search

Examples: Ap4e1, Abnormal Heart Rate, Bernard-Soulier Syndrome

Find

- Genes
- Phenotypes
- Gene expression
- Embryonic phenotypes
- Biological systems phenotypes
- Sexual dimorphism

Human Diseases

- Rare Human Diseases
- 4601 human diseases associated with IMPC mouse models

Order Models

- Mouse lines
  ES cells
  targeting vectors

About

- What is IMPC?
- What does IMPC do?
- How does IMPC work?
- IMPReSS phenotyping pipeline
- How to explore?

Analyze

- Tools
- Data release statistics
- Data download

More

- Consortium publications
- All publications
- IDG orthologs
- IMPC Presentations
- IMPC YouTube channel
- Contact / feedback

Tweets by @impc

DMDD UK
@dmdduk

We have a new article in @JAnatomy on the range of normal #cardiovascular development. More on our blog: bit.ly/2hPrr1I #devbio

WHAT DOES NORMAL HEART DEVELOP...
Every developing heart is subtly different. He...
blog.dmdd.org.uk

Embed View on Twitter

IMPC website – phenotypes

Phenotype associations for Cib2

All Phenotypes Summary

Based on automated MP annotations supported by experiments on knockout mouse models.
Click on icons to go to all Cib2 data for that phenotype.

All Data: Body Weight Data | Cib2 Measurements | Heatmap / Table

Significant Phenotypes

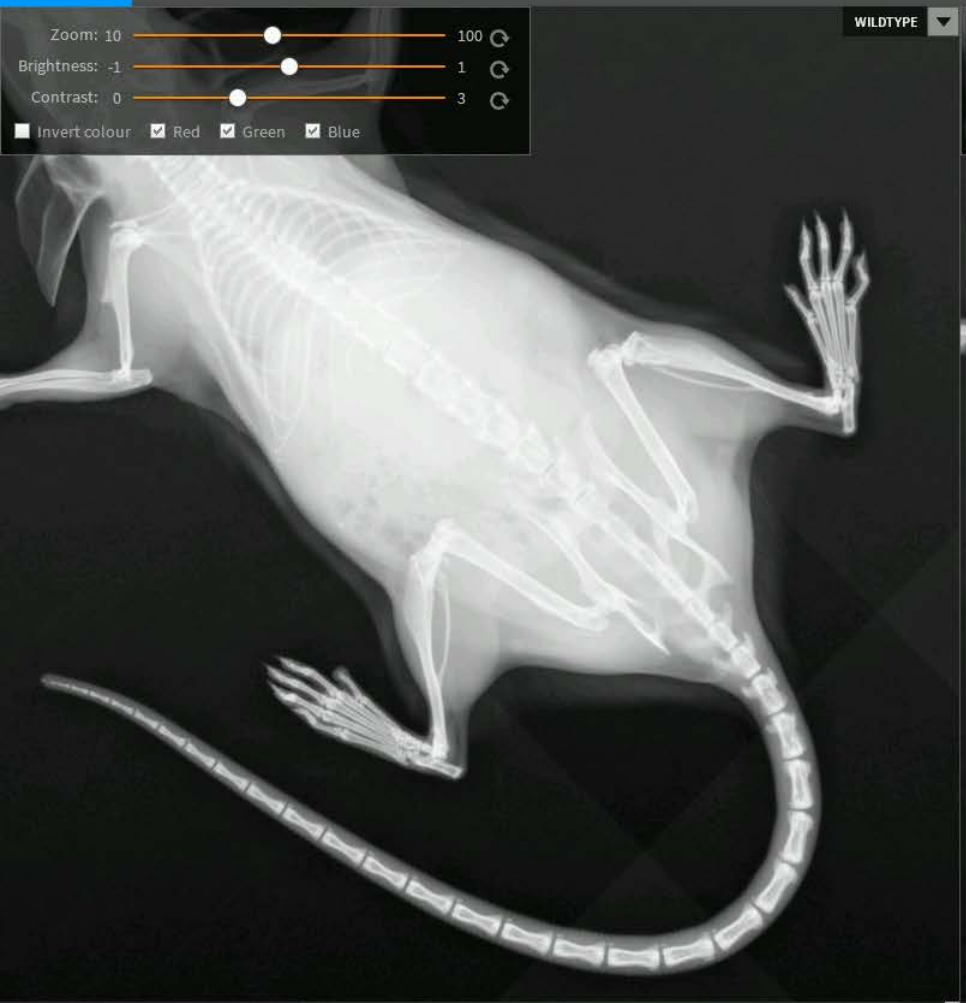
▸ Phenotype: All

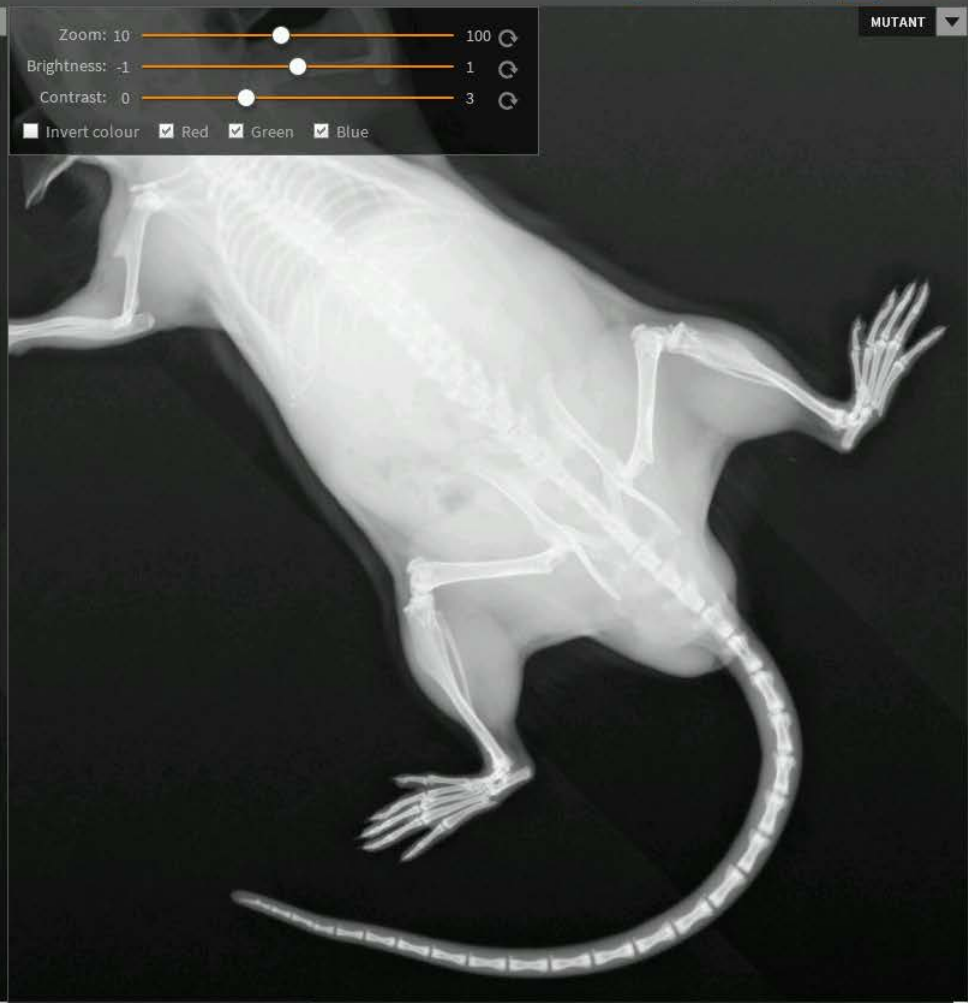
Show 10 entries

System	Phenotype	Allele	Zyg	Sex	Life Stage	P Value	Data
	absent startle reflex	Cib2$^{tm1b(EUCOMM)Wtsi}$	HOM	♀♂	postnatal	9.2E-20	
	decreased startle reflex	Cib2$^{tm1b(EUCOMM)Wtsi}$	HOM	♀♂	postnatal	5.47E-14	
	increased circulating cholesterol level	Cib2$^{tm1b(EUCOMM)Wtsi}$	HOM	♀♂	postnatal	2.28E-10	
	abnormal ear morphology	Cib2$^{tm1b(EUCOMM)Wtsi}$	HOM	♀♂	postnatal	8.04E-10	
	increased circulating HDL cholesterol level	Cib2$^{tm1b(EUCOMM)Wtsi}$	HOM	♀♂	postnatal	8.49E-8	

Significant annotations in a number of parameters

Exit viewer | Rbrc • C57BL/6NTac • Dnase1l2$^{tm1(KOMP)Wtsi}$ • X-ray • XRay Images Dorso Ventral





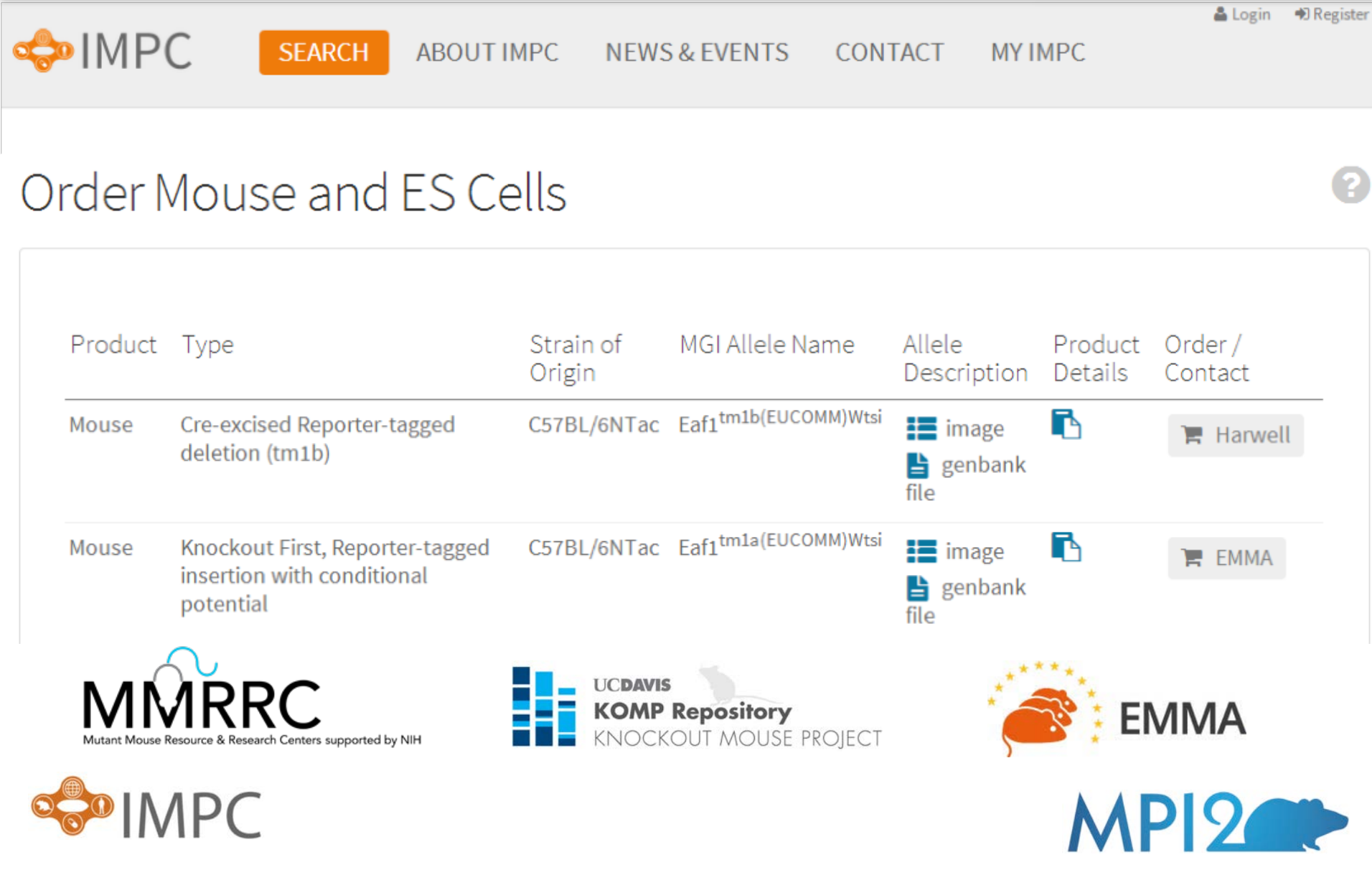
Name: JMC300001246
Date: 4 September 2013, Wednesday
Sex: Female (wildtype)
Zygosity: Homozygous

Name: JMC300001247
Date: 4 September 2013, Wednesday
Sex: Female (wildtype)
Zygosity: Homozygous

Name: JMC300001248
Date: 4 September 2013, Wednesday
Sex: Male (wildtype)
Zygosity: Homozygous

Name: JMC400007107
Date: 13 November 2013, Wednesday
Sex: Male (mutant)
Zygosity: Homozygous

IMPC Obtain Mouse Lines and Reagents



Building partnerships to maximize impact

KOMP2

- Centers for Mendelian Genomics
- Gabriella Miller Kids First

Baylor College of Medicine

- Undiagnosed Disease Network
- Baylor Genetics

The Jackson Laboratory

- Center for System Neurogenetics of Addiction
- MODEL-AD

MRC Harwell Institute, UK

- Genomics England (sequencing 100k genomes)
- Genome Editing Mice in Medicine funding
- UK Dementia Research Institute

The Centre for Phenogenomics, Toronto

- Care4Rare
- Province of Ontario Neurodevelopmental Disorders (POND) Consortium

The UC Davis Mouse Biology Program

- Center for In Vivo Characterization of ENCODE Elements (CIViC)
- Undiagnosed Disease Network

Opportunities for collaboration

- Null alleles for genes discovered in Kids First program
  - Genes with clear mouse orthologue
  - Novel gene knockouts prioritized (no existing knockout)
  - Report back on existing IMPC models, assignments, and knockouts in progress

- Modeling of precision variants
  - Develop framework for nominating clinically relevant disease variants for modeling
  - Define reporting milestones and timelines; develop useful reporting tools
  - Receive nominations for specific disease variants from Kids First team for production
  - Discuss potential custom phenotyping packages suited for disease of interest
  - Establish guidelines for data sharing and publication

IMPC

International Mouse Phenotyping Consortium

- National Institutes of Health (USA)
- The Centre for Phenogenomics (Canada)
- Medical Research Council & MRC Harwell (UK)
- The Wellcome Trust Sanger Institute (UK)
- Wellcome Trust
- Helmholtz Zentrum Munich (Germany)
- Phenomin
- UC Davis
- European Bioinformatics Institute
- The Jackson Laboratory
- Children's Hospital Oakland Research Institute
- Consiglio Nazionale delle Ricerche (Italy)

- European Commission (EU)
- Infrafrontier (EU)
- Australian Phenomics Network (Australia)
- RIKEN BioResource Center (Japan)
- Genome Canada
- National Laboratory Animal Center (Taiwan)
- Model Animal Research Center (Nanjing)
- Baylor College of Medicine
- Charles River Laboratories
- Korea Mouse Phenotyping Center
- Universitat Autònoma de Barcelona

Canadian Institutes of Health Research

Cambridge-SUDA Genomic Resource Centre (Soochow)

PCDDP
DST/NWU Preclinical Drug Development Platform

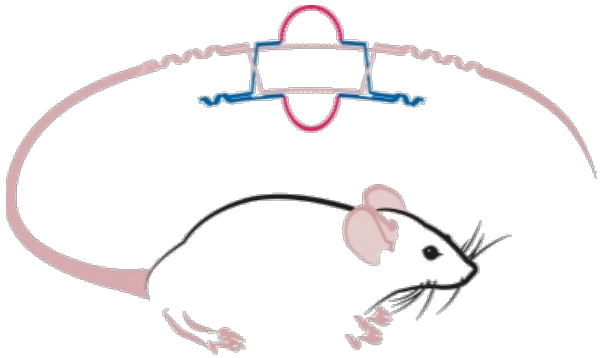
IMPC

MPI2

Kids First-KOMP2 collaboration:
Precision Modeling of Pediatric Conditions

September 21, 2018

Knockout Mouse Phenotyping Project (KOMP2)



IMPC

International Mouse Phenotyping Consortium

Gabriella Miller

Kids First

PEDIATRIC RESEARCH PROGRAM

Today's Webinar

1) **<u>International Mouse Phenotyping Consortium (IMPC)/Knockout Mouse Phenotyping (KOMP2):</u>**
   - KOMP2 background and goals of this collaboration
   - *Presented by Steve Murray, PhD, The Jackson Laboratory*
2) **<u>Gabriella Miller Kids First Pediatric Research Program (Kids First):</u>**
   - How to nominate variants for this opportunity
   - *Presented by James Coulombe, PhD, NICHD, NIH*
3) **Questions**

Brief Kids First Program Update

Vision

Alleviate suffering from childhood cancer and structural birth defects by fostering collaborative research to uncover the etiology of these diseases and supporting data sharing within the pediatric research community.

Kids First Data Resource Portal is live!

Available datasets: :

- Congenital Diaphragmatic Hernia (FY15) – phs001110
- Orofacial Cleft Birth Defects (FY15) – phs001168
- Ewing sarcoma (FY15) – phs001228
- Structural Heart Defects/PCGC (FY15) – phs001138
- Congenital Cranial Dysinnervation Disorders – phs001247

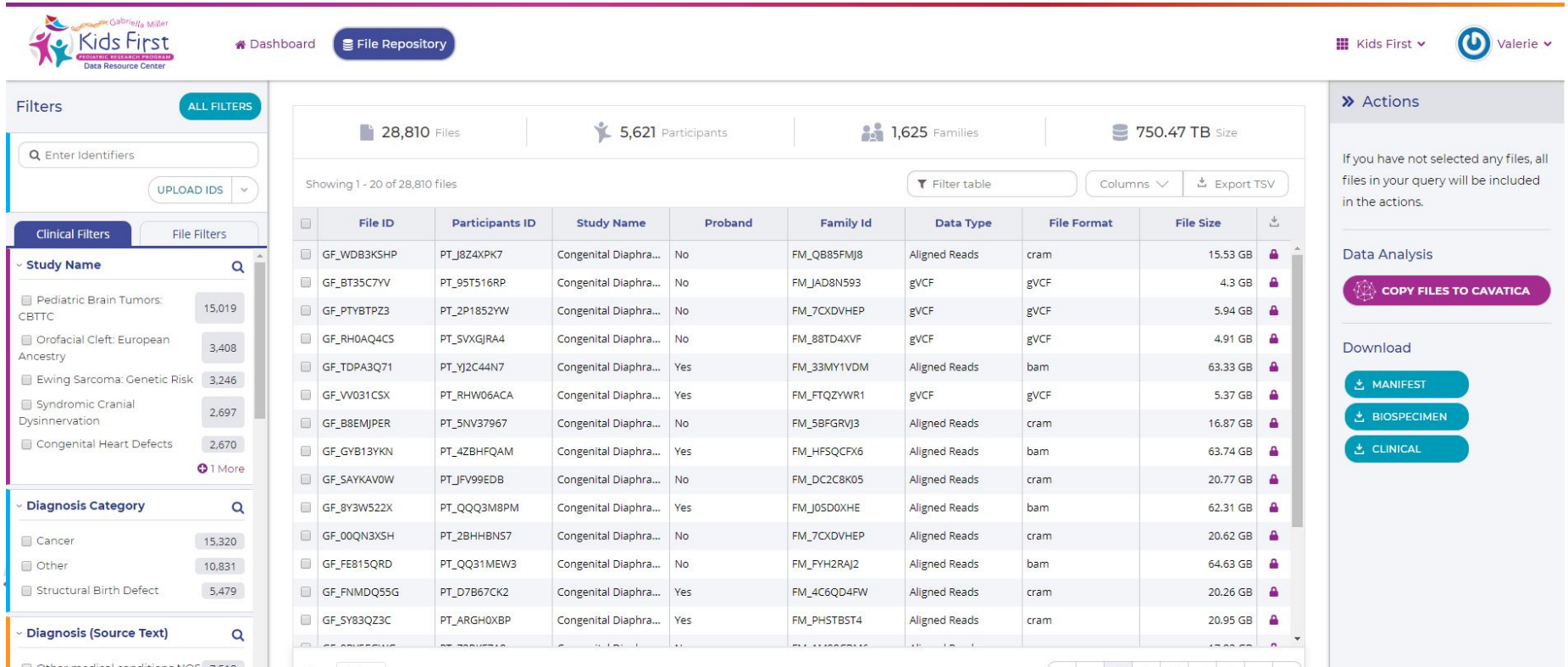
Sept 26: Kids First Data Resource Center (DRC) & Portal Webinar

The Kids First DRC will share progress in their mission to accelerate discoveries for childhood cancer and birth defect communities, including a demonstration of the new Kids First Data Resource Portal.

Date: Wednesday, September 26, 2018
Time: 10:00 AM – 5:00 PM EDT
Location: **WebEx only**
Register at https://www.eventbrite.com/e/kids-first-data-resource-center-webinar-tickets-49098180981

The webinar will cover:

- Overview of the Kids First Program and Data Resource Center progress
- Update on the DRC's engagements with patients and foundations
- Live demonstration of the Data Resource Portal
- Currently available datasets and how to access Kids First data
- Questions from the Kids First Community



Kids First X01 Cohorts (Years 1-3)

Adolescent Idiopathic Scoliosis (FY16)
Cancer Susceptibility (FY16)
Congenital Diaphragmatic Hernia (FY15, 16, 17)
Craniofacial Microsomia (FY17)
Disorders of Sex Development (FY15)
Enchondromatoses (FY17)
Ewing Sarcoma (FY15, 17)
Familial Leukemia (FY16)
Hearing Loss (FY16)
Infantile Hemangiomas (FY17)
Neuroblastomas (FY16)
Nonsyndromic Craniosynostosis (FY17)
Orofacial Clefts; Caucasian (FY15), Latin American (FY16), Asian & African (FY17)
Osteosarcoma (FY15)
Patients with both childhood cancer and birth defects (FY17)
Structural Heart & Other Defects (FY15, 16)
Syndromic Cranial Dysinnervation Disorders (FY15)

> 18,000 genomes

> 6,000 cases

Blue = Released Datasets

2018 X01 Cohorts (Year 4)

BEEC (Bladder extrophy, Epispadias, Complex)

Congenital Heart Defects and Acute Lymphoblastic Leukemia in Children with Down Syndrome**

Congenital Heart Disease

Cornelia de Lange Syndrome

Esophageal Atresia and Tracheoesophageal Fistulas

Fetal Alcohol Spectrum Disorders*

Intracranial Germ Cell Tumors

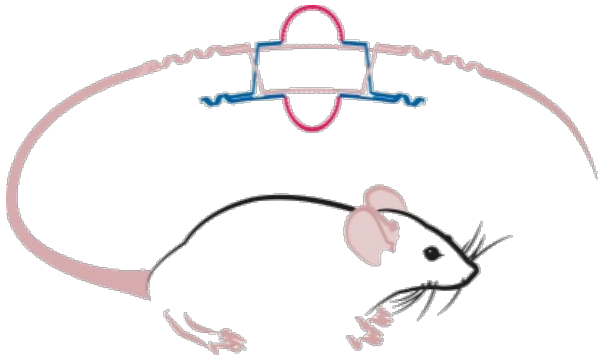
Kidney and Urinary Tract Defects

Microtia

Myeloid Malignancies + overlap with Down syndrome**

Vascular Anomalies, Overgrowth

> 8,000 genomes



How to Nominate Variants

Gabriella Miller Kids First
PEDIATRIC RESEARCH PROGRAM

Goal

Develop mouse strains to study, phenotype, and validate coding and noncoding genetic variants identified from Kids First whole genome datasets. You are invited to nominate variants identified through your analysis of Kids First datasets for mouse model production and phenotyping.

Evaluations

Nominations will be reviewed administratively by a subcommittee of NIH staff from the Kids First Working Group and variants will be prioritized based on the strength and breadth of the supporting evidence. Decisions will be finalized in consultation with KOMP2 staff.

Variant Justification

In no more than **three pages** per nominated variant, please address the following:

1. **Kids First data sets used**
2. **Variant(s) you are proposing to model and mouse ortholog (if known)**
3. **Phenotype of the human case(s) associated with the variant.**
4. **The predicted mouse phenotype associated with the variant and the predicted value of the data for your study (e.g. pathogenicity confirmation, further mechanistic study, etc.)**
5. **Supporting evidence that this variant is associated with this phenotype. Summarize findings from bioinformatic analyses, literature review, and entries in relevant databases, including existing animal models (e.g. IMPC, MGI, Zfin, Xenbase).**
6. **Provide any additional justification that should be considered.**

Nulls

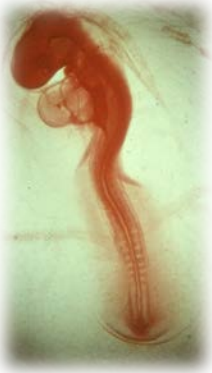
- Null variants will be considered as part of KOMP2's existing/standard pipeline and process
- For questions related this Kids First collaboration or KOMP's pipeline for null/knockout models, contact: KidsFirstKOMP@nih.gov.

Deadline

- **Please submit variant nominations by email to valerie.cotton@nih.gov by COB October 26, 2018.**
- Additional information may be requested after preliminary review.

Other Model Organisms?

- The program intends to use this process to spur other opportunities within NIH.



Questions?

- For technical questions or additional information about this variant production pipeline contact: KidsFirstKOMP@nih.gov (this email connects to KOMP2 staff)

Questions?

- Un-mute yourself by selecting *6 on your telephone or clicking on the mic symbol under “Audio Connection”,
  or
- Message us via the WebEx chat function

Upcoming Events

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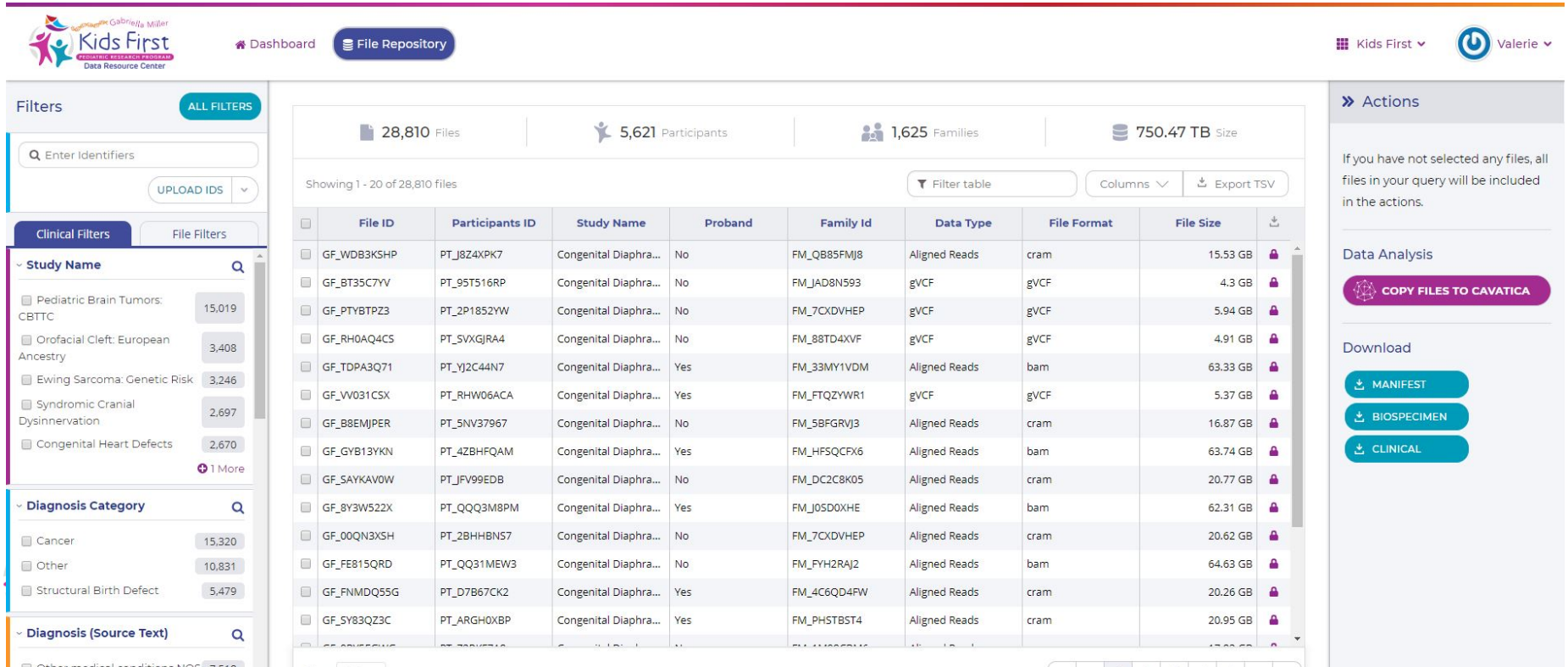
Time: 10:00 AM – 5:00 PM EDT
Location: **WebEx only**
Register at https://www.eventbrite.com/e/kids-first-data-resource-center-webinar-tickets-49098180981

The webinar will cover:

- Overview of the Kids First Program and Data Resource Center progress
- Update on the DRC's engagements with patients and foundations
- Live demonstration of the Data Resource Portal
- Currently available datasets and how to access Kids First data
- Questions from the Kids First Community

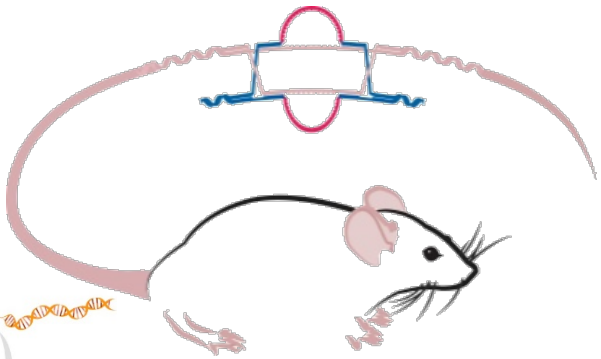


Oct 2: KOMP2/IMPC "Collaboration Day"

You're invited to join the **KOMP2/IMPC Annual Meeting on Tuesday, October 2nd**. This one day meeting will be focused on collaborations with various human disease gene discovery programs. The day will feature talks and discussions from current and potential collaborators, specifically groups focused on human genes and variants who may find KOMP data helpful for their efforts. These include the Centers for Mendelian Genetics (CMG), Trans-Omics for Precision Medicine (TopMed), Gabriella Miller Kids First Pediatric Research Program (Kids First), and Undiagnosed Disease Network (UDN).

Please feel free to view the live webcast at https://www.genome.gov/27572031."

Knockout Mouse Phenotyping Project (KOMP2)



IMPC

International Mouse Phenotyping Consortium

Oct 18: Kids First Poster Session and Meet & Greet at the American Society of Human Genetics (ASHG) Annual Meeting

This evening poster session will focus on analyses of Kids First cohorts, and existing collaborative efforts across Kids First projects. The poster session is an opportunity for the scientific community, and public to engage with Kids First investigators, Data Resource Center staff, collaborators and Kids First leadership. Attendees will gain a broad understanding of the utility of genomic data generated by Kids First, and how researchers can use Kids First data to accelerate research and promote new discoveries.

Date: Thursday, October 18, 2018

Time: 7:00pm-10:00pm PDT

Location: **Marriott Marquis San Diego Marina**
333 West Harbor Drive
San Diego, CA 92101

Register at https://www.eventbrite.com/e/nih-kids-first-poster-session-and-meet-greet-at-ashg-tickets-48285354796

ASHG
American Society of Human Genetics

Thank You!

Email Additional Questions to:

KidsFirstKOMP@nih.gov.