

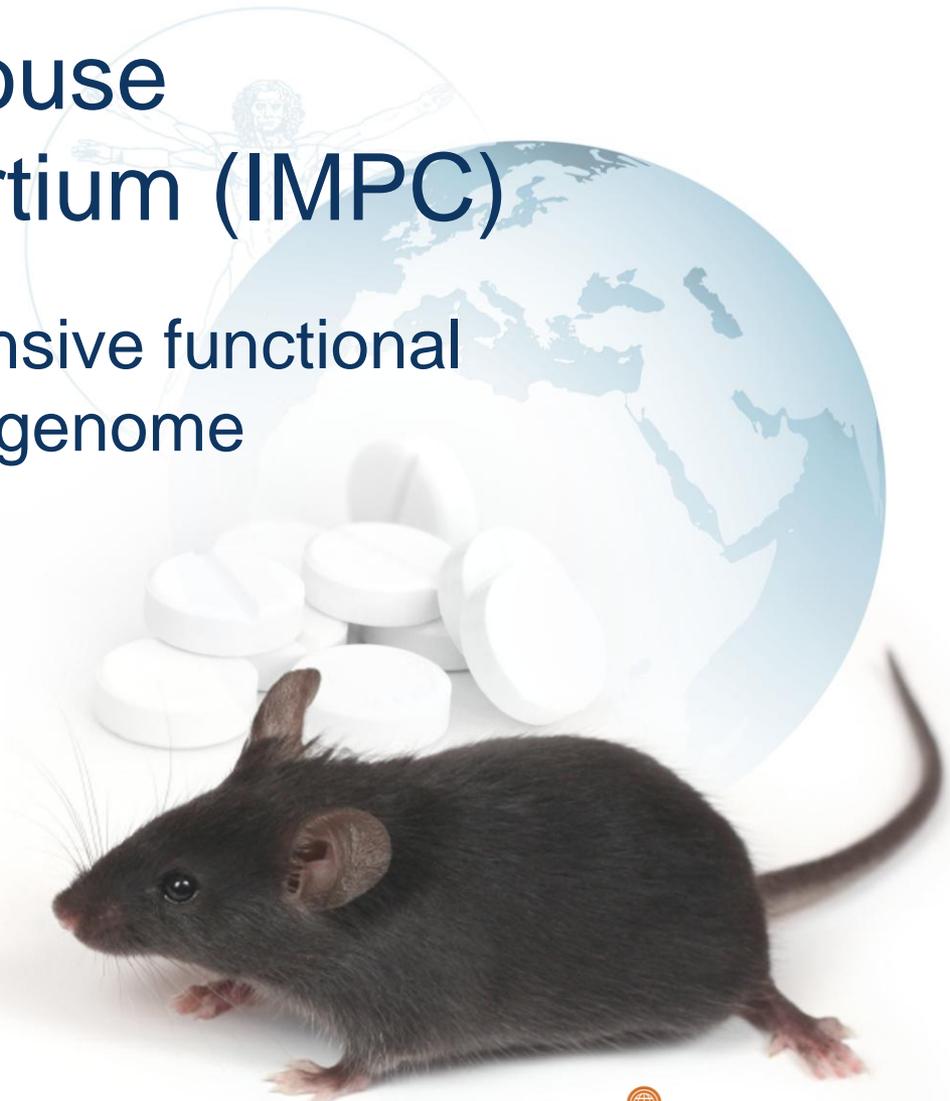
The International Mouse Phenotyping Consortium (IMPC)

Building the first comprehensive functional catalogue of a mammalian genome

Mark Moore, Ph.D.
Executive Director, IMPC

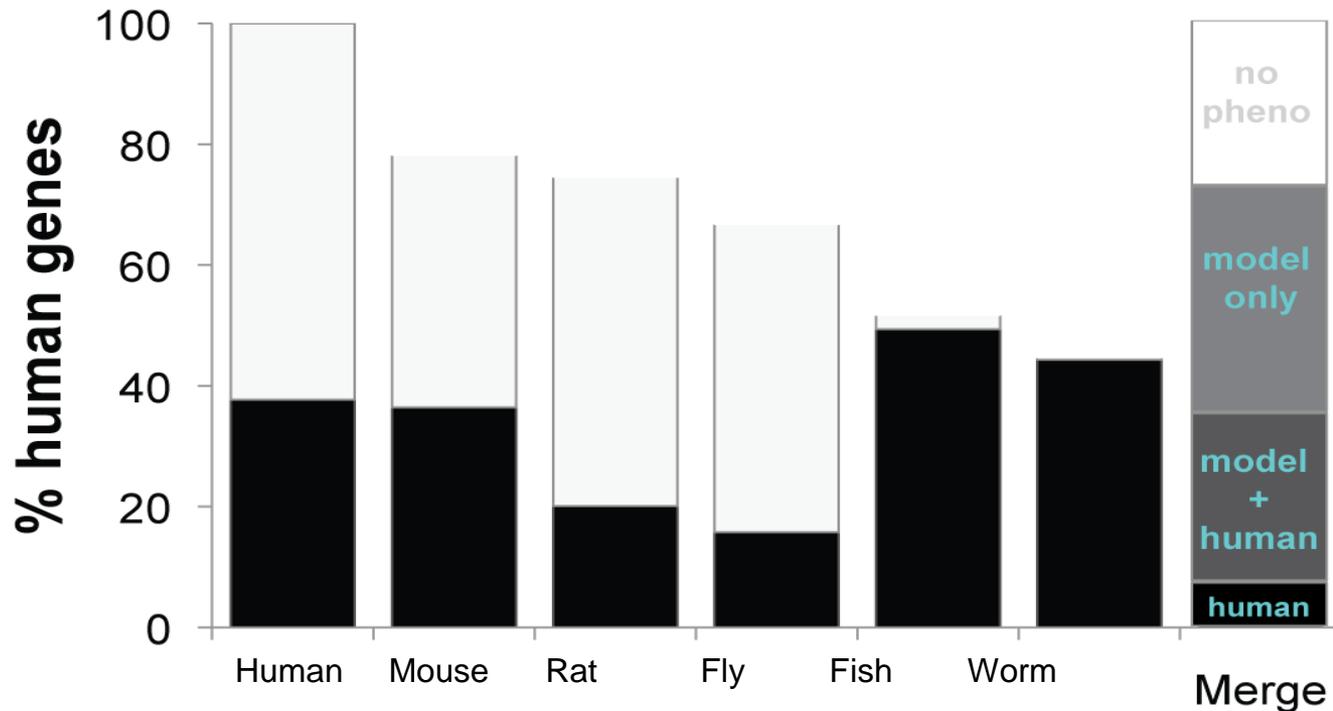
IRDiRC November 8, 2014

www.mousephenotype.org



How much phenotype data?

- ◆ Human genes have poor phenotype coverage (~35%)
- ◆ Mouse models available for ~35% of human genes
- ◆ All animal models and human phenotypes linked to >75% human genes.



IMPC – the context

- The function of the majority of genes in the mouse (and human) genomes is unknown
- We are remarkably poor at predicting the function of genes – **pleiotropy** will be key to understanding systems
- KOs have been generated and analysed in only some 30% of mouse genes
- Data for these genes is patchy – dependent on the interests and experience of the investigator
- Develop approaches for broad based phenotyping, to provide a comprehensive picture of disease states and to integrate with human and clinical genetics

IMPC activities

- **Undertake broad-based phenotyping of 20,000 mutants from the IKMC resource**
 - A coordinated activity of mouse centres worldwide
- **Phase 1 (2011-2016): Phenotype up to 5,000 lines**
 - Pipeline development, logistics
 - Phenotype technology developments
 - Economies of scale
- **Phase 2 (2016-2021): Phenotype 15,000 mutants**
 - Business plan in preparation
- **Data freely available through a Data Coordination Centre**
- **Mice available through the global network of mouse repositories**



IMPC

International Mouse Phenotyping Consortium

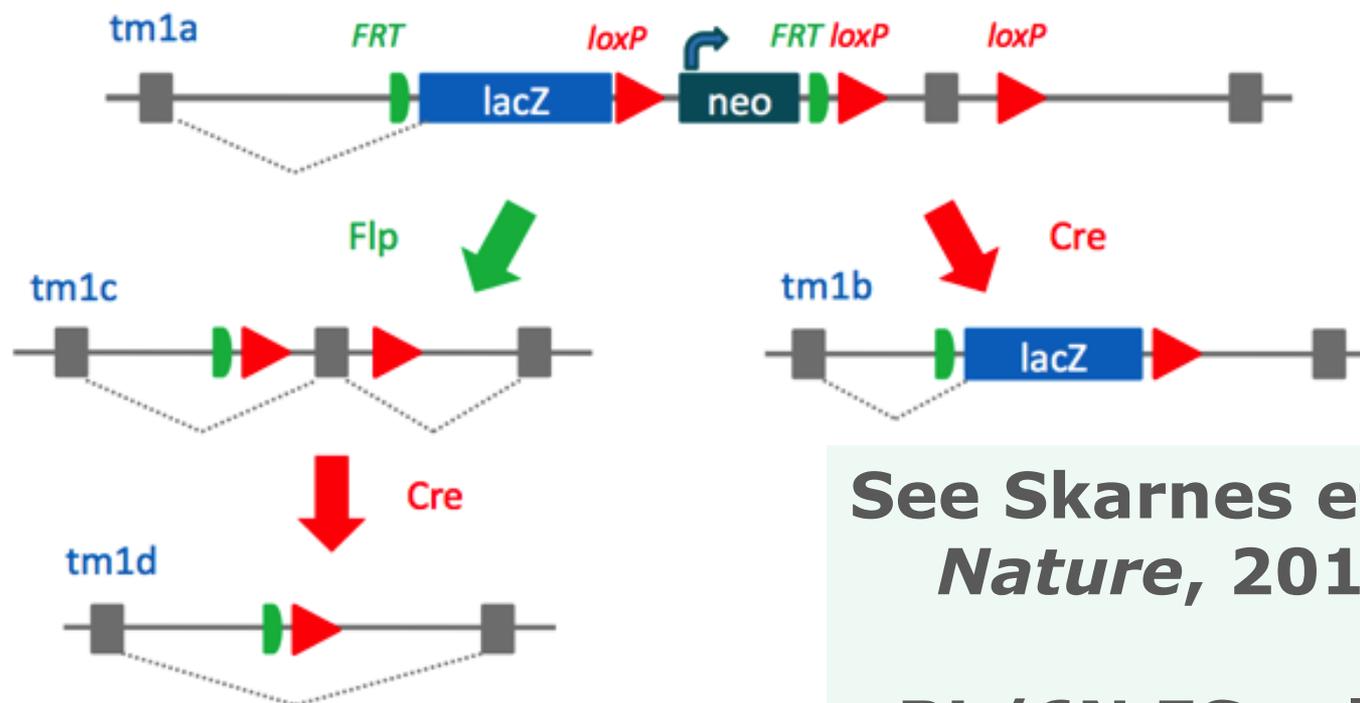


www.mousephenotype.org

IMPC alleles from IKMC >15,000 KO ES cell lines



Knockout-first, conditional-ready allele:



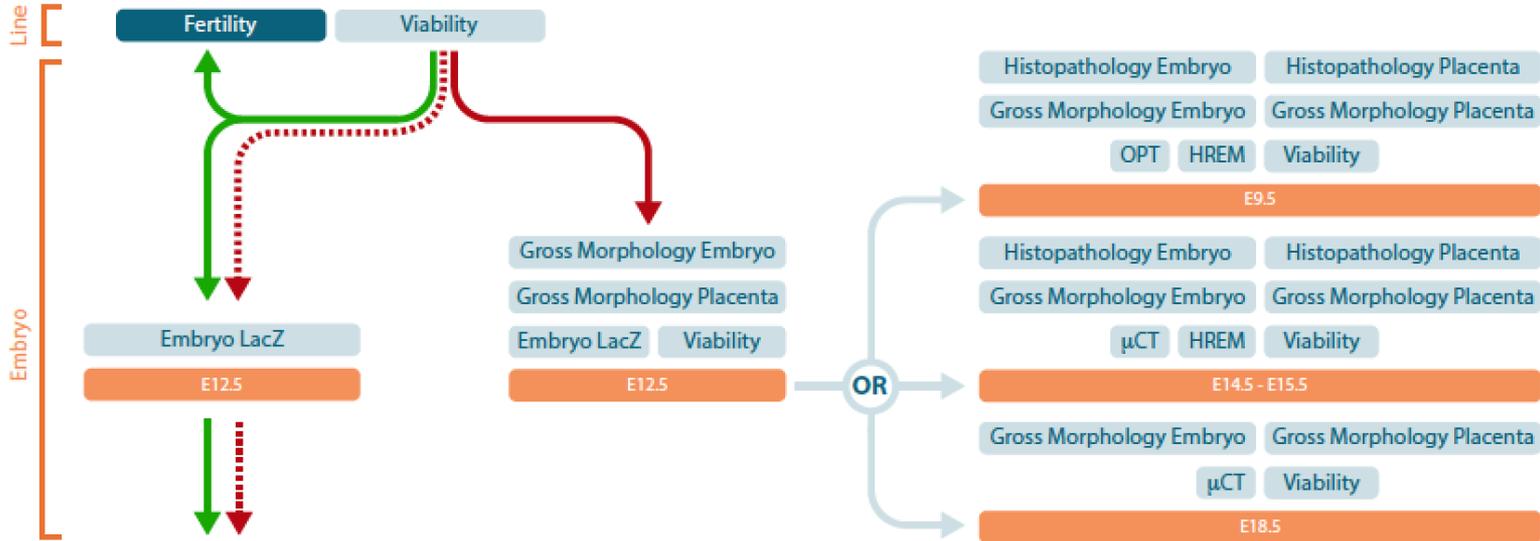
**See Skarnes et al.
Nature, 2011**

BL/6N ES cells

IMPC phenotyping pipeline

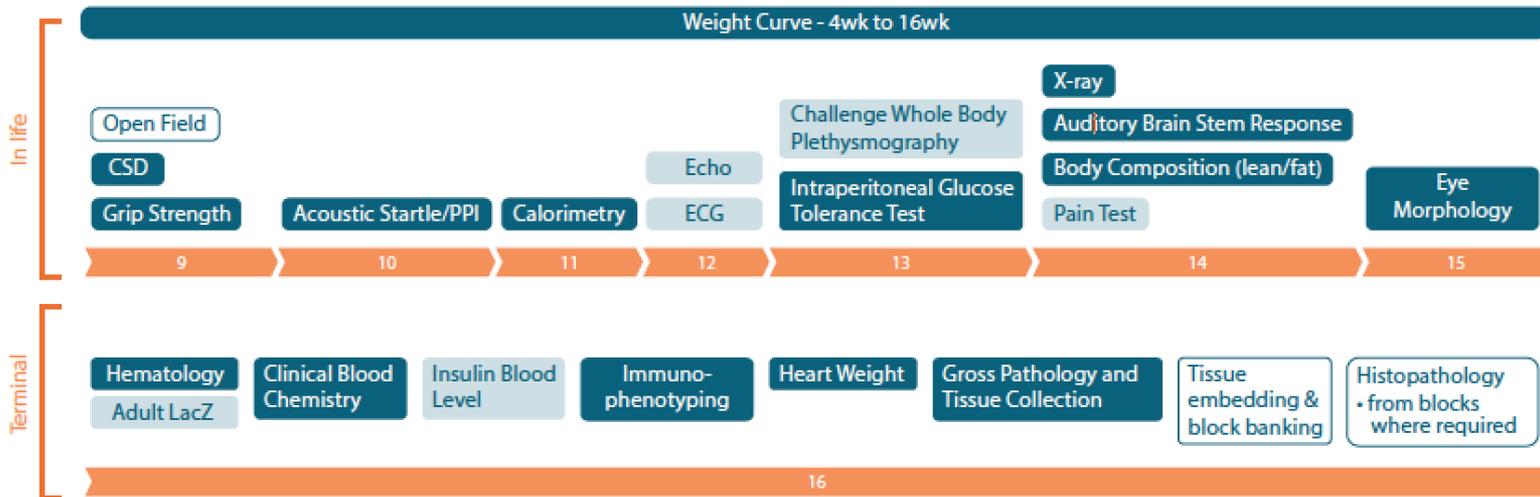
KEY: — HOM Viable line — HOM Lethal line - - - HET Viable line Mandatory tests Non-Mandatory tests Tests in development or under consideration

Embryonic



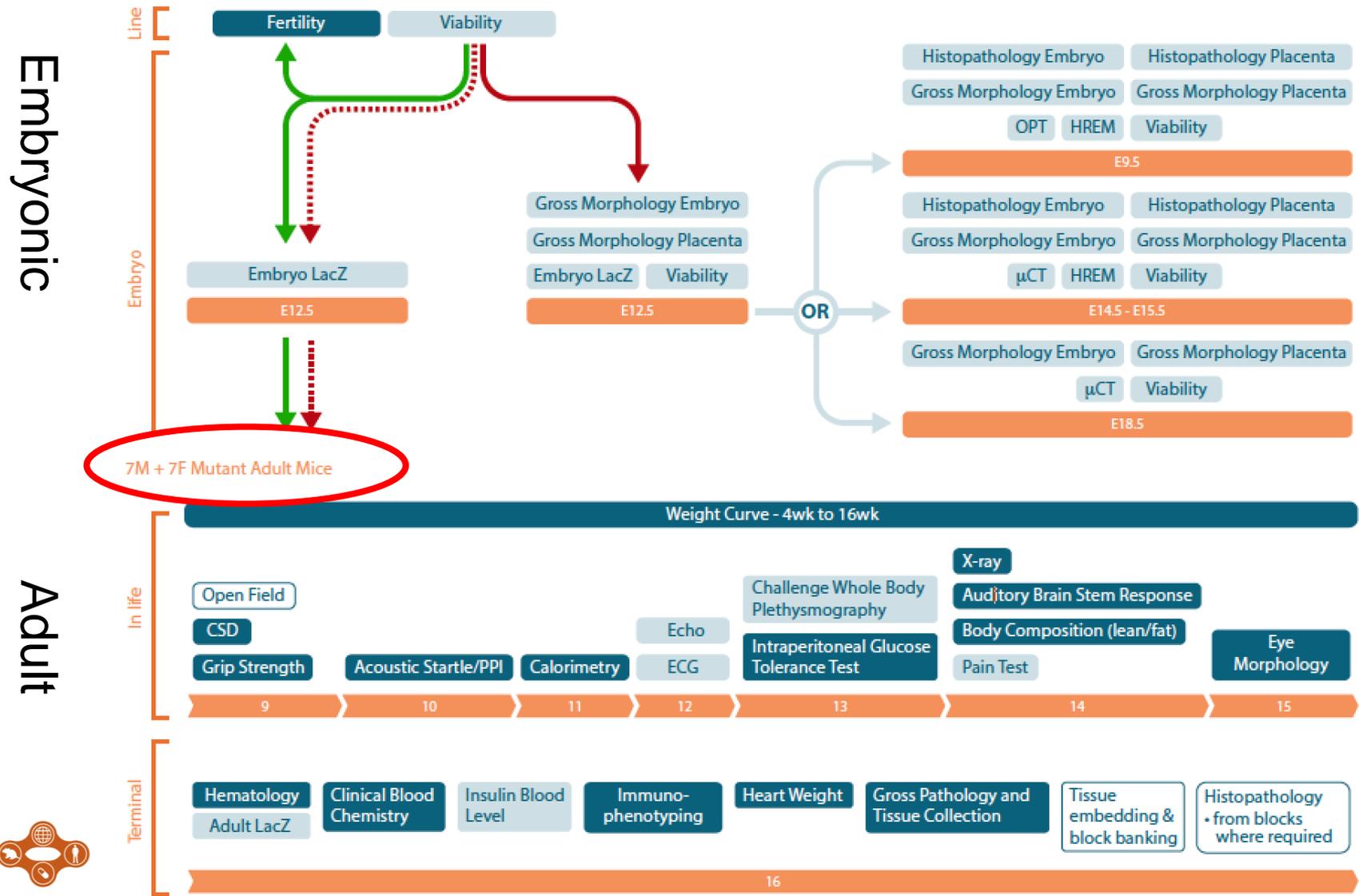
7M + 7F Mutant Adult Mice

Adult

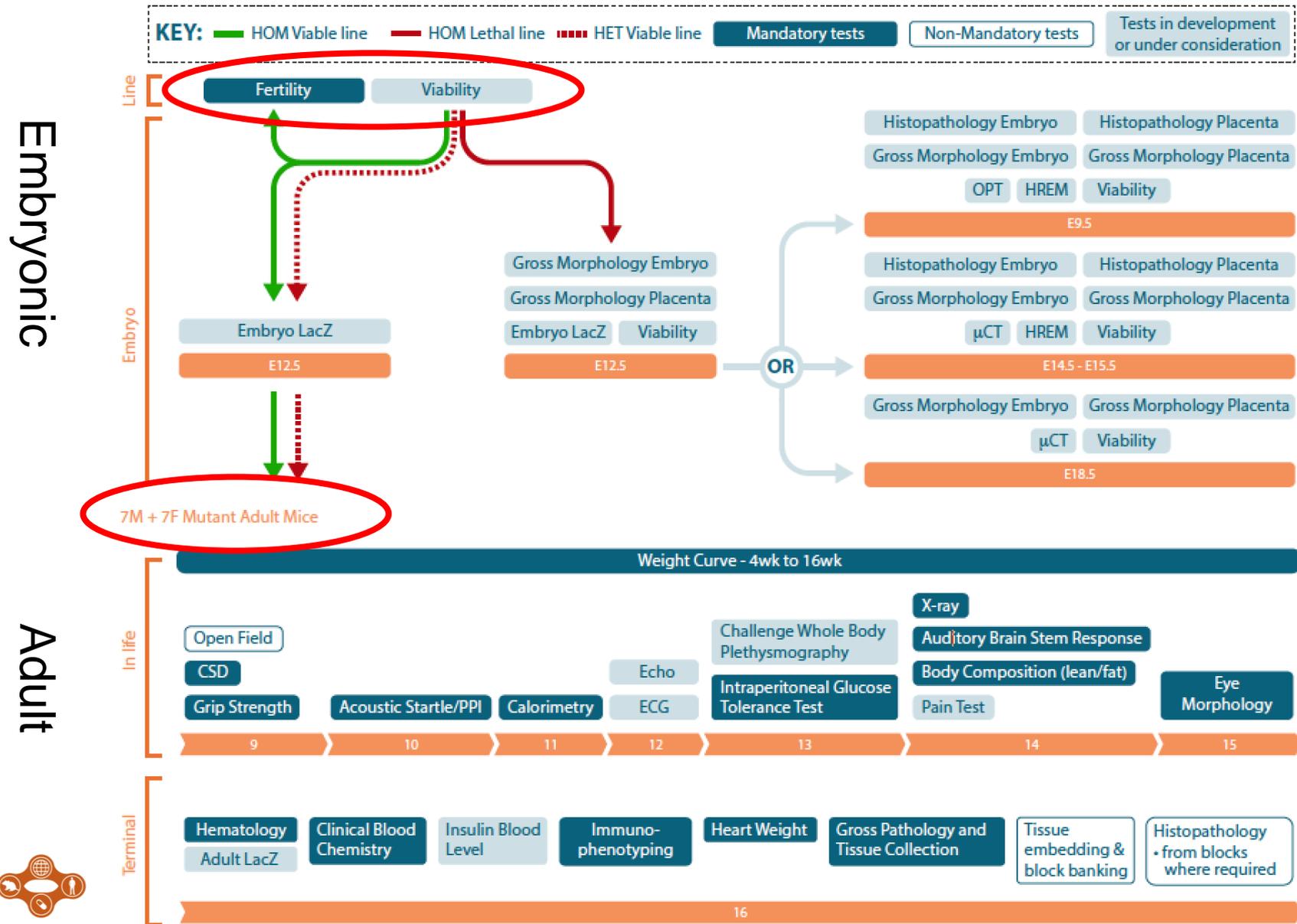


IMPC phenotyping pipeline

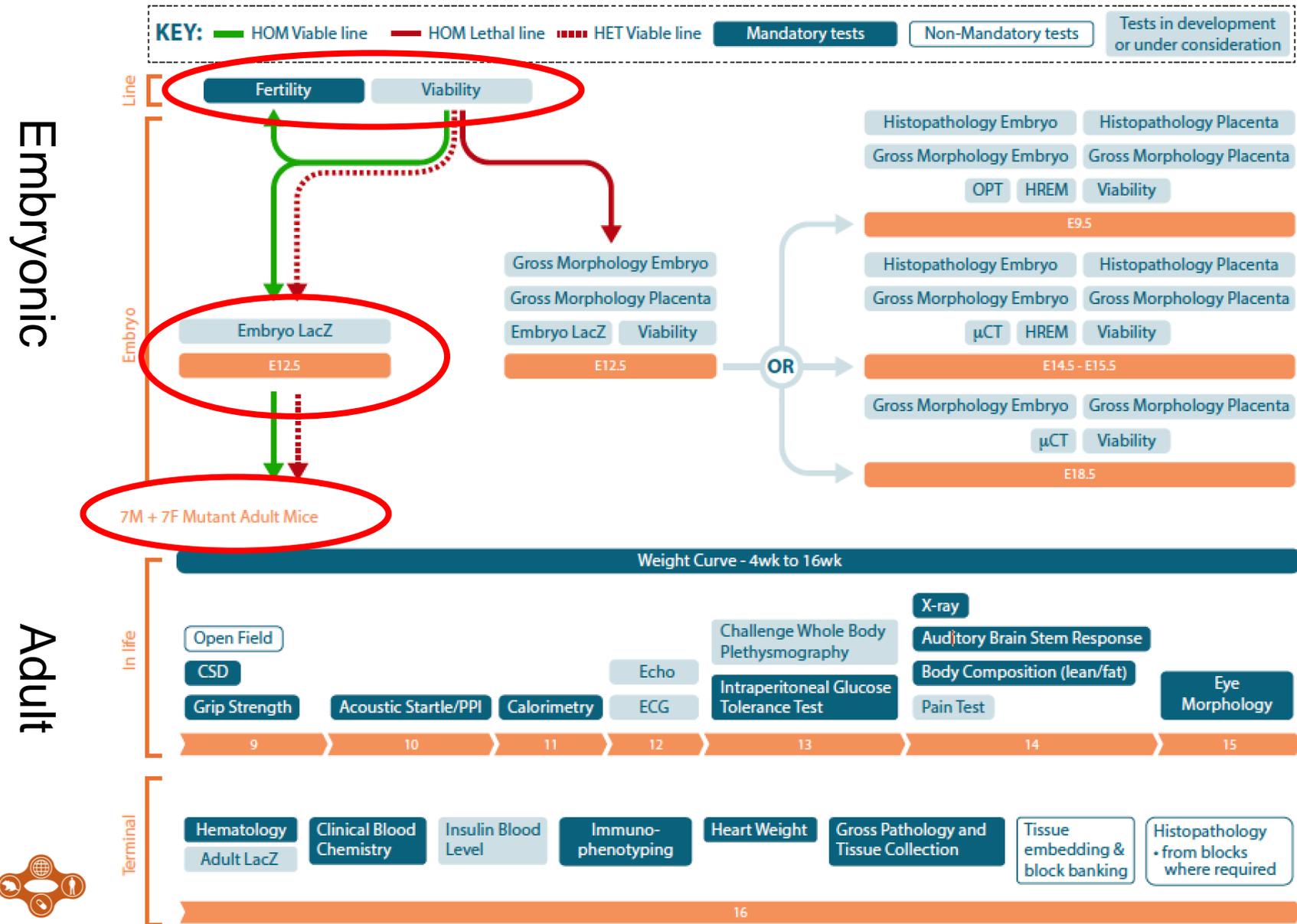
KEY: — HOM Viable line — HOM Lethal line - - - HET Viable line Mandatory tests Non-Mandatory tests Tests in development or under consideration



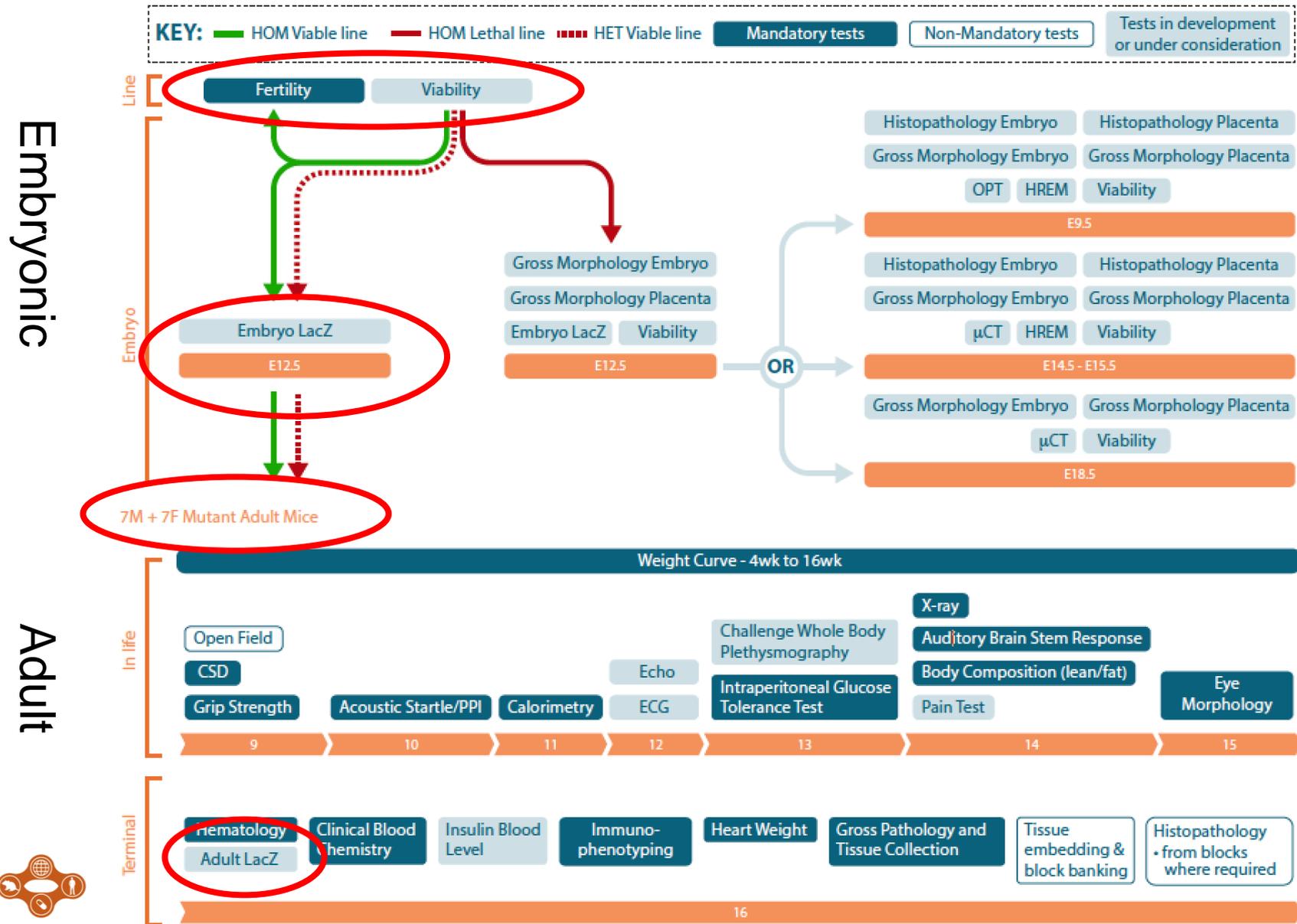
IMPC phenotyping pipeline



IMPC phenotyping pipeline



IMPC phenotyping pipeline



Mandatory tests

Non-mandatory tests

**Neurological/
Behaviour**

Open Field

Modified SHIRPA/Dysmorphology

Grip Strength

Acoustic Startle/PPI

Pain Test

Metabolism

Weight

Calorimetry

Intraperitoneal Glucose Tolerance Test

Body Composition (DEXA)

Clinical Blood Chemistry

Insulin Blood Level

Cardiovascular

ECG / Echo

Heart Weight

Pulmonary

Challenge Whole Body Plethysmography

Reproduction

Fertility

**Tests in
development or
under consideration**

Sensory

Auditory Brain Stem Response (2+2)

Slit Lamp

Ophthalmoscope

**Musculo-
skeletal**

Grip Strength

Body Composition (DEXA)

X-ray (5 + 5)

Immune

Hematology

FACS analysis – blood/spleen

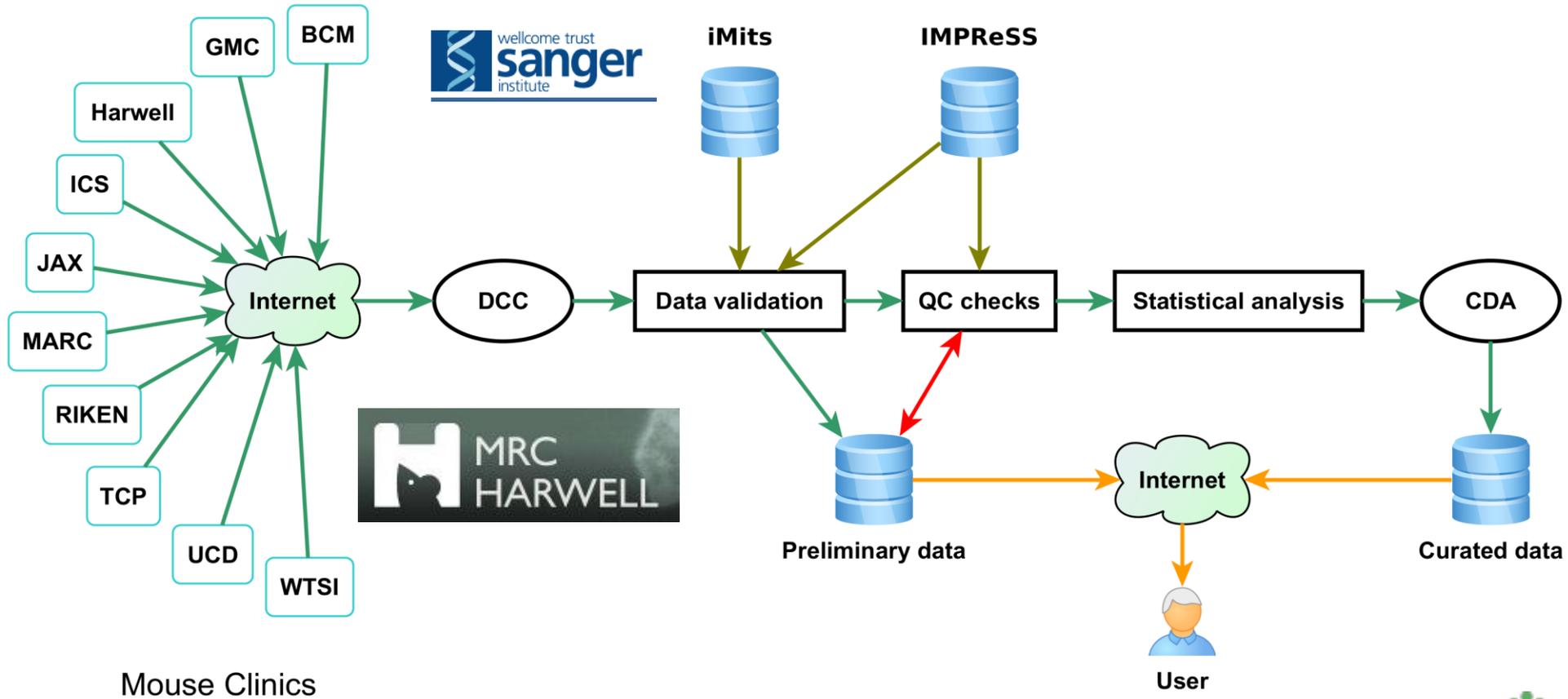
General

Modified SHIRPA/Dysmorphology

Gross Pathology & Tissue Collection (2+2)

Tissue embedding & Block Banking (2+2)

Histopathology (2+2)
- from blocks where required



IMPC status:

Current iMits (October 2014)

Centre	Total Clones Injected	Genotype Confirmed	Cre excision	Phenotype started (Data in the DCC)
Baylor	769	371	127	52
Harwell	603	253	234	159
HMGU	541	177	117	71
ICS	128	106	74	59
JAX	1033	556	354	224
MARC	83	69	2	15
Monterotondo	37	17	4	0
RIKEN	73	34	21	7
TCP	402	173	78	159
UCD	1785	520	431	198
WTSI	1594	733	154	389
TOTAL	7048	3009	1596	1333



International Mouse Phenotyping Consortium

SEARCH

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MY IMPC

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We are building the first truly comprehensive, functional catalogue of a mammalian genome.

Learn more



The Knockout Mouse

A powerful tool for precision medicine.

Read why

News and Events

March 18, 2014
[Successful IMPC Phenotyping Meeting held in San Francisco](#)

Search IMPC database

Enter your favorite gene, phenotype, anatomy or protocol to find IMPC data important to your research.

Or browse

new gene-phenotype associations

Rare Disease Models



[Home](#) » [Search](#)

Filter your search



- ▼ Genes 49492
- ▼ IMPC Phenotyping Status ?
 - Complete 438
 - Started 671
 - Attempt Registered 1485
 - Legacy 615
- ▶ IMPC Mouse Production Status
- ▶ IMPC Mouse Production Center
- ▶ IMPC Mouse Phenotype Center
- ▶ Subtype
- ▶ Phenotypes 607
- ▶ Diseases 7137
- ▶ Anatomy 382
- ▶ Procedures 4540
- ▶ Images 100126



[View example search](#)

Found 49492 genes

[Download](#)

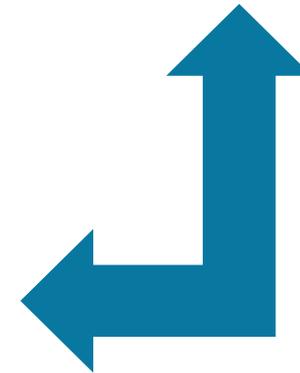
Gene	Production Status	Phenotype Status	
Rxfp2	ES Cells Mice	phenotype data available	Register interest
Dlg2	ES Cells Mice	phenotype data available	Register interest
1110059G10Rik	ES Cells Mice	phenotype data available	Register interest
Aff3	ES Cells Mice	phenotype data available	Register interest

Follow genes of interest

Found 288 genes [View example search](#) Download

Gene	Production Status	Phenotype Status	
Smyd5	ES cells Mice	phenotype data available	Interest
Apol7a	ES cells Mice	phenotype data available	Interest
Slc38a10	ES cells Mice	phenotype data available	Interest
Xbp1	ES cells Mice	phenotype data available	Interest

Follow genes you are interested in
IMPC will send an email when new data is published



- 1100 registrations
- 2867 genes
- Average 3 genes per person

The ignorome – annotating genes with no known function

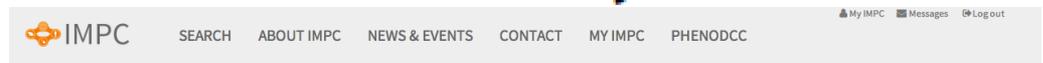
OPEN ACCESS Freely available online



Functionally Enigmatic Genes: A Case Study of the Brain Ignorome

Ashutosh K. Pandey^{1*}, Lu Lu¹, Xusheng Wang¹

¹UT Center for Integrative and Translational Genomics and Department of Biology, University of Tennessee, United States of America, ²St. Jude Children's Research Hospital, Department of Biostatistics, Memphis, Tennessee, United States of America, ³Bioinformatics Program, University of Memphis, Memphis, Tennessee, United States of America



Home > Search > Genes > Elmod1

Gene: Elmod1

Name ELMO/CED-12 domain containing 1
MGI Id MGI:3583900

Register interest

Status ES Cells Mice tm1b Mice tm1a phenotype data available

Order

ENSEMBL Links Gene View Location View Compara View

Gene Browser ENU(12)

Elmod1

Belongs to the large class of genes expressed in the brain for which there is no functional information

Phenotype associations for Elmod1

Phenotype Summary based on automated MP annotations supported by experiments on knockout mouse models.

In homozygote:

Both sexes have the following phenotypic abnormalities

- nervous system phenotype. Evidence from IMPC, EuroPhenome (16)
- adipose tissue phenotype. Evidence from IMPC (4)
- integument phenotype. Evidence from EuroPhenome (2)
- immune system phenotype. Evidence from IMPC, EuroPhenome (6)
- hearing/vestibular/ear phenotype. Evidence from IMPC (2)
- behavior/neurological phenotype. Evidence from IMPC, EuroPhenome (69)
- homeostasis/metabolism phenotype. Evidence from IMPC, EuroPhenome (22)
- growth/size/body phenotype. Evidence from IMPC, EuroPhenome (50)
- hematopoietic system phenotype. Evidence from IMPC, EuroPhenome (16)
- Following phenotypic abnormalities occurred in females only
 - skeleton phenotype. Evidence from IMPC (3)



Pre-QC phenotype heatmap



Caution
 This is the results of a preliminary statistical analysis. Data are still in the process of being quality controlled and results may change.

#	Descriptor	Gene symbol	Background strain	Allele	Phenotyping center
1	Elmod1	Elmod1	C57BL/6NTac	Elmod1 ^{tm1b(EUCOMM)Hmgu}	MRC Harwell

Elmod1
Overview

? Help
 Procedural
Ontological

■ Significant
 Insignificant
 No data
 Show gradient
p-value threshold:

0
1
↻

	Mouse anatomical entity	Pigmentation	Nervous system	Renal / urinary system	Limbs / digits / tail
Elmod1		1	0.0000017384	0.039729	3.9759e-8
	Adipose tissue	Homeostasis / metabolism	Hearing / vestibular / ear	Growth / size	Craniofacial
Elmod1	5.5511e-16	1.5464e-7	4.0034e-34	9.4939e-9	1.0000
	Cardiovascular system	Behavior / neurological	Immune system	Respiratory system	Reproductive system
Elmod1	0.000079829	0.0000	0.16766	0.10489	1
	Skeleton	Vision / eye	Other	Hematopoietic system	Mortality / aging
Elmod1	7.4044e-8	0.0020249	0.66540	6.1029e-8	1
	Integument				
Elmod1	1				

Home » Search » Genes » Elmod1

Gene: Elmod1

Name ELMO/CED-12 domain containing 1
MGI Id [MGI:3583900](#)

[Register interest](#)

Status [ES Cells](#) [Mice tm1b](#) [Mice tm1a](#) [phenotype data available](#)

[Order](#)

ENSEMBL Links [Gene View](#) [Location View](#) [Compara View](#)

[Gene Browser](#) [ENU\(12\)](#)

Phenotype associations for Elmod1



Phenotype Summary based on automated MP annotations supported by experiments on knockout mouse models.

In homozygote :

- **Both sexes** have the following phenotypic abnormalities
 - [nervous system phenotype](#). Evidence from IMPC, EuroPhenome (16)
 - [adipose tissue phenotype](#). Evidence from IMPC (4)
 - [integument phenotype](#). Evidence from EuroPhenome (2)
 - [immune system phenotype](#). Evidence from IMPC, EuroPhenome (6)
 - [hearing/vestibular/ear phenotype](#). Evidence from IMPC (2)
 - [behavior/neurological phenotype](#). Evidence from IMPC, EuroPhenome (69)
 - [homeostasis/metabolism phenotype](#). Evidence from IMPC, EuroPhenome (22)
 - [growth/size/body phenotype](#). Evidence from IMPC, EuroPhenome (50)
 - [hematopoietic system phenotype](#). Evidence from IMPC, EuroPhenome (16)
- Following phenotypic abnormalities occurred in **females** only
 - [skeleton phenotype](#). Evidence from IMPC (3)



Gene Page



Phenotype: abnormal glucose homeostasis

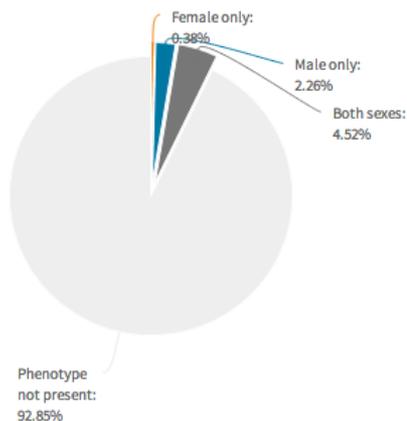
Definition	anomaly in the processes involved in the maintenance of an internal equilibrium of glucose in the fluids and tissues
Synonyms	abnormal glucose metabolism , metabolism: abnormal glucose homeostasis
Procedure	<ul style="list-style-type: none">• Simplified IPGTT (EUMODIC Pipeline 1)
MGI MP browser	MP:0002078

Phenotype associations stats

7.15% of tested genes with null mutations on a B6N genetic background have a phenotype association to abnormal glucose homeostasis (57/797)

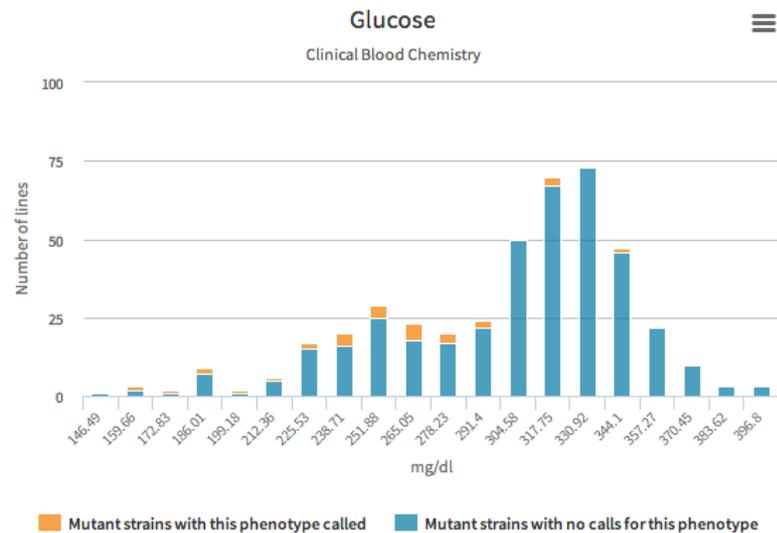
4.89% females (39/797)

6.78% males (54/796)



Select a parameter

Glucose (IMPC_CBC_018_001)



Center Sex

Gene variants with abnormal glucose homeostasis



► Phenotype: All

► Gene: All

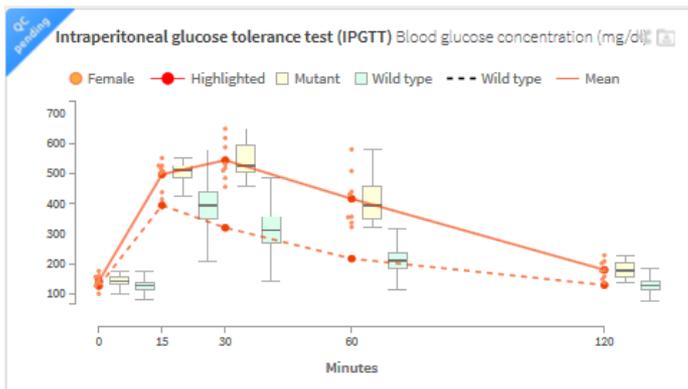
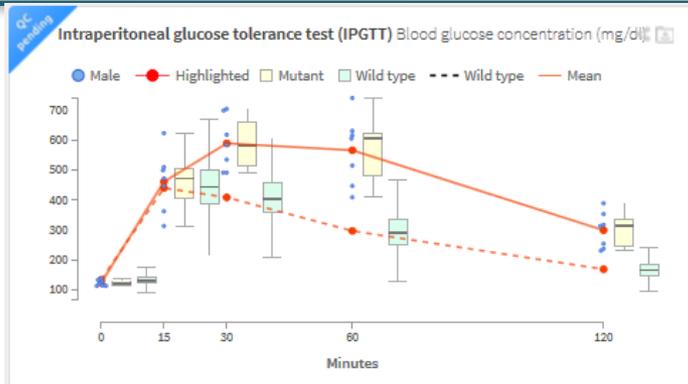
► Procedure: All

► Source: All

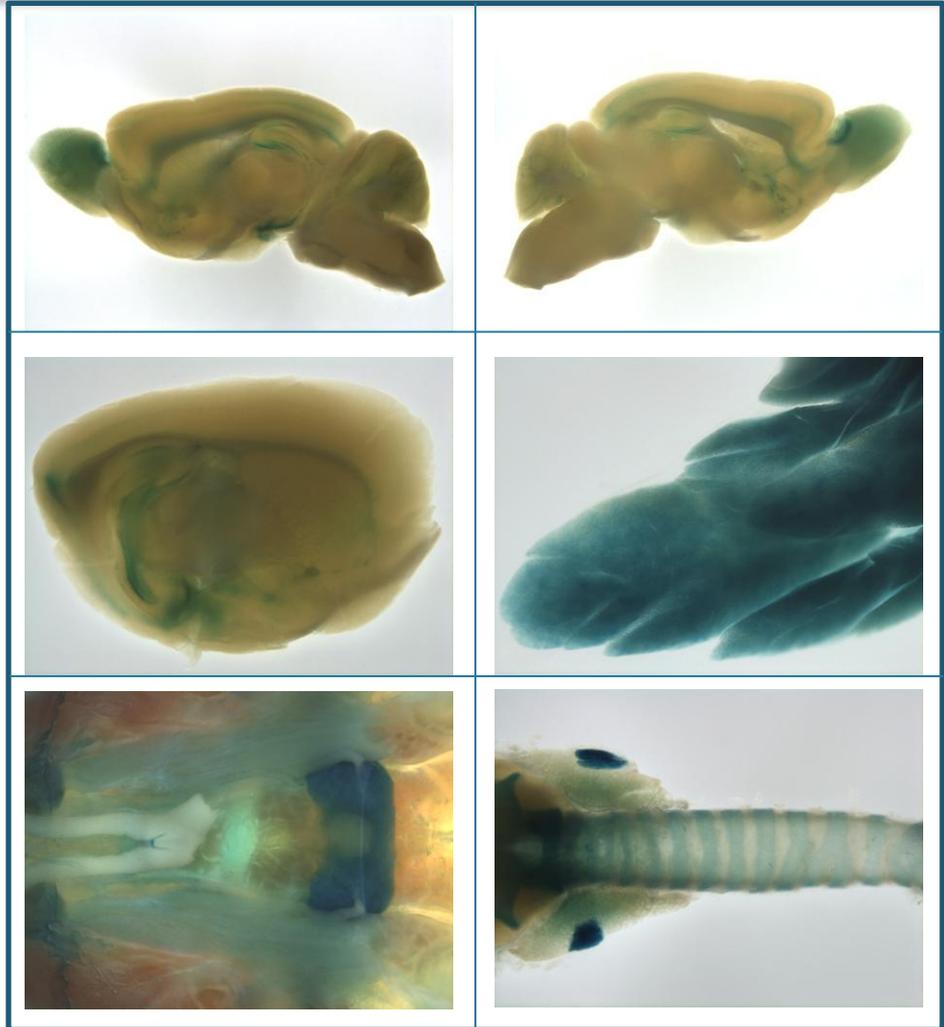
Total number of results: 132

Gene / Allele	Zygoty	Sex	Phenotype	Procedure Parameter	Phenotyping Center	Source	P Value	Graph
Agl Agl ^{tm1b(EUCOMM)Wtsi}	homozygote	♀ ♂	decreased circulating glucose level	Clinical Blood Chemistry Glucose	MRC Harwell	IMPC	0.0	
Gtpbp2 Gtpbp2 ^{tm1b(KOMP)Mbp}	homozygote	♀ ♂	increased circulating glucose level	Clinical Blood Chemistry Glucose	TCP	IMPC	3.44E-15	
Gys2 Gys2 ^{tm1a(KOMP)Wtsi}	homozygote	♀ ♂	decreased circulating glucose level	Fasted Clinical Chemistry Glucose	WTSI	EuroPhenome	1.04E-14	
Gys2 Gys2 ^{tm1a(KOMP)Wtsi}	homozygote	♀ ♂	decreased circulating glucose level	Clinical Chemistry Glucose	WTSI	EuroPhenome	1.23E-14	
Macrod2 Macrod2 ^{tm1.1(KOMP)Vcgl}	homozygote	♀ ♂	decreased circulating glucose level	Clinical Blood Chemistry Glucose	JAX	IMPC	1.99E-13	
Cbx6 Cbx6 ^{tm1a(EUCOMM)Wtsi}	homozygote	♀ ♂	decreased circulating glucose level	Clinical Blood Chemistry Glucose	WTSI	IMPC	1.65E-12	
Ghrhr Ghrhr ^{tm1.1(KOMP)Vcgl}	homozygote	♀ ♂	decreased circulating glucose level	Plasma Chemistry Glucose	JAX	IMPC	9.13E-12	

Nbr1^{tm1b/tm1b} Neighbour of Brca1 gene 1

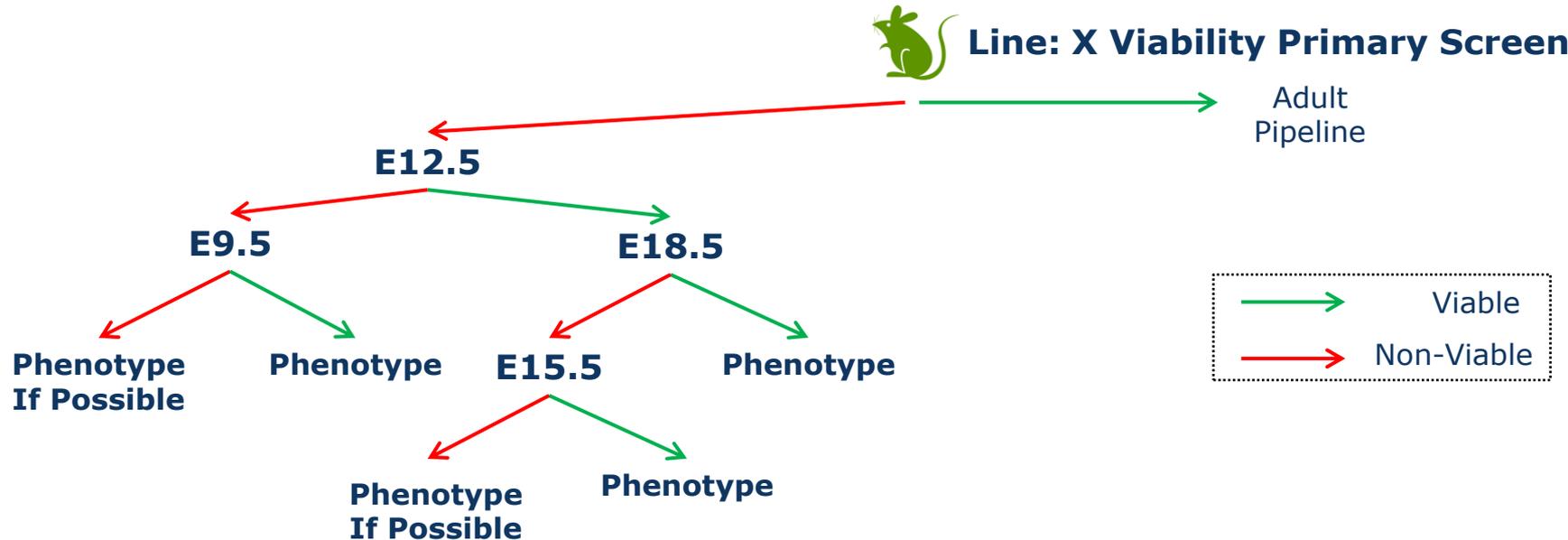


Decreased ability to clear glucose (males and females). Expression seen in a broad range of organs, including brain, pancreas, pituitary, thyroid and parathyroid glands



IMPC – Embryonic Lethal Triage Pipeline

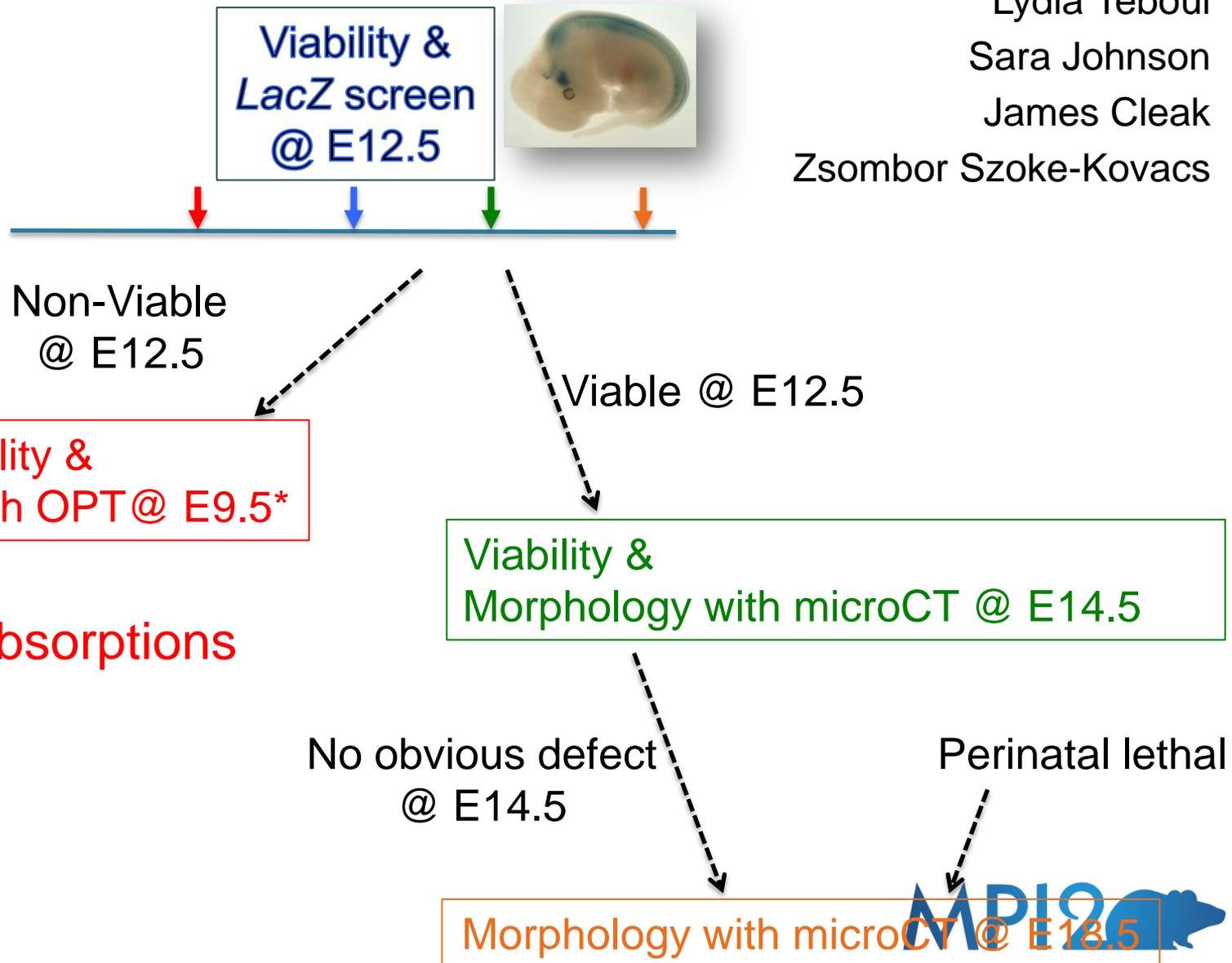
Number of Lines : ~30% to go through the Embryo Pipeline



Harwell: Triaging strategy for viability and morphology screen of embryonic lethal lines

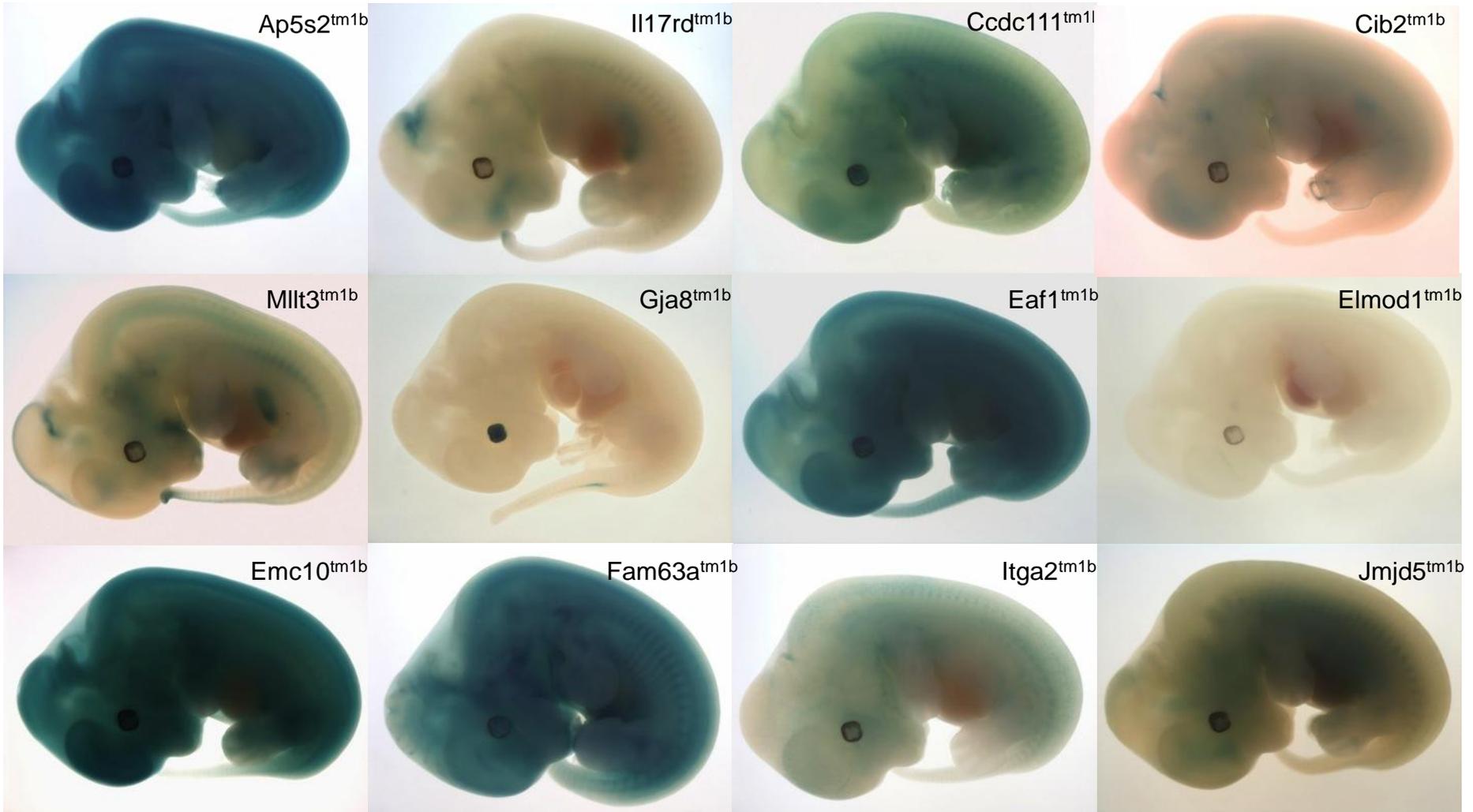
Lydia Teboul
Sara Johnson
James Cleak

Zsombor Szoke-Kovacs



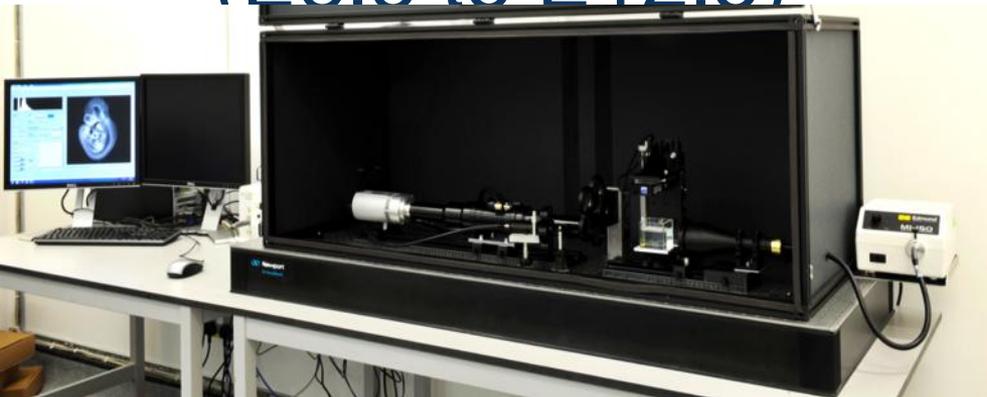
Analysis of expression patterns at E12.5

Over 130 lines characterised so far



Two imaging platforms

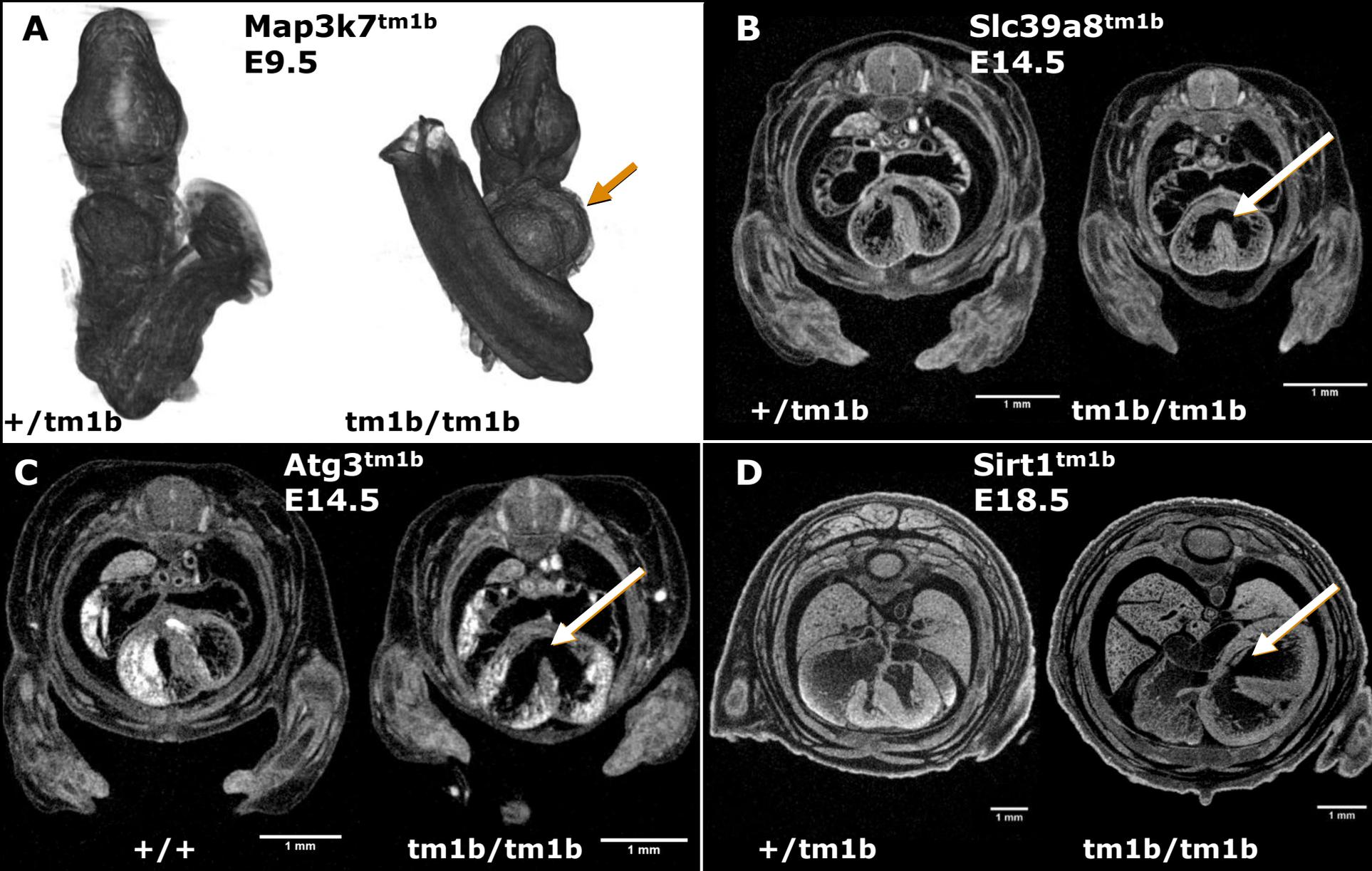
OPT
Optical Projection
Tomography
(E8.5 to E12.5)



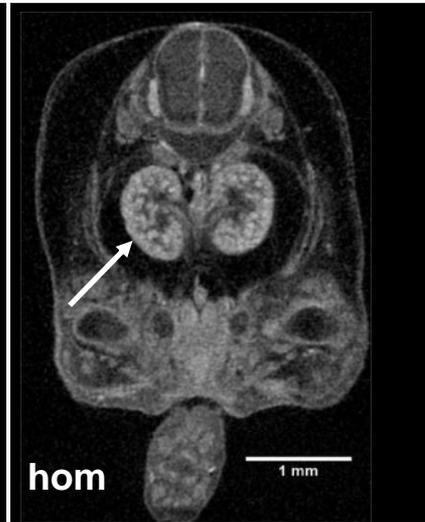
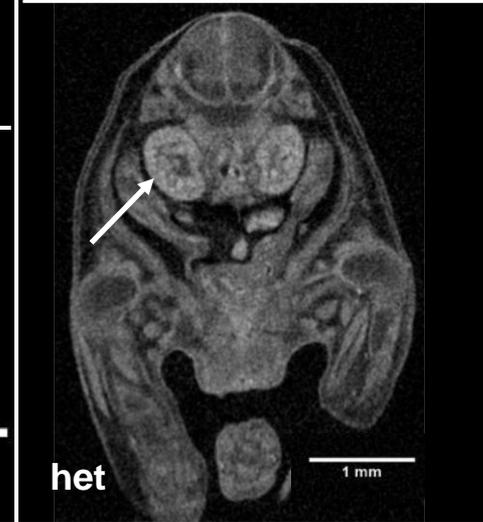
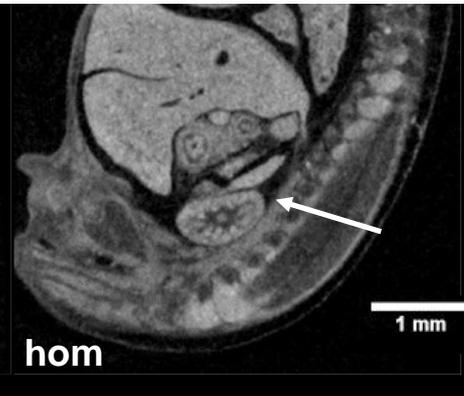
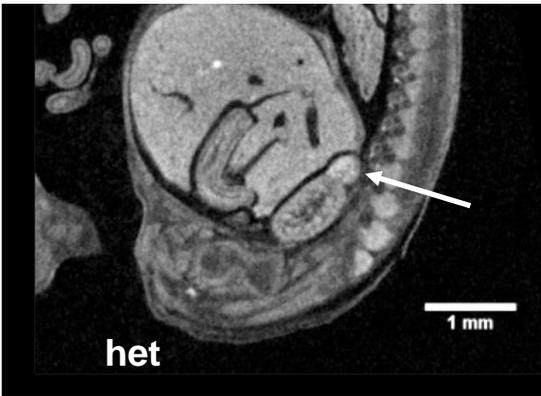
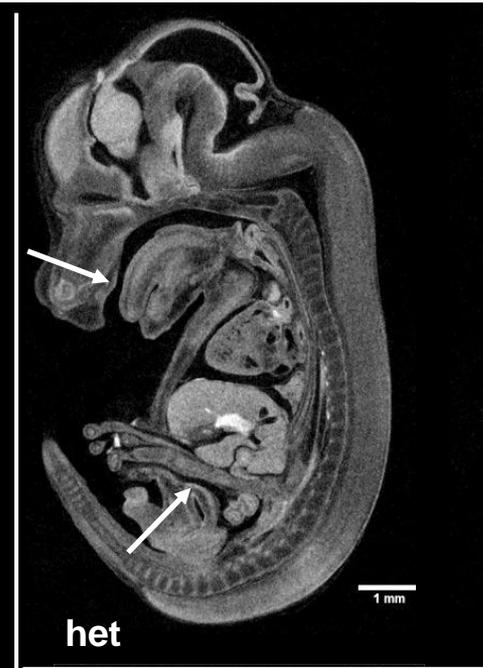
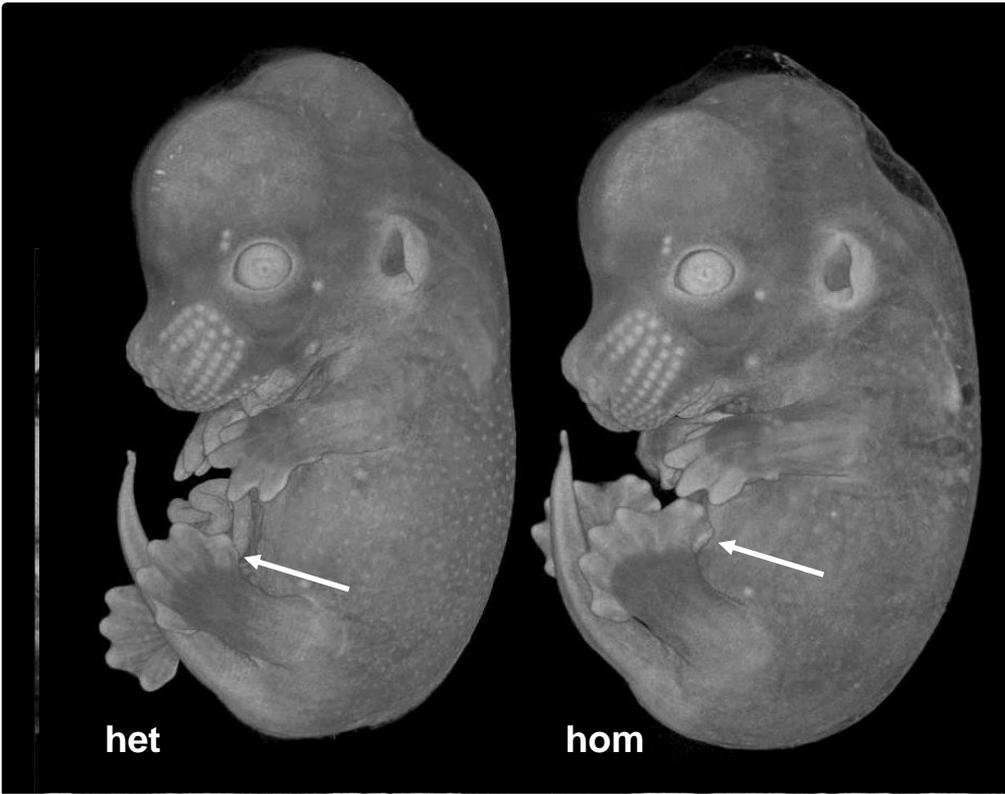
microCT
micro Computed
Tomography
(E12.5 to E18.5)



Examples of new phenotypes: Screen identified 4 mutants lines with abnormal cardiac morphology so far



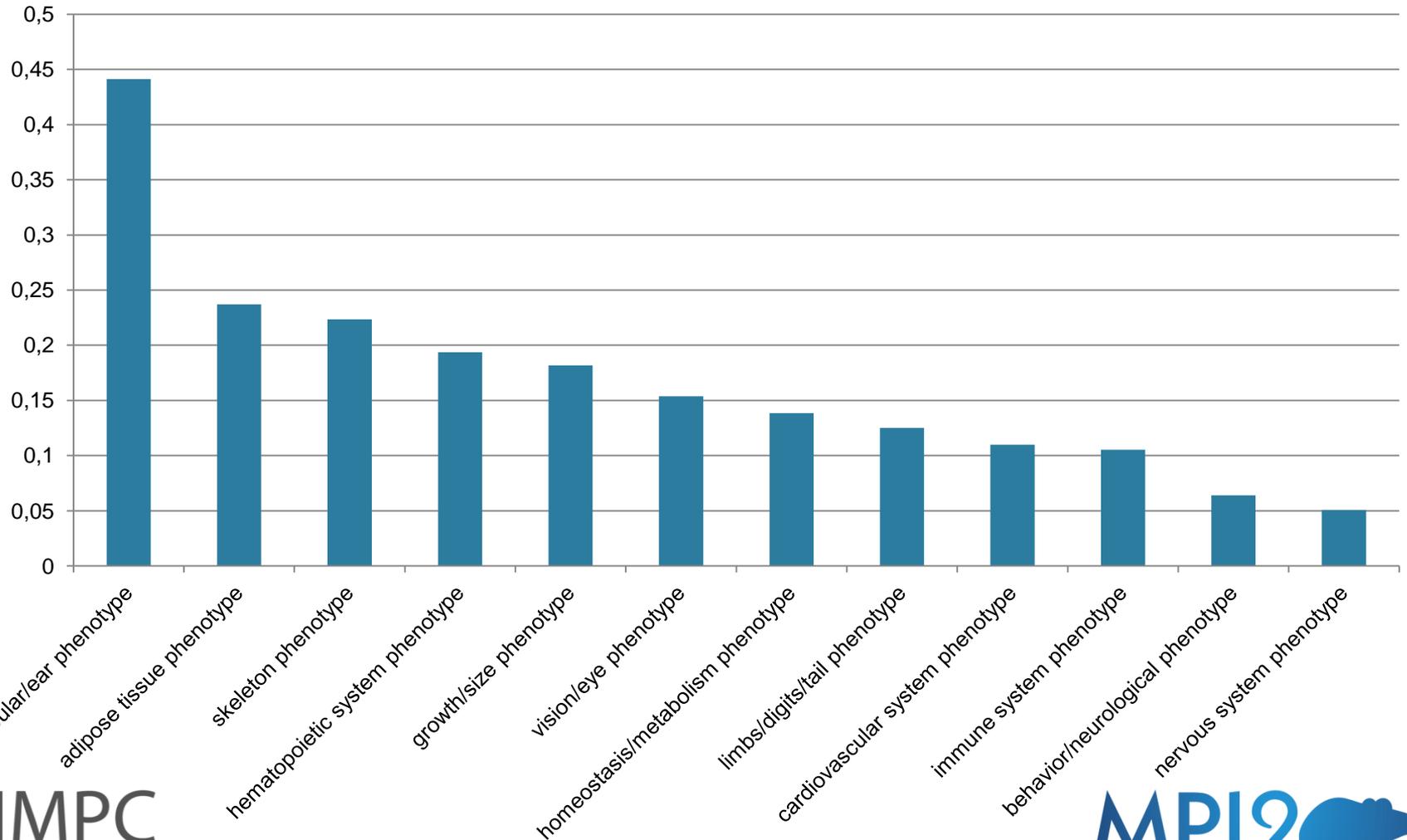
Klhdc2: embryonic lethal with multiple defects



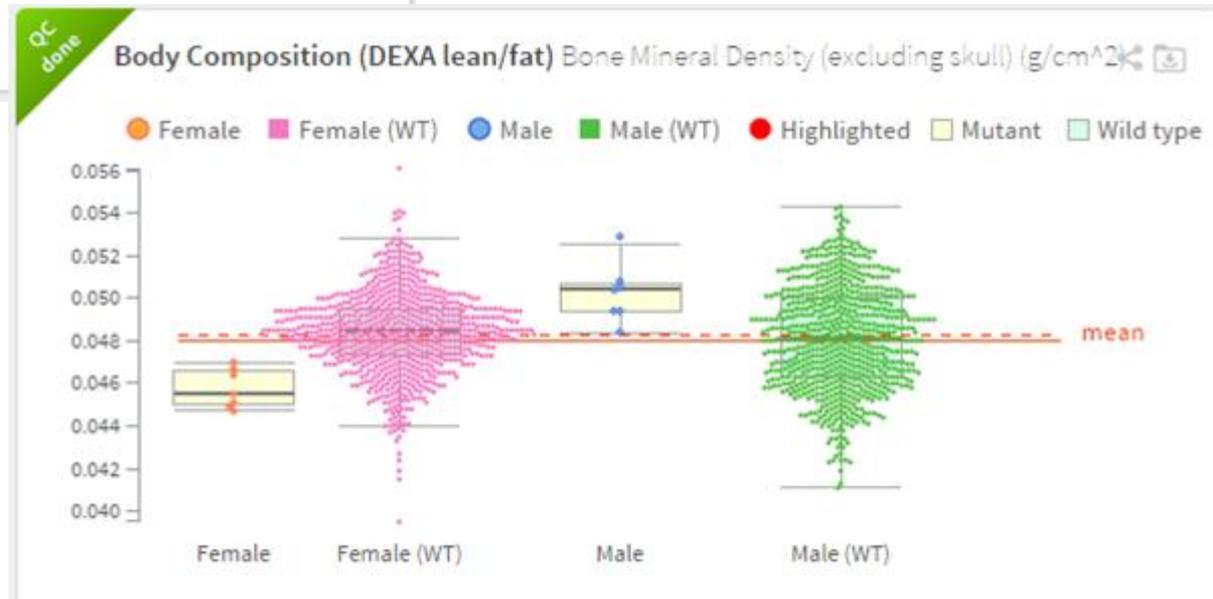
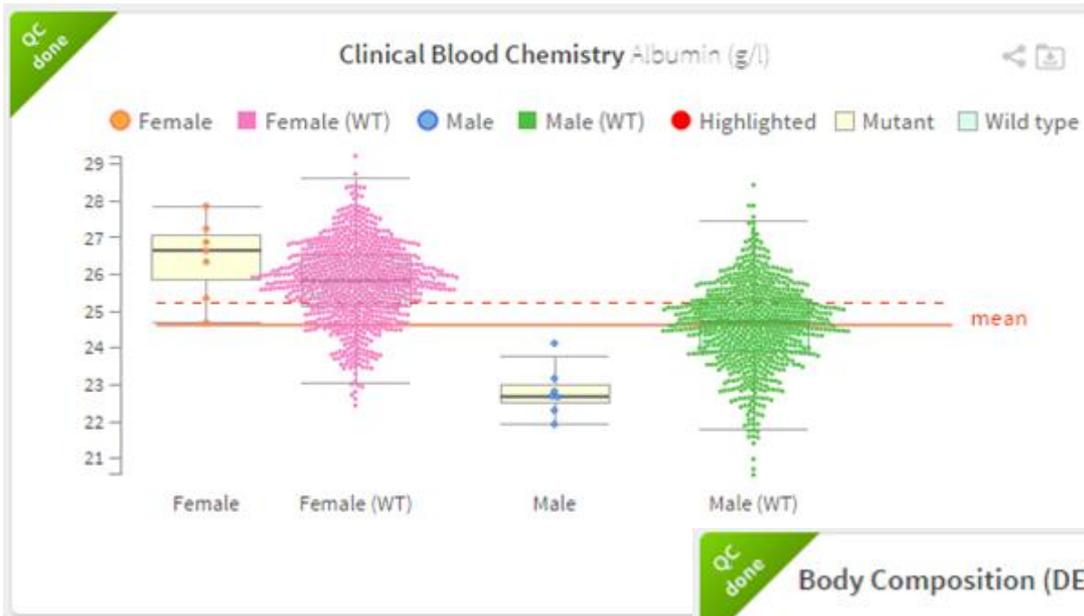
Numerical annotations by sexual dimorphism status, using $p < 0.0001$

Class	Number	% of Hits
Hits where 2 genders analysed	3378	100.00%
Which were classified a		
Hits equal across sexes	2874	85.08%
Hits with sexual dimorphism	504	14.92%
These could be classified as		
Hits 1 sex only	307	9.09%
Hits sex different magnitude	92	2.72%
Hits sex different direction	99	2.93%
Hits unclassified dimorphism	6	0.18%

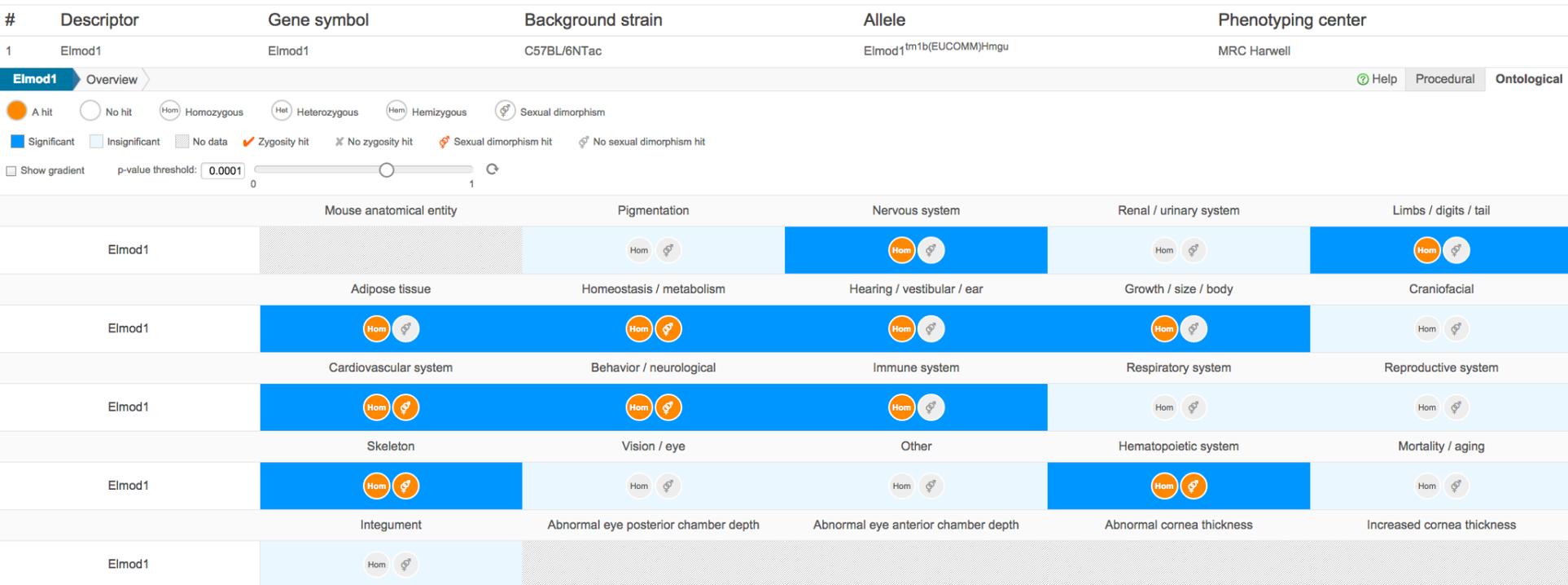
Percentage of hits that are sexually dimorphic by top level term



Zlyvezo2 knockout show opposite direction of bone mineral density change (skeleton phenotype), and males only have significantly increased albumin concentration (homeostasis/metabolism phenotype)



New Gene Heatmap – zygosity and sexual dimorphism illustrated



CONNECT- Disease pages

Disease: Hermansky-Pudlak Syndrome

Name Hermansky-Pudlak Syndrome 7
Synonyms -
Locus 6p22.3
Associated Human Genes [DTNBP1](#)
Mouse Orthologs [Dtnbp1](#)
Source [OMIM:614076](#)

OMIM:614076 Disease Phenotype Terms

- Bruising susceptibility
- Albinism
- Ocular albinism
- Impaired platelet aggregation

Associated Mouse Models (PhenoDigm predicted)

78.96: [Dtnbp1^{sdv}/Dtnbp1^{sdv}](#) involves: DBA/2J (Source: MGI)
 diluted coat color
 abnormal eye pigmentation
 abnormal kidney physiology
 abnormal blood coagulation
 decreased platelet cell number
 abnormal platelet dense granule number
 decreased platelet serotonin level
 abnormal choroid morphology
 abnormal choroid pigmentation
 abnormal retinal pigment epithelium morphology
 abnormal platelet physiology
 decreased platelet aggregation

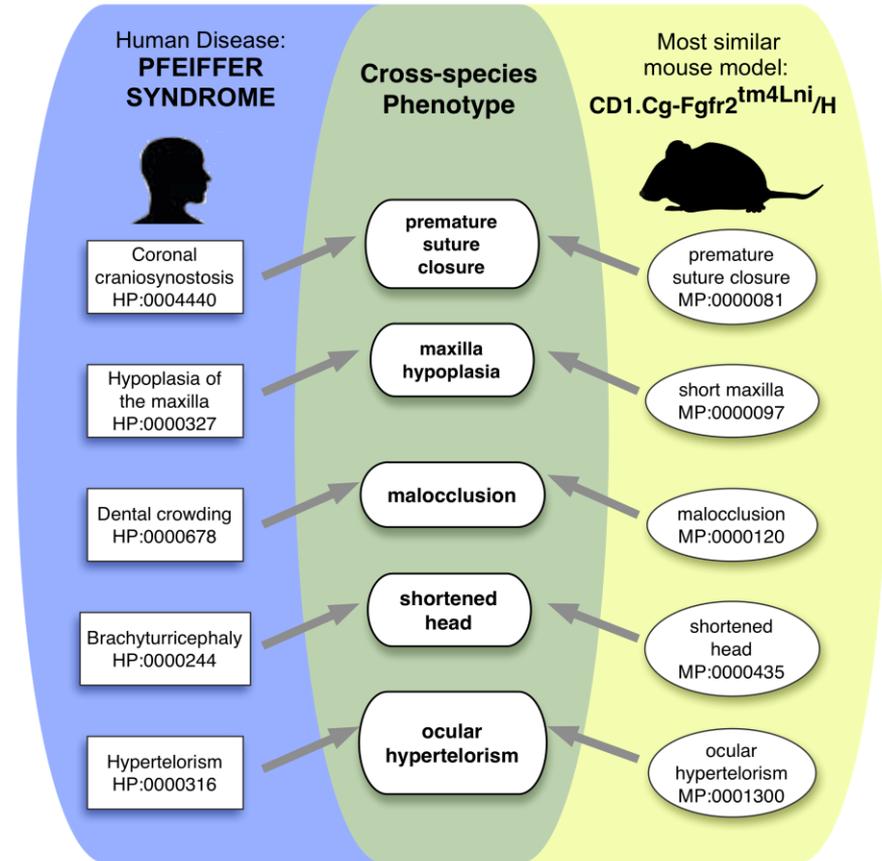
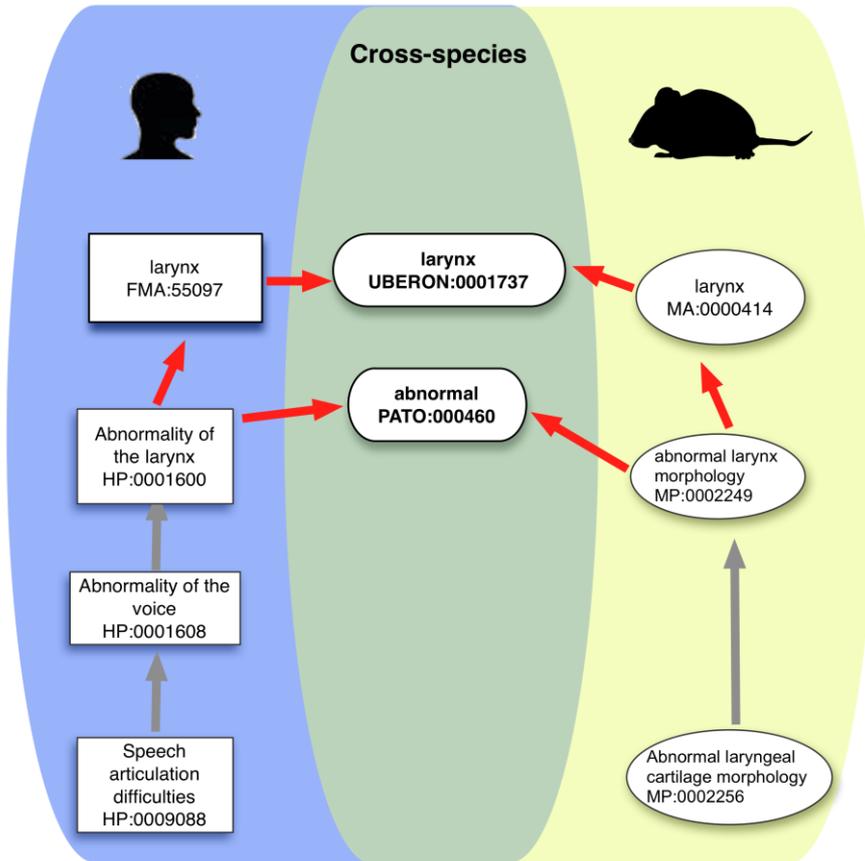
73.61: [Dtnbp1^{sdv}/Dtnbp1^{sdv}](#) DBA/2J-Dtnbp1/J (Source: MGI)
 diluted coat color
 decreased eye pigmentation
 increased bleeding time

66.52: [Dtnbp1^{tm1b\(EUCOMM\)Hmgu}/Dtnbp1^{tm1b\(EUCOMM\)Hmgu}](#) C57BL/6J
 increased circulating calcium level
 increased leukocyte cell number
 increased circulating phosphate level
 abnormal skin morphology
 abnormal coat/hair pigmentation
 abnormal iris pigmentation
 abnormal retinal pigmentation
 increased circulating cholesterol level
 decreased circulating serum albumin level
 increased circulating glucose level
 decreased mean corpuscular hemoglobin concentration

Potential Mouse Models

Mouse Gene Symbol	Disease Gene Ortholog	Syntenic Disease Locus	Mouse Literature Evidence (MGI)	MGI Mouse Phenotype Evidence (Phenodigm)	IMPC Mouse Phenotype Evidence (Phenodigm)	
Dtnbp1	Yes	Yes	Yes	78.96	66.52	+
Hps3				88.9		+
Tyr				87.95		+

PHENODIGM - Cross-species phenotype comparisons by semantic similarity



IMPC and the Rare Disease Community

Number of RDGenes with any phenotype data on portal: 248

Number of RDGenes with a cre-ex (tm1b) mouse or better: 417

Number of RDGenes with a genotype confirmed (tm1a) mouse or better: 877

Number of RDGenes with any mouse production or better: 1151

Number of RDGenes with any intention of mouse production via IMPC: **2185**



Building the first truly comprehensive,
catalogue of a mammalian genome.

se Phenotyping Resource of Standardised Screens.

onal Mouse Phenotype Consortium

The International Mouse Phenotyping Consortium (IMPC) is to
onal insight for every gene by generating and systematically
0,000 knockout mouse strains

Search IMPC database

Enter your favorite **gene**, **phenotype**, or **protocol** to find IMPC data important to your research.

Or browse

[▶ new gene-phenotype associations](#)



Rare Disease Models

Find mouse models of rare diseases with a shared gene or shared phenotype

[▶ Visit Disease Models](#)

IMPreSS

Found 786 diseases

✕ Remove all facet filters



624

0

786

734

50

2

Gene Associations

Data (OMIM, Orphanet) 472

Data (MGI) 168

Gene Associations by

Data 786

Data in linkage locus 24

Data 786

Data in linkage locus 263

Disease	Source	Curated Genes	Candidate by phenotype
Aniridia	OMIM	human mice	IMPC MGI
Aniridia, Microcornea, And Spontaneously Reabsorbed Cataract	OMIM		IMPC MGI
Tooth Agenesis, Selective, 1	OMIM	human mice	IMPC MGI
Anterior Segment Mesenchymal Dysgenesis	OMIM	human mice	IMPC MGI
Antiphospholipid Syndrome, Familial	OMIM		IMPC MGI
Atelosteogenesis, Type I	OMIM	human	IMPC MGI
Atherosclerosis Susceptibility	OMIM		IMPC MGI
Axial Osteomalacia	OMIM		IMPC MGI

Where do we go from here?

- *“Phase 2” (2016-2021)... ‘completing’ the mouse genome*
 - *~12,000 new mutant mouse lines over 5 years*
 - *Less costly per mutant than Phase 1*
- *Significant, fully-validated resource for research community...*
 - *reagents, tools, SOP’s, data, information, expertise*
 - *highly quality controlled (e.g., gender balance) processes*
 - *ensures reliability and reproducibility throughout*
 - *foundation of infrastructure, capacity, and capability*
- *Metabolomics profiling of select KOMP2 lines by KOMP2-BaSH*
- *Adopt CRISPR/Cas9 genome editing technology*
- *New, data-rich, intense phenotyping platforms*

Launchpads

- **Technology development**
Zi media, Permeable Cre, "Prefect Host" blastocyst

- **Leveraging NIH programs**

[Phenotyping Embryonic Lethal Knockout Mice \(R01\)](#)
(PAR-13-231)

Eunice Kennedy Shriver National Institute of Child Health and Human Development

- **Rare, Undiagnosed Disease Models**

- **Coordinating with other CF Projects**

- **Mouse "Networks" for follow-up phenotyping**

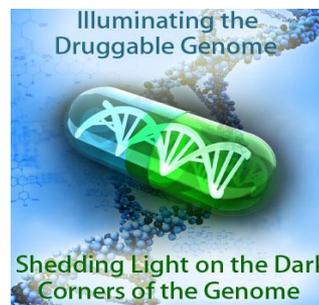
- **"Innovation at the edge"...annotating unannotated genes**

Transgenic Res (2014) 23:177–185
DOI 10.1007/s11248-013-9764-x

TECHNICAL REPORT

Rapid conversion of EUCOMM/KOMP-CSD alleles in mouse embryos using a cell-permeable Cre recombinase

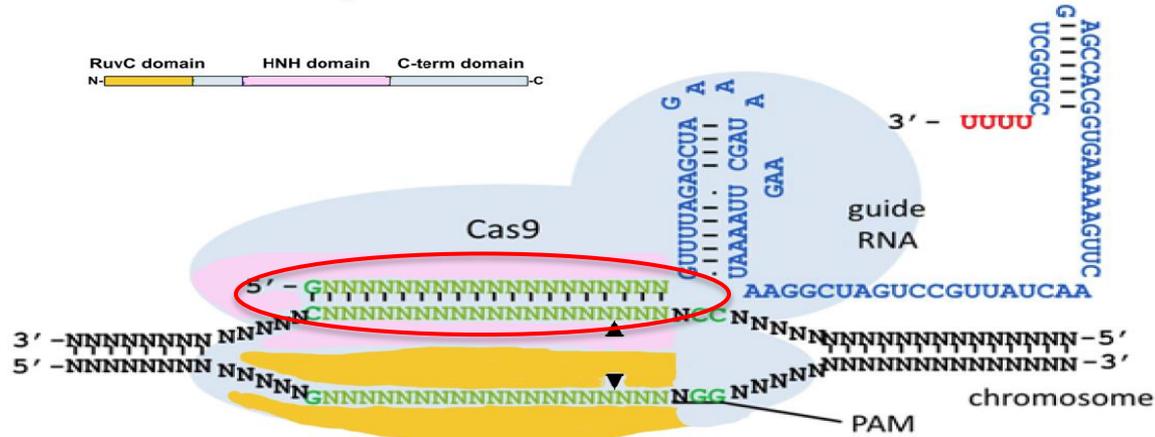
Edward Ryder · Brendan Doe · Diane Gleeson · Richard Houghton · Priya Dalvi · Evelyn Grau · Bishoy Habib · Evelina Miklejewska · Stuart Newman · Debarati Sethi · Caroline Sinclair · Sapna Vyas · Hannah Wardle-Jones · Sanger Mouse Genetics Project · Joanna Bottomley · James Bussell · Antonella Galli · Jennifer Salisbury · Ramiro Ramirez-Solis



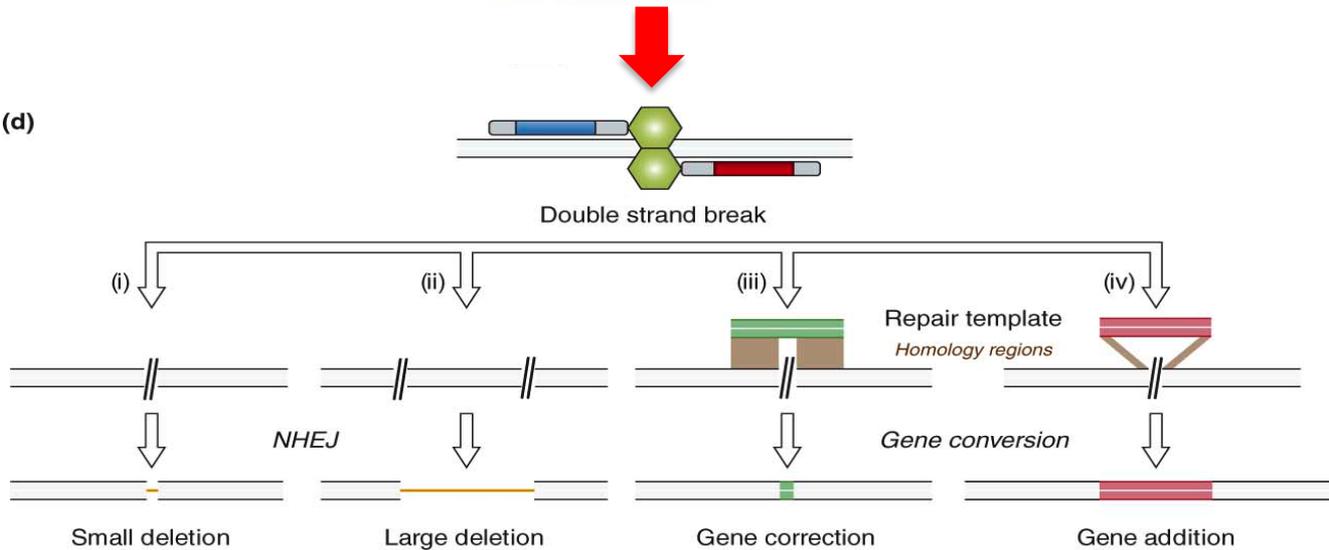
MRC

Consortium	Nominal Genes	Mutant lines made	Assay development	0 site enquiry	Mouse line sent	Outstand
Accelerated Drug Discovery				1		
Disorders of Bone and Cartilage				1		
Cardiovascular Trait Consortium				1	5	
Developmental Disorders				5	5	
Diabetes and Obesity				3	3	
Vision Research Consortium				2		
Tissue Remodelling and Fibrosis						
Haematopoiesis						
Ion Channels				2	1	
Liver Disease Consortium						
Processes of Ageing				1	2	
Neuromouse				5	13	
Kidney and Urogenital System				2		
Respiratory				1	3	
Macrophages				2		
immune system				1	1	
Total for MMN				27	33	
Rest of the community				80	41	

CRISPR Cas9



(d)



Slide courtesy KOMP2-JAX

IMPC Future Developments

□ Future Developments: CRISPR/Cas9

- Pilots underway at IMPC centres to inform future planning
- Pronuclear/cytoplasmic injection; breeding of F0
- Exon deletions; introduction of loxP sites
- **Development of a STANDARDISED, HIGH QUALITY ALLELE**

□ Future Developments: Phenotyping

- A step change in phenotyping for Phase 2
- More data per animal, complex longitudinal data, lower cost
- Use of home cage monitoring, telemetry, biomarkers, imaging approaches, histopathology, ageing

IMPC Conclusions

- ❑ IMPC is set to deliver 5,000 mouse lines and associated phenotype information by 2016
- ❑ Phenotype data from the first 1300 phenotyped lines is available at www.impc.org
- ❑ Plans for Phase 2 of IMPC, to finish the genome, are being developed
- ❑ The Catalogue of Mammalian Gene Function, developed by IMPC, and the associated mouse resources will be truly transformative for biology and biomedical sciences



IMPC

International Mouse Phenotyping Consortium



National Institutes of Health (USA)



Toronto Centre for Phenogenomics (Canada)



Medical Research Council & MRC Harwell (UK)



The Wellcome Trust Sanger Institute (UK)



Wellcome Trust



Helmholtz Zentrum Munich (Germany)



Institute Clinique de la Souris (France)



UC Davis



European Bioinformatics Institute



The Jackson Laboratory



Children's Hospital Oakland Research Institute



Consiglio Nazionale delle Ricerche

Consiglio Nazionale delle Ricerche (Italy)



European Commission (EU)



Infrafrontier (EU)



Australian Phenomics Network (Australia)



RIKEN BioResource Center (Japan)



GenomeCanada

Genome Canada



Model Animal Research Center (Nanjing)



Baylor College of Medicine



Charles River Laboratories



Korean Mouse Phenotyping Centre



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