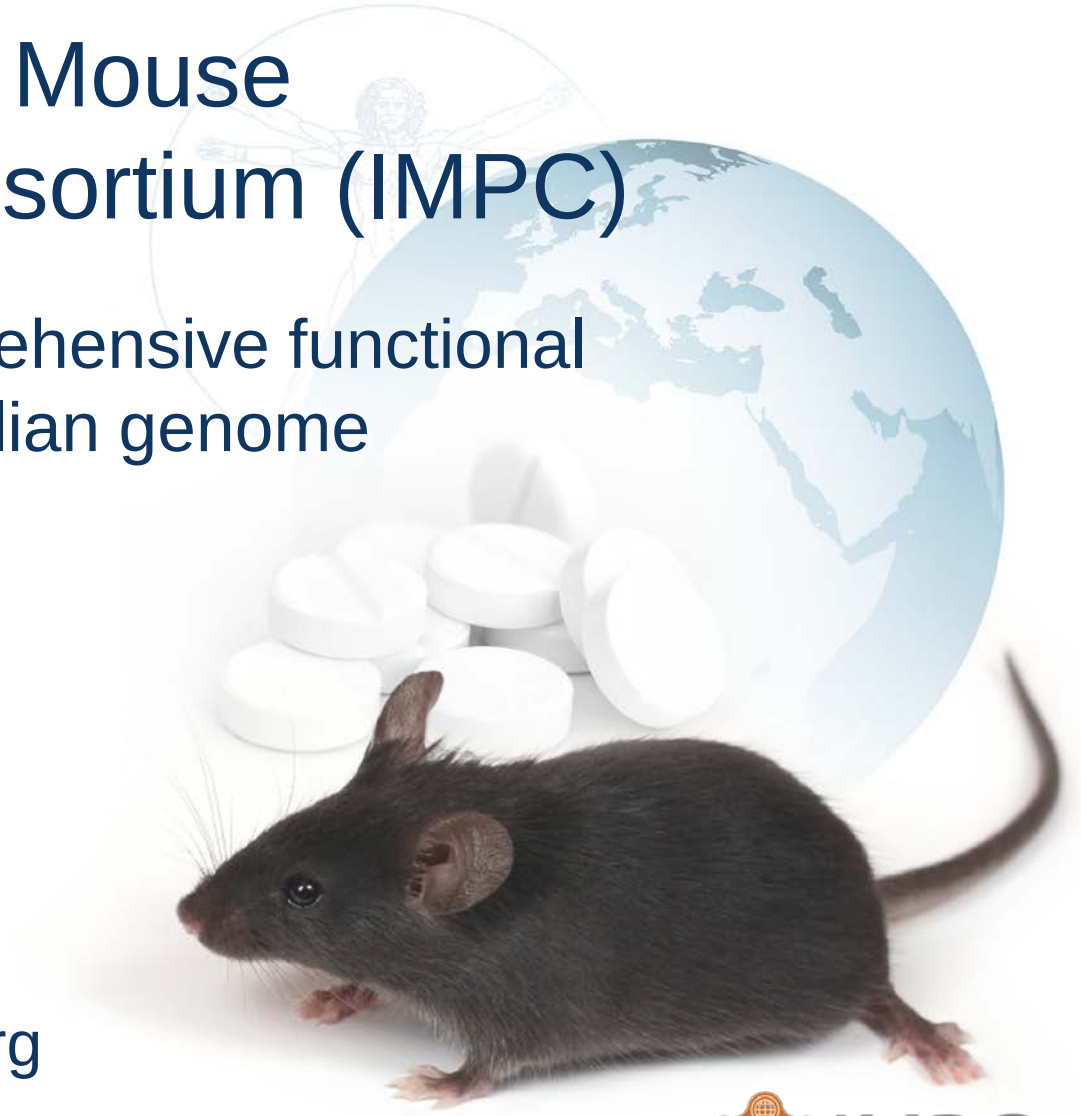
The International Mouse Phenotyping Consortium (IMPC)

Building the first comprehensive functional catalogue of a mammalian genome



www.mousephenotype.org

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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

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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**

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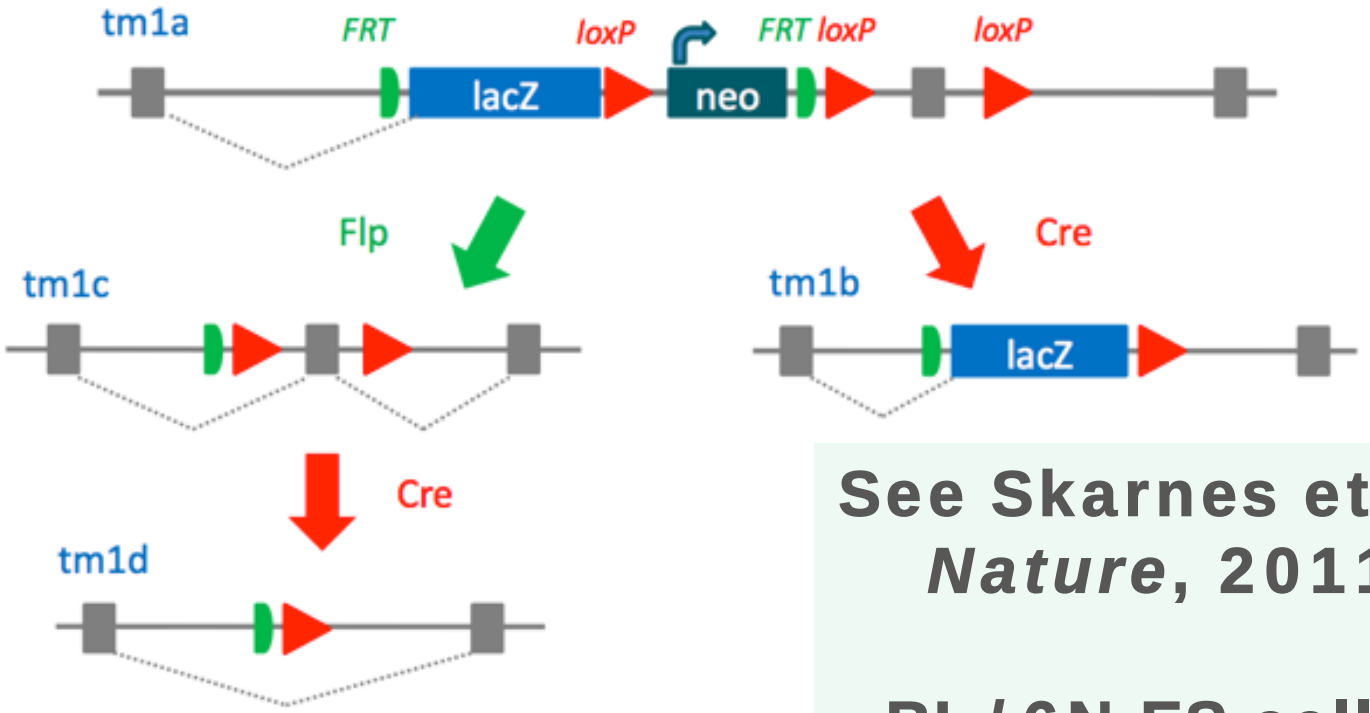
IMPC alleles from IKMC >15,000 KO ES cell lines

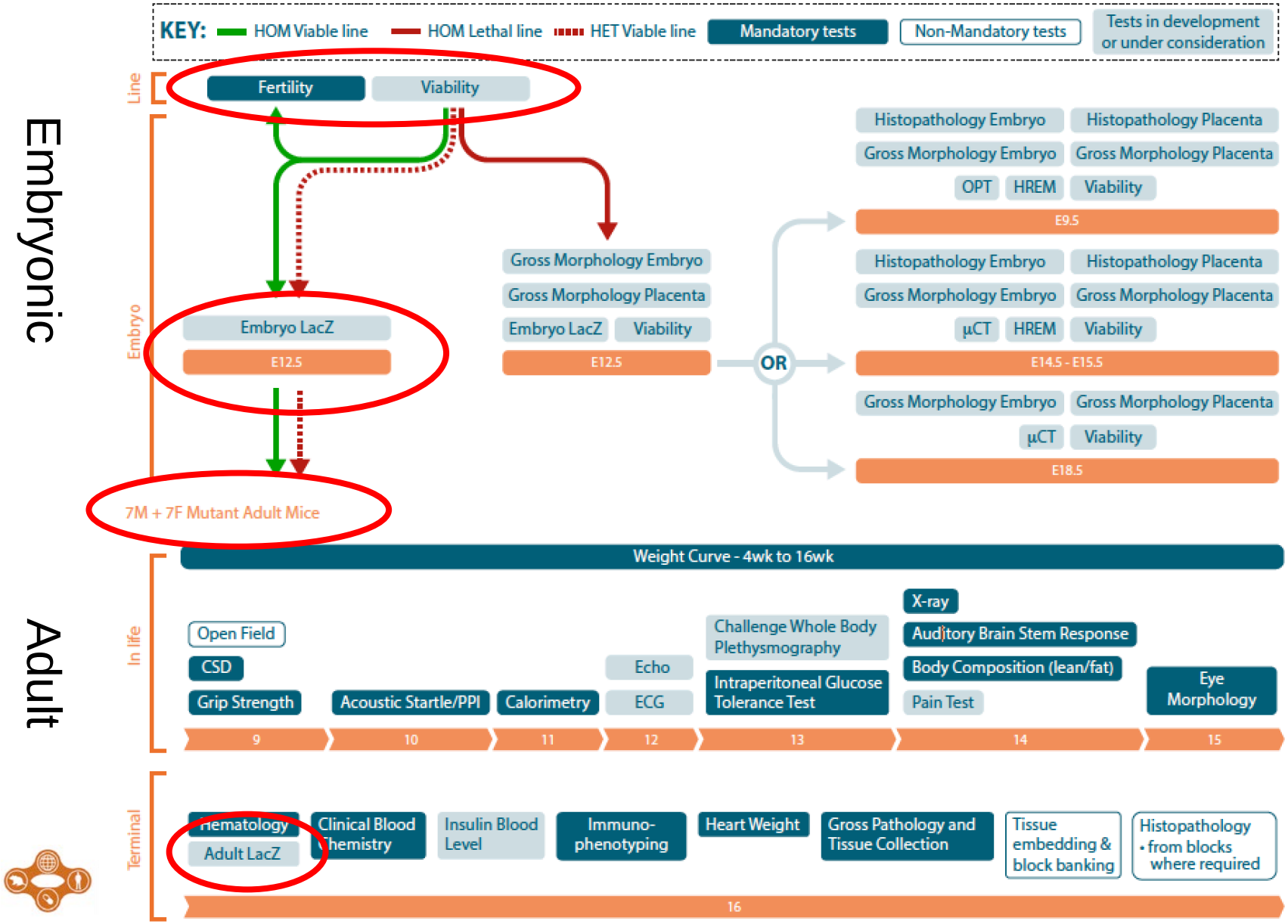
Knockout-first, conditional-ready allele:



See Skarnes et al. *Nature*, 2011

BL/6N ES cells

IMPC phenotyping pipeline



Mandatory tests

Non-mandatory tests

Tests in development or under consideration

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

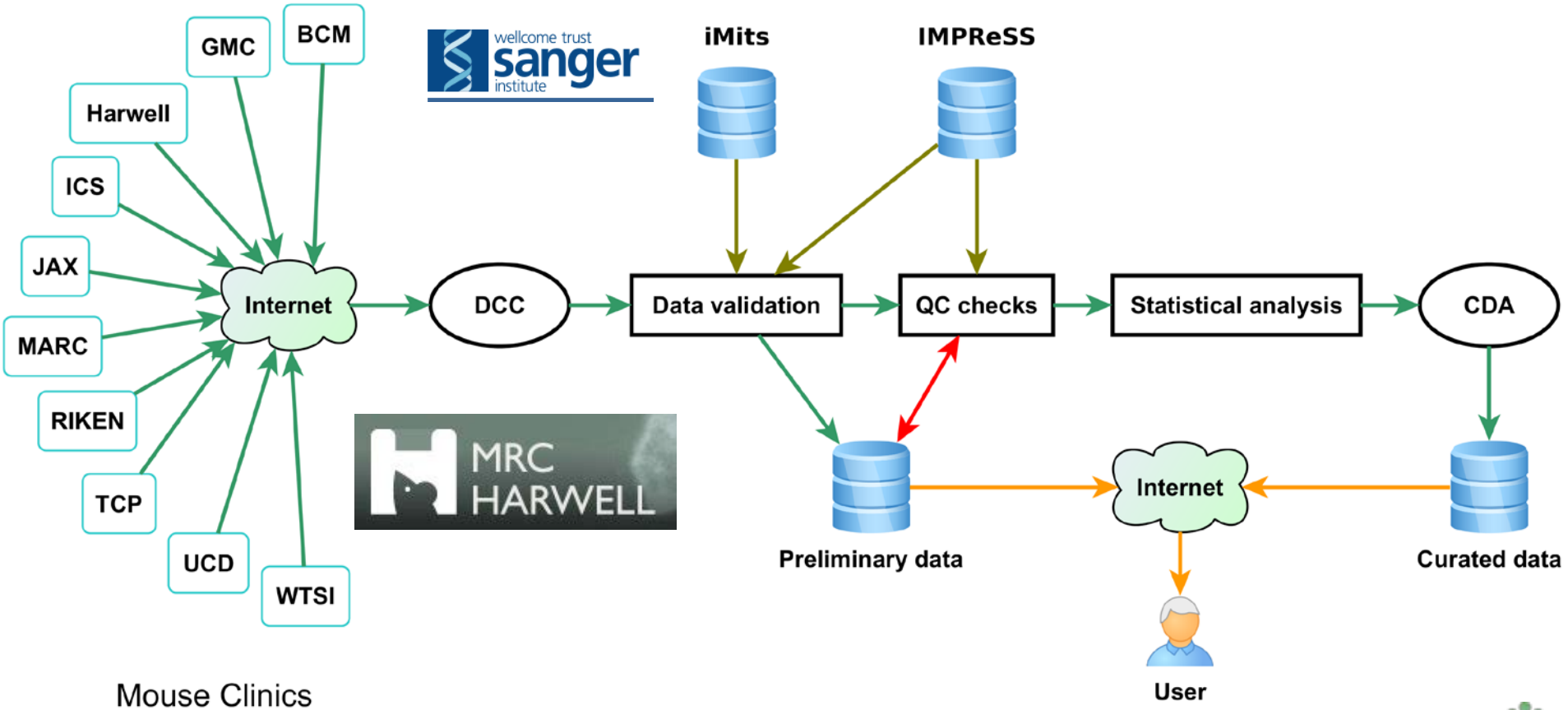
Sensory
- Auditory Brain Stem Response (2+2)
- Slit Lamp
- Opthalmoscope

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 Informatics Team



EMBL-EBI

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IMPC status:

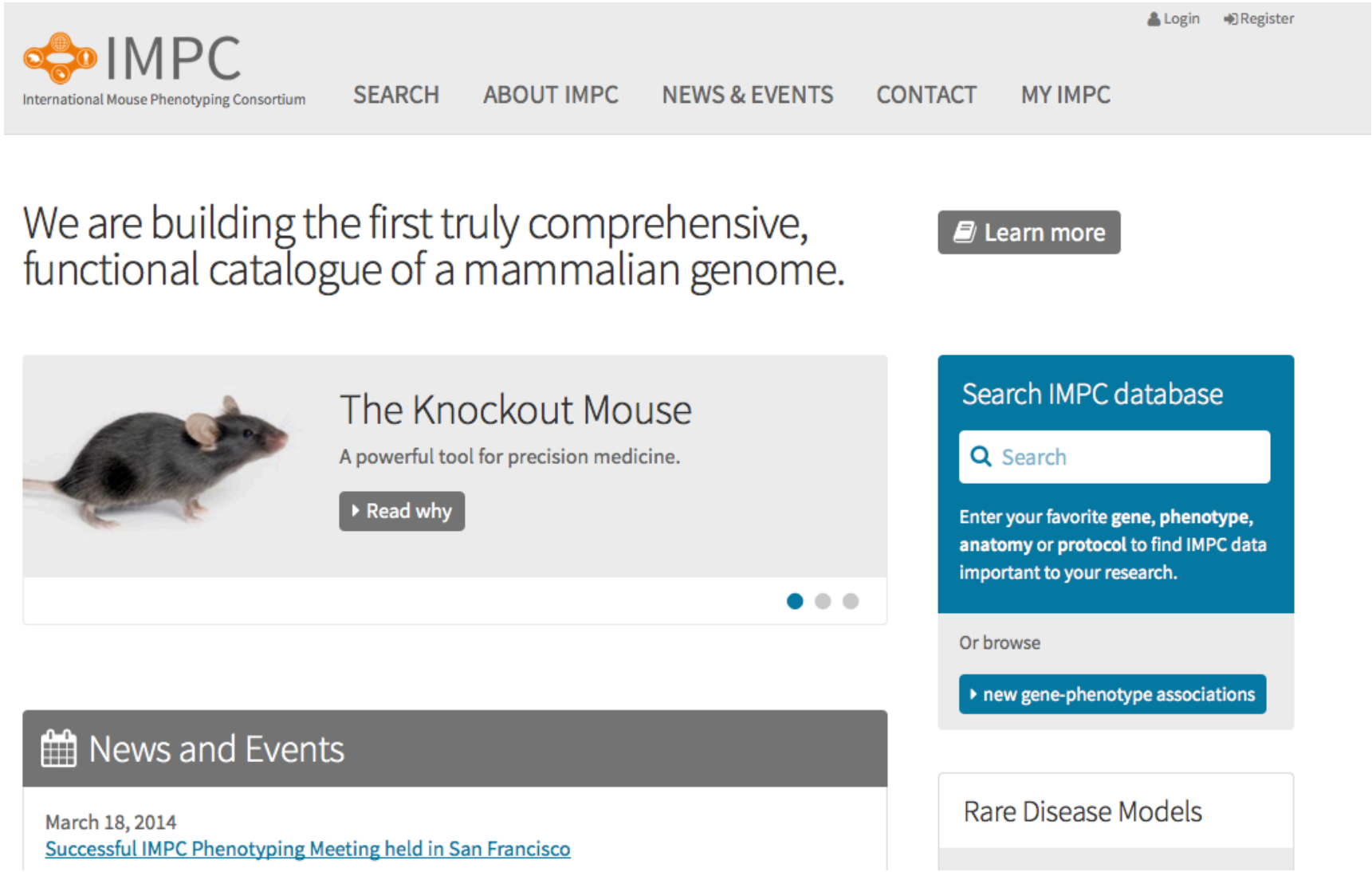
Current iMits (November 2014)

Centre	Total Clones Injected	Genotype Confirmed	Cre excision	Phenotype started (Data in the DCC)
Baylor	790	385	133	62
Harwell	625	260	245	165
HMGU	548	199	130	73
ICS	128	106	76	63
JAX	1062	571	387	236
MARC	84	71	2	15
Monterotondo	37	17	6	0
RIKEN	76	35	24	7
TCP	414	174	79	164
UCD	1786	771	435	212
WTSI	1616	745	159	347
TOTAL	**7166**	**3334**	**1676**	**1344**

Programme Highlights

- 7166 microinjections
- 3334 genotype confirmed lines
- 1676 cre excised lines
- 1344 lines with phenotype information

IMPC portal impc.org mousephenotype.org



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MPI2

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

Gene: Elmod1

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

Status ES Cells | Mice tm1b | Mice tm1a | phenotype data available

Register interest

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 occured in **females** only
  - skeleton phenotype. Evidence from IMPC (3)

Gene Page

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.

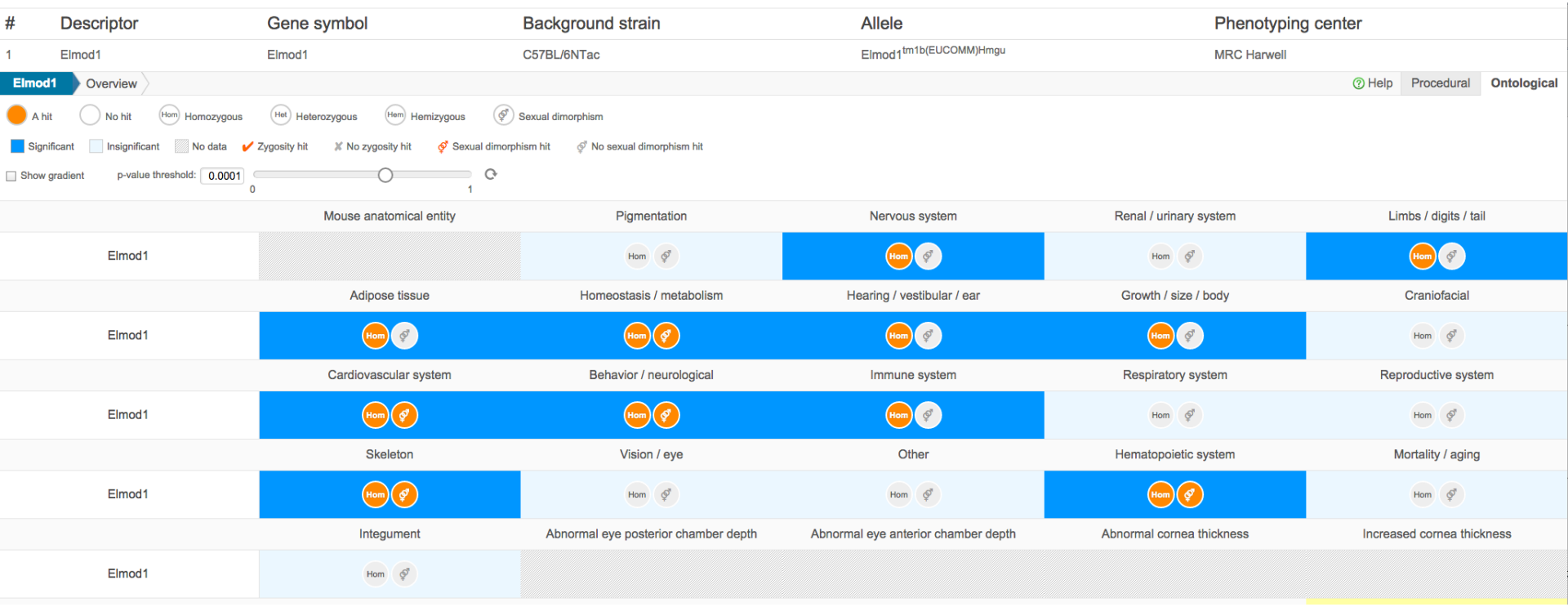
#	Descriptor	Gene symbol	Background strain	Allele	Phenotyping center
1	Elmod1	Elmod1	C57BL/6NTac	Elmod1$^{tm1b(EUCOMM)Hmgu}$	MRC Harwell

Elmod1 | Overview | Help | Procedural | **Ontological**

Significant | Insignificant | No data | Show gradient | p-value threshold: 0.0001 (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				

New Gene Heatmap – zygosity and sexual dimorphism illustrated



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MPI2

Significant annotations in a number of parameters

MPI2

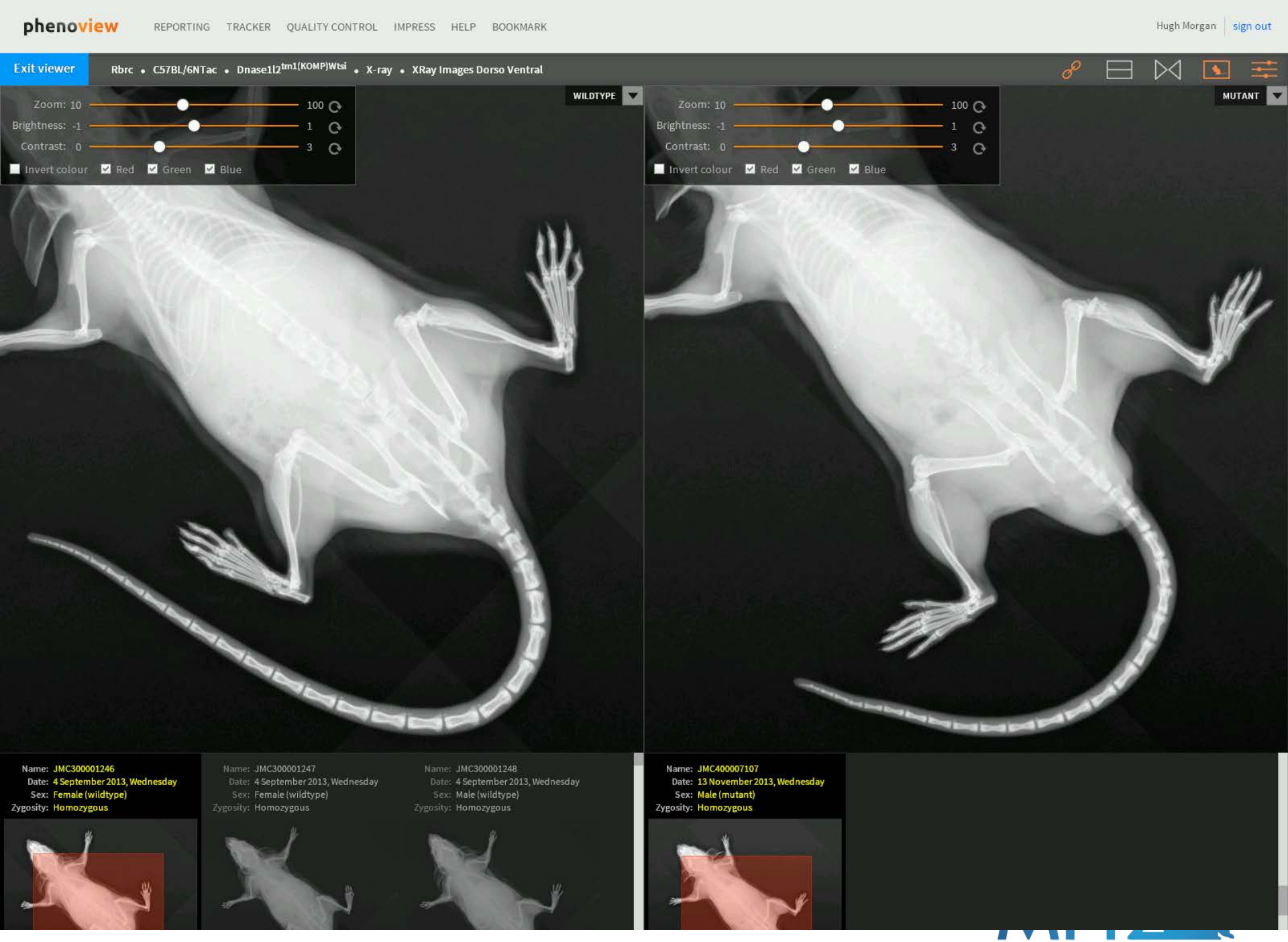
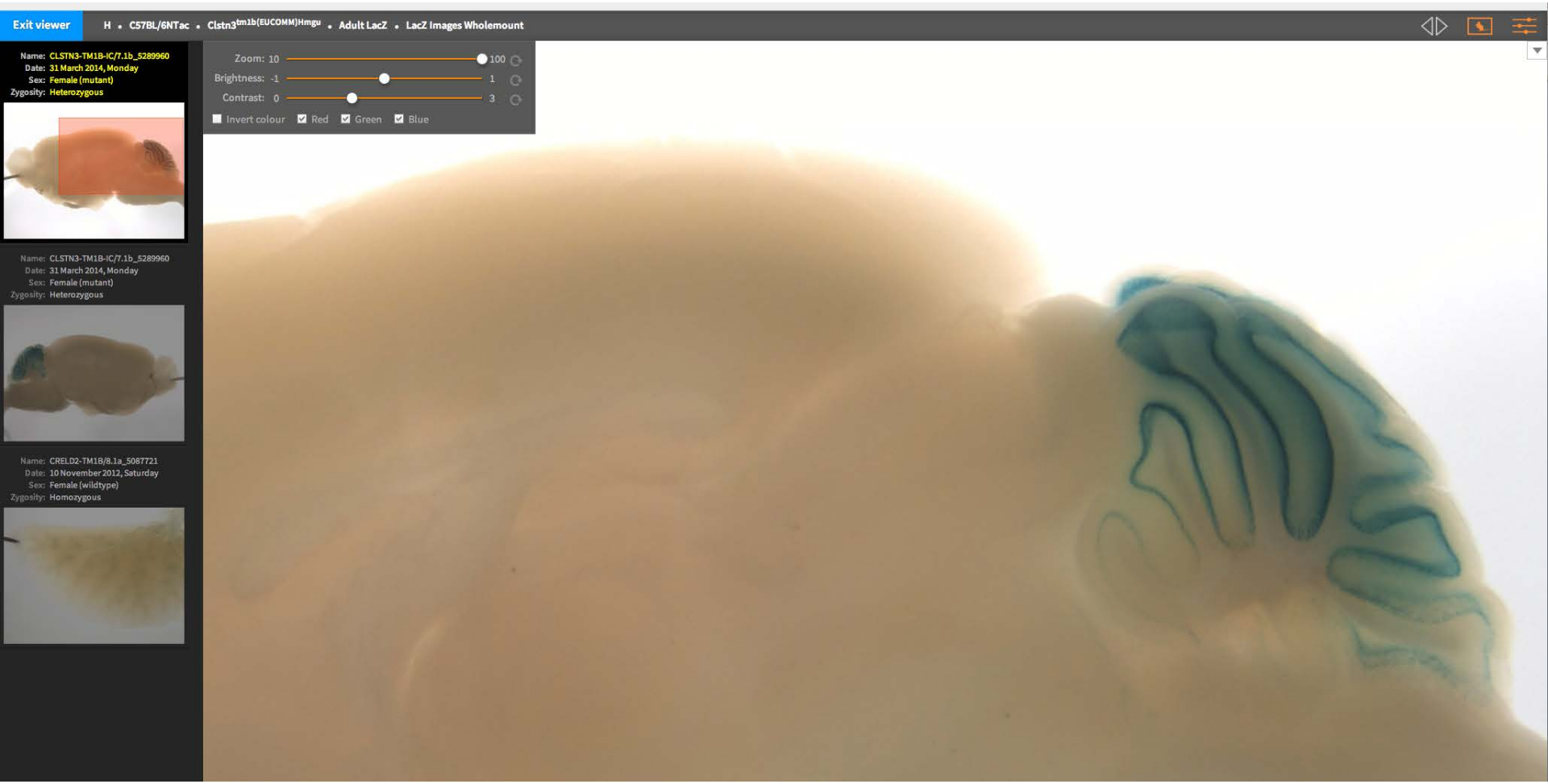

phenoview
REPORTING
TRACKER
QUALITY CONTROL
IMPRESS
HELP
BOOKMARK
Hugh Morgan
sign out
Exit viewer
Rbrc • C57BL/6NTac • Dnase1l2tm1(KOMP)Wtsi • X-ray • XRay Images Dorso Ventral
Zoom: 10 100
Brightness: -1 1
Contrast: 0 3
Invert colour
Red
Green
Blue
WILDTYPE
MUTANT
Name: JMC300001246
Date: 4 September 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

Image Display - LacZ



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Phenotype: abnormal glucose homeostasis

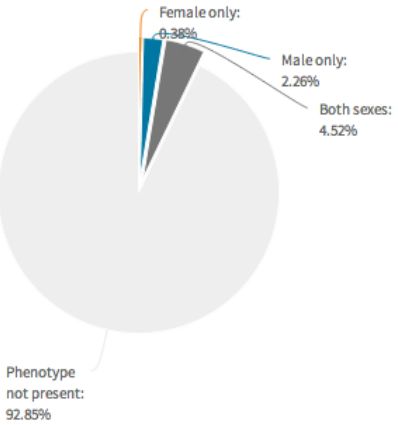
Definition	anomaly in the processes involved in the maintenance of an internal equilibrium of glucose in the fluids and tissues
Synonyms	abnormal glucose metabolism , metabolism: abnormal glucose homeostasis
Procedure	• Simplified IPGTT (EUMODIC Pipeline 1)
MGI MP browser	MP:0002078

Phenotype associations stats

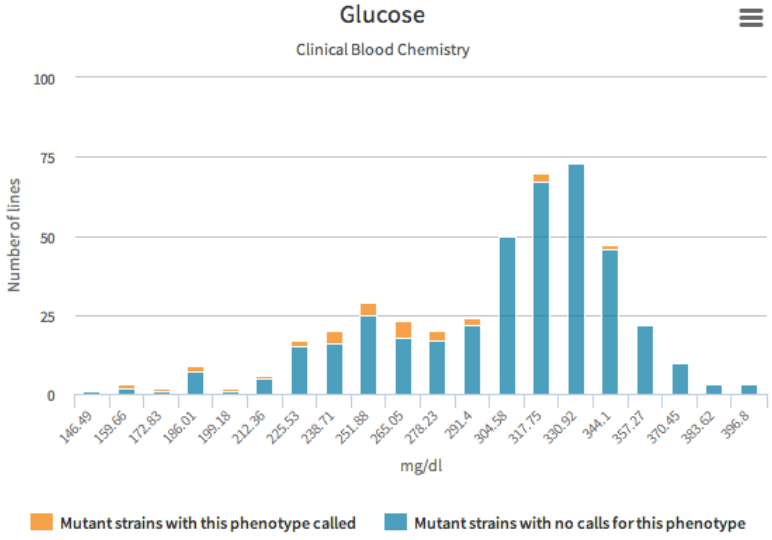
7.15% of tested genes with null mutations on a B6N genetic background have a phenotype association to abnormal glucose homeostasis (57/797)

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	Zygosity	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 $Macrod2^{tm1.1(KOMP)Vlcg}$	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 $Ghrhr^{tm1.1(KOMP)Vlcg}$	homozygote	♀ ♂	decreased circulating glucose level	Plasma Chemistry | Glucose	JAX	IMPC	9.13E-12	

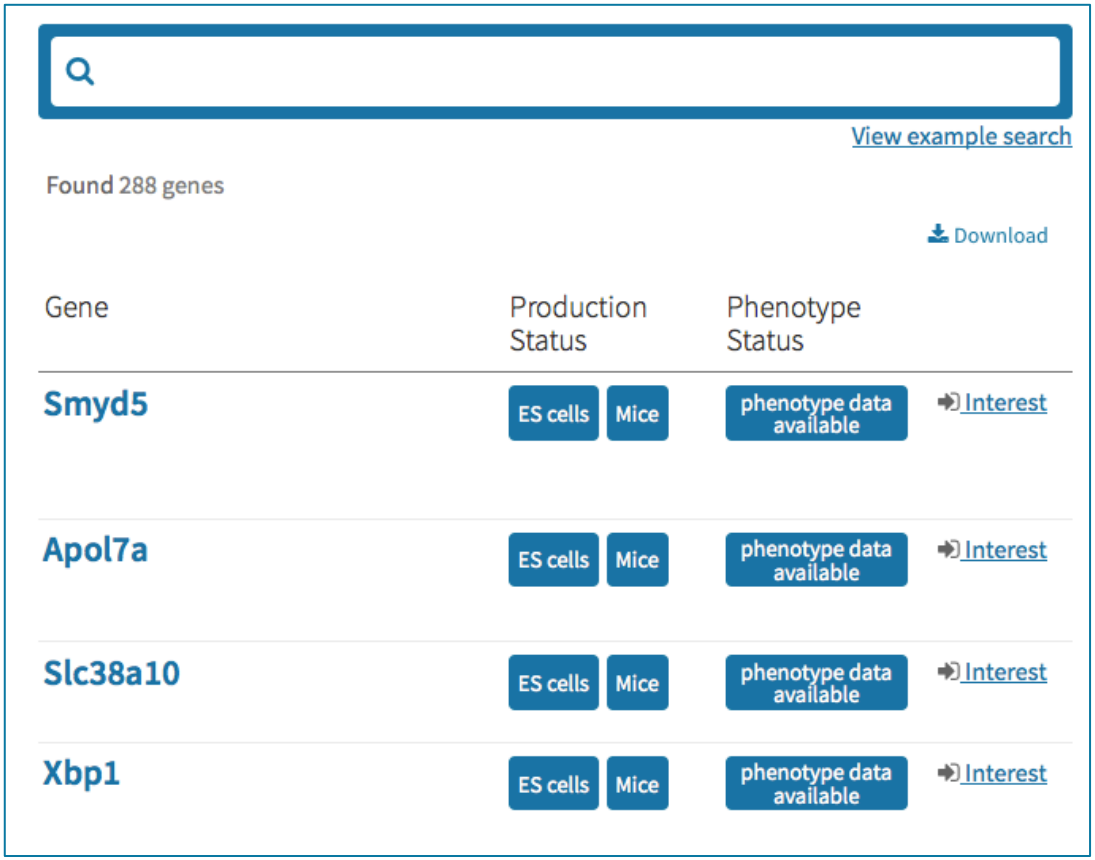
Gene phenotyping heatmap for abnormal glucose homeostasis

	Increased Circulating Glucose Level	Impaired Glucose Tolerance	Decreased Circulating Glucose Level	Improved Glucose Tolerance	Abnormal Glucose Tolerance	Decreased Circulating Insulin Level	Abnormal Circ Insulin Le
1110059G10Rik	0.90964				0.0064484		0.0000652
3110043O21Rik	0.53879	0.31778	0.24020	0.000016238		0.00014654	
4930449E01Rik	0.77286	0.55491					0.0005323
5330417C22Rik	0.00014402	0.51898	0.26106				
A430005L14Rik			0.83237	0.71033			0.0000594
A830019P07Rik		0.66758	0.42774				0.0000492
Abcb11			0.0012501	0.077711		0.00037204	

Follow genes of interest

Follow genes you are interested in

IMPC will send an email when new data is published



- 2300 registrations
- 2867 genes

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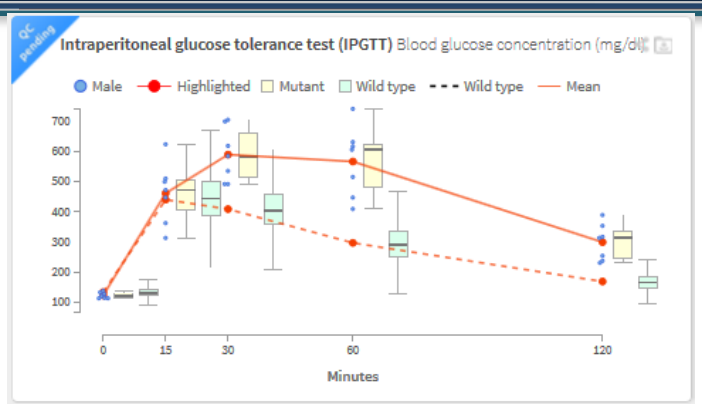
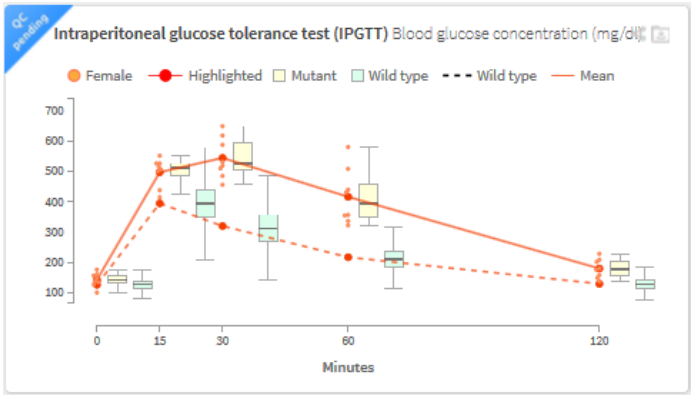
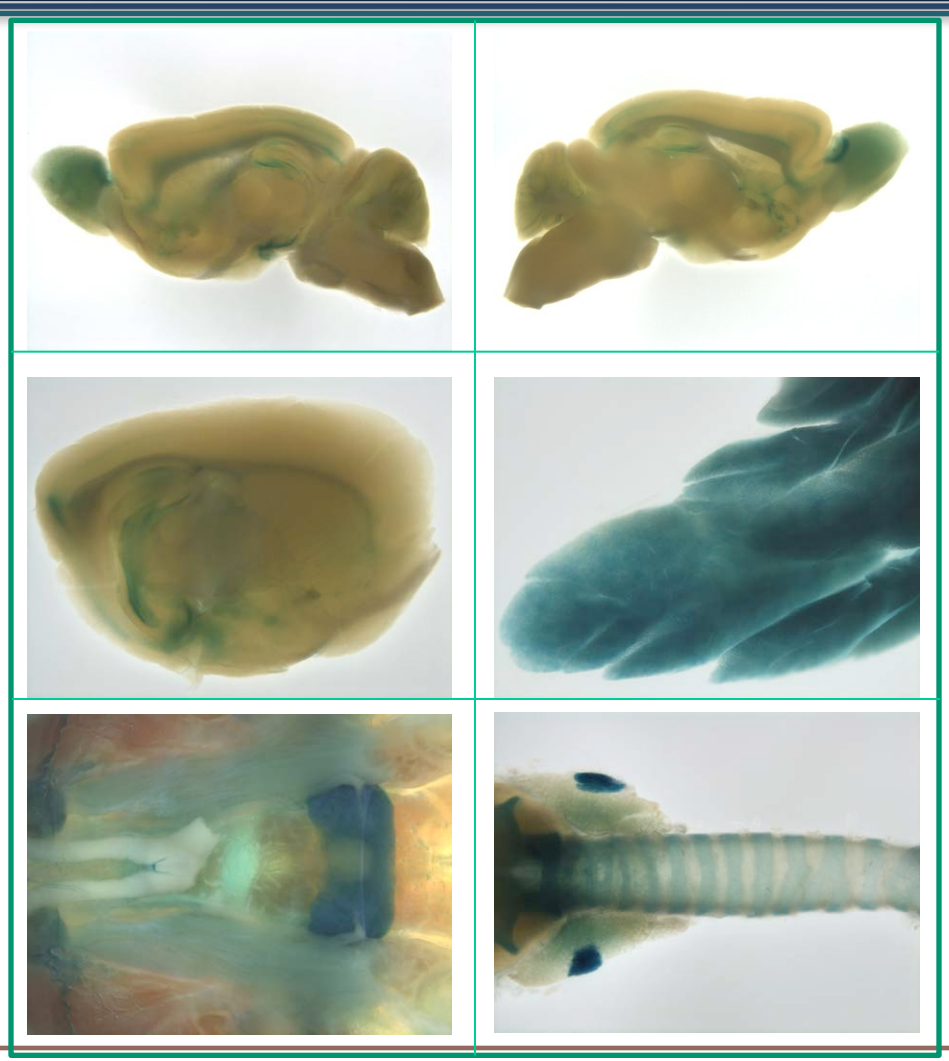
MPI2

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



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The ignorome – annotating genes with no known function

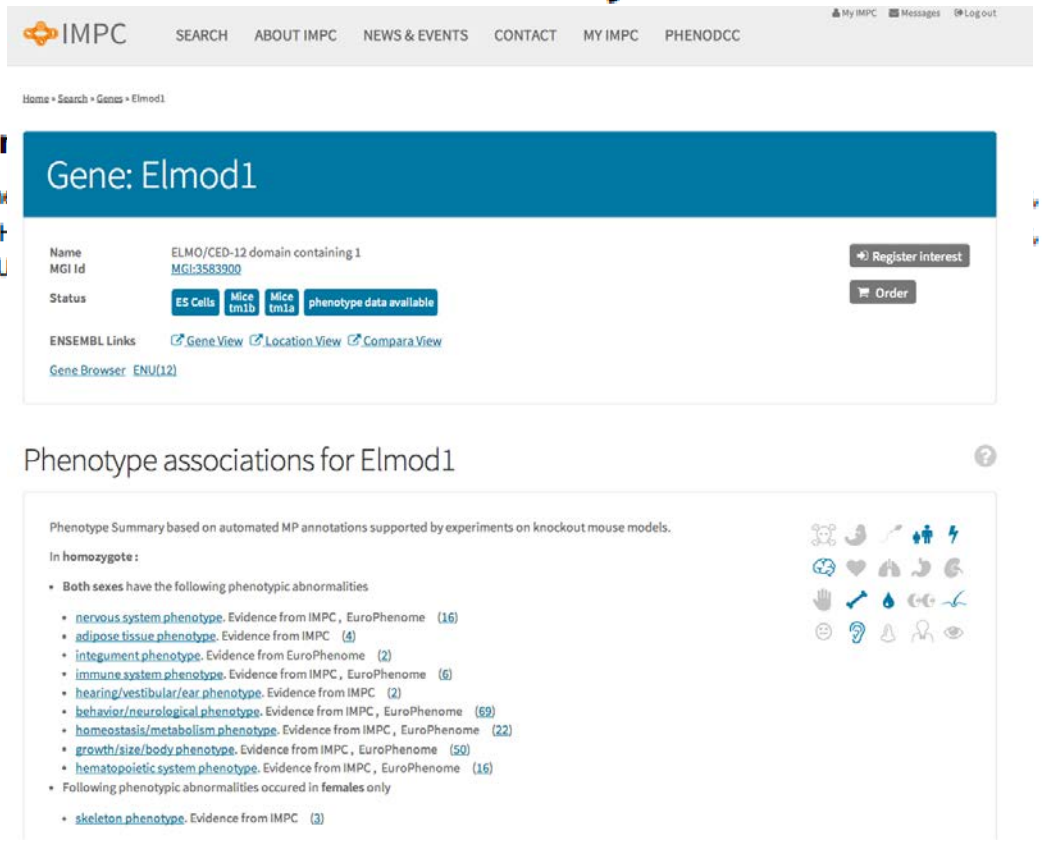
OPEN ACCESS Freely available online

PLOS ONE

Functionally Enigmatic Genes: A Case Study of the Brain Ignorome

Ashutosh K. Pandey[1]*, Lu Lu[1], Xusheng Wa

1 UT Center for Integrative and Translational Genomics and Departm
Tennessee, United States of America, 2 St. Jude Children's Research H
Bioinformatics Program, University of Memphis, Memphis, Tennessee, U



Elmod1

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

IMPC

MPI2

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.

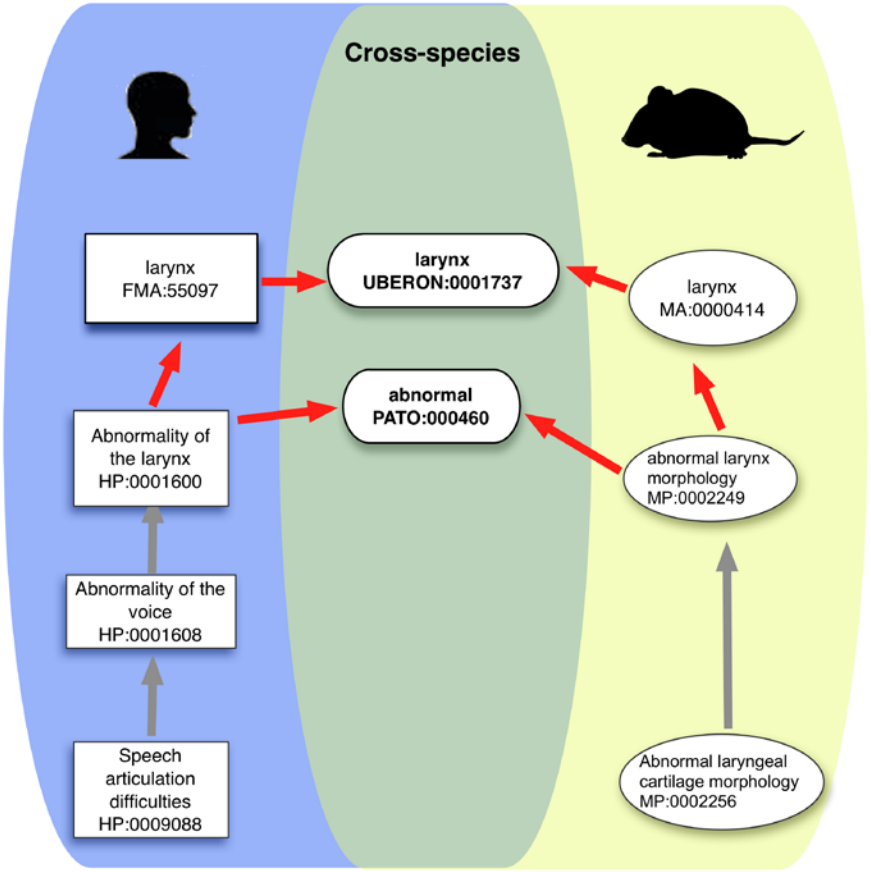
#	Descriptor	Gene symbol	Background strain	Allele	Phenotyping center
1	Elmod1	Elmod1	C57BL/6NTac	Elmod1$^{tm1b(EUCOMM)Hmgu}$	MRC Harwell

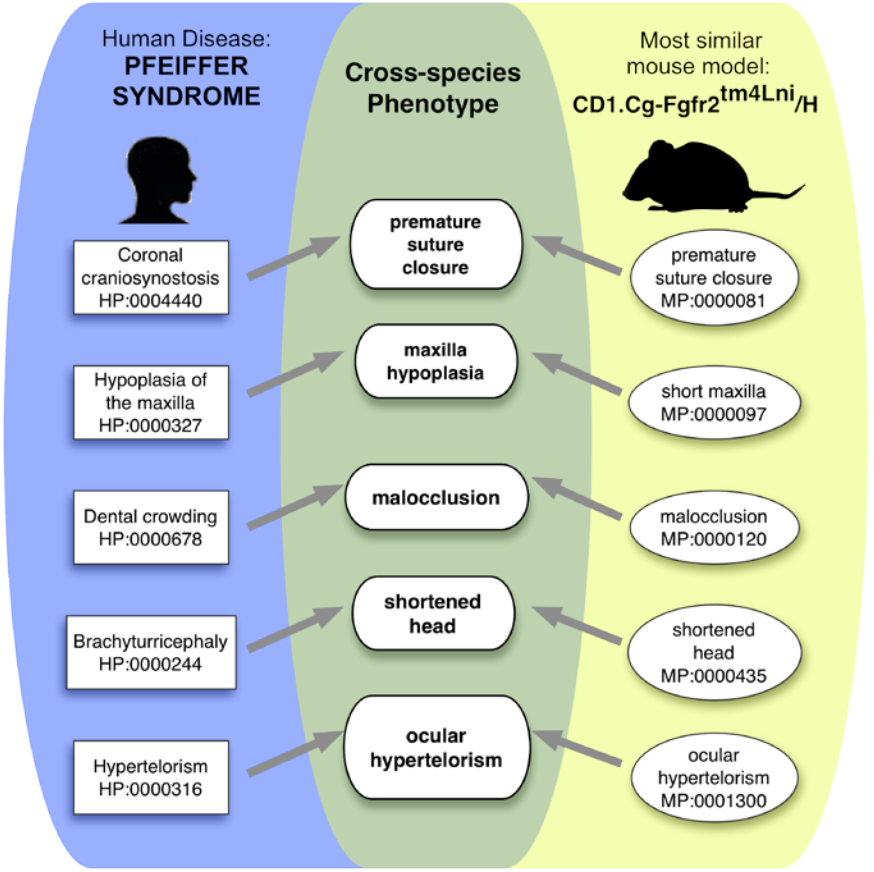
Elmod1 | Overview | Help | Procedural | **Ontological**

Significant | Insignificant | No data | Show gradient | p-value threshold: 0.0001 (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				

PHENODIGM - Cross-species phenotype comparisons by semantic similarity





Damien Smedley, Sanger

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

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		⊞

OMIM:614076 Disease Phenotype Terms

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

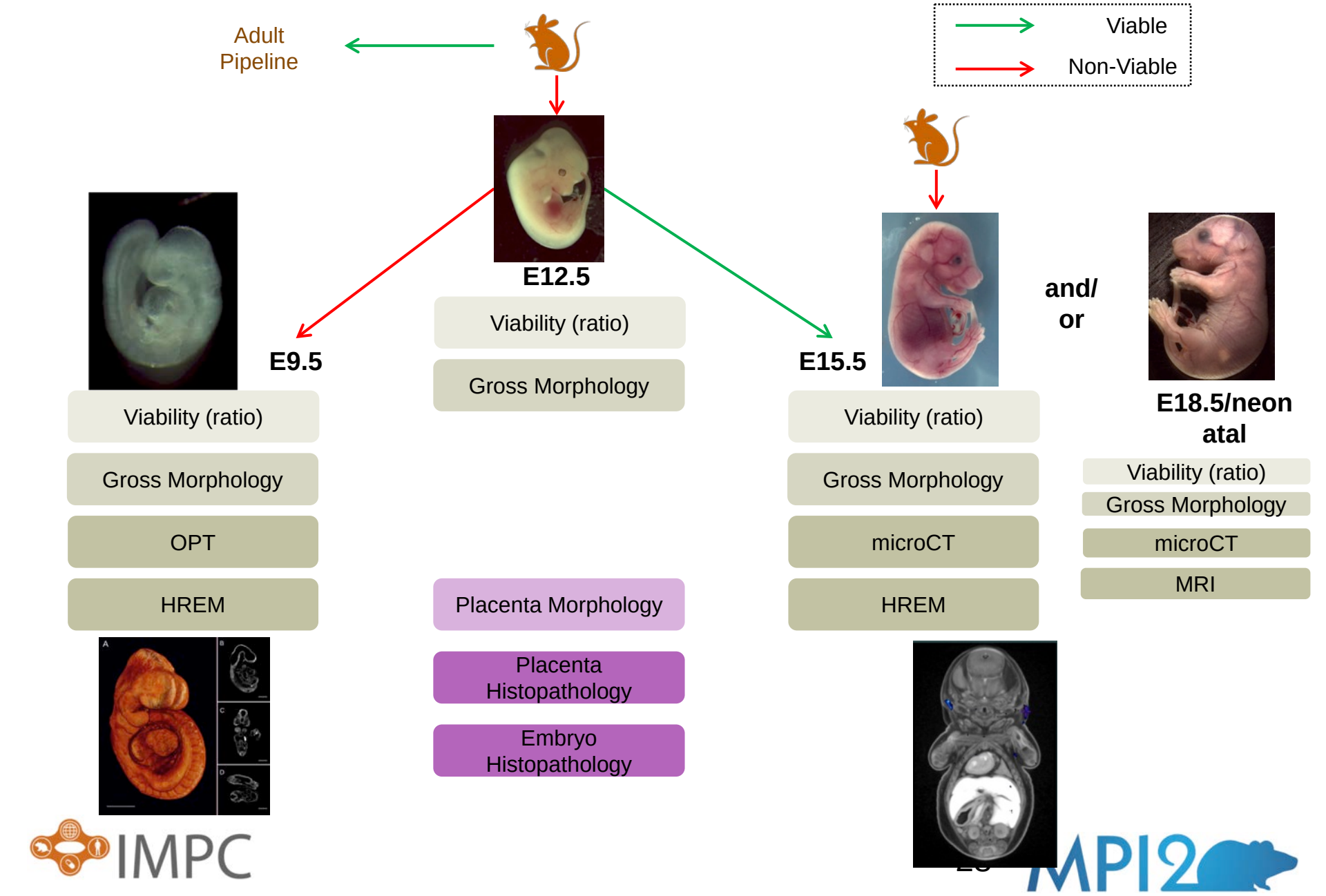
Associated Mouse Models (PhenoDigm predicted)

78.96: Dtnbp1^{sdy}/Dtnbp1^{sdy} 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^{sdy}/Dtnbp1^{sdy} DBA/2J-Dtnbp1/J (Source: MGI)
- diluted coat color
- decreased eye pigmentation
- increased bleeding time

66.52: Dtnbp1$^{tm1b(EUCOMM)Hmgu}$/Dtnbp1$^{tm1b(EUCOMM)Hmgu}$ C5
- 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

Embryo lethal pipeline: stages and components



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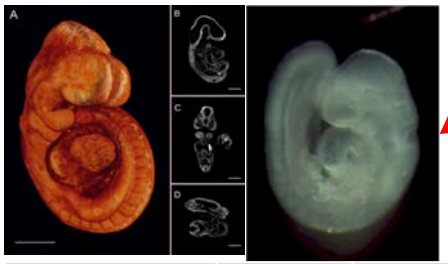
Embryo lethal pipeline: progress through stages

Adult Pipeline

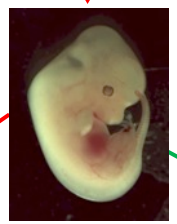
Viable

Non-Viable



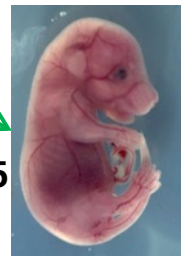
E9.5

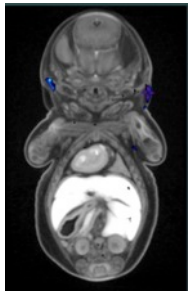
	Viable	Lethal
JAX	0	5
BCM	8	0
DTCC	16	6
Harwell (pilot)	4	13
DMDD	5	18
NorCOMM2	12	0
Totals	**45**	**42**



E12.5

	Viable	Lethal
JAX	8	19
BCM	8	4
DTCC	16	13
Harwell (pilot)	25	17
NorCOMM2	15	1
Totals	**72**	**54**





E15.5

	Viable	Lethal
JAX	1	0
BCM	4	3
DTCC	6	15
Harwell (pilot)	24	1
DMDD	21	27
NorCOMM2	0	2
Totals	**56**	**48**

317 complete stages screened (many more in progress)

IMPC Future Developments

- **Future Developments: CRISPR/Cas9**
  - Pilots underway at IMPC centres to inform future planning
  - Exon deletions; conditional allele, lacZ reporter
  - **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, 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 (Italy)
- European Commission (EU)
- Infrafrontier (EU)
- Australian Phenomics Network (Australia)
- RIKEN BioResource Center (Japan)
- Genome Canada
- Model Animal Research Center (Nanjing)
- Baylor College of Medicine
- Charles River Laboratories
- Korean Mouse Phenotyping Centre

www.mousephenotype.org

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MPI2 Informatics Group

- **MRC Harwell**
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  - Armida Di Fenza
  - Duncan Sneddon
  - Gagarine Yaikhom
  - Henrik Westerberg
  - Luis Santos
  - Hugh Morgan
  - Natalie Ring
  - Tanja Fiegel
  - Hilary Gates
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IMPC – the context

Significant association and co-morbidities between Mendelian and complex disease

Common variants associated with complex disease are enriched in Mendelian loci

Utility of assessing loss-of-function phenotypes in mouse

Cell

A Nondegenerate Code of Deleterious Variants in Mendelian Loci Contributes to Complex Disease Risk

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SUMMARY

Although countless highly penetrant variants have been associated with Mendelian disorders, the genetic etiologies underlying complex diseases remain largely unresolved. By mining the medical records of over 110 million patients, we examine the extent to which Mendelian variation contributes to complex disease risk. We detect thousands of associations between Mendelian and complex diseases, revealing a nondegenerate, phenotypic code that links each complex disorder to a unique collection of Mendelian loci. Using genome-wide association results, we demonstrate that common variants associated with complex diseases are enriched in the genes indicated by this "Mendelian code." Finally, we detect hundreds of comorbidity associations among Men-

certain chromosomal abnormalities (such as Down and Kleinfelter syndromes), and severely deleterious copy-number variants (CNV) often predispose patients to more common, apparently nonMendelian diseases. For example, patients with beta-thalassemia, Huntington disease and Friederichs ataxia often develop type 2 diabetes mellitus (De Sanctis et al., 1988; Podolsky et al., 1972; Ristow, 2004), and carriers of the genetic variants associated with Lujan-Fryns and DiGeorge (velo-cardio-facial) syndromes display an increased risk for schizophrenia (De Hert et al., 1996; Sinibaldi et al., 2004). Additionally, bearers of the 16p11.2 microdeletions and microduplications often develop autism (Kumar et al., 2008; Tabet et al., 2012). In such cases, the simple and complex diseases have been long suspected of sharing genetic architecture; whether there is a broader pattern of such associations, however, remains unclear.

A large and growing number of Mendelian and chromosomal diseases have been precisely assigned to particular causal genetic events. Although Mendelian disorders often manifest

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