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 – the context

Cell

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

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

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SUMMARY

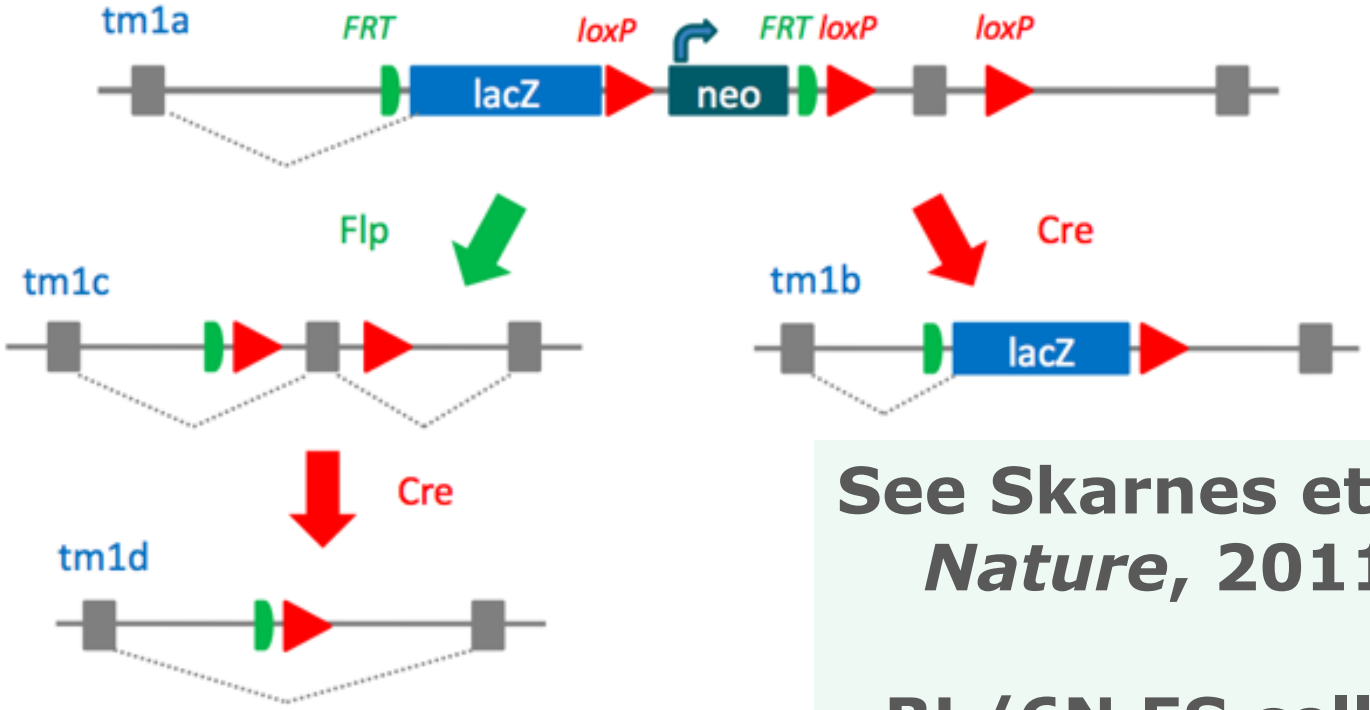
Although countless highly penetrant variants have been associated with Mendelian disorders, the genetic etiologies underlying complex diseases remain largely unresolved. By mining the medical records of over 110 million patients, we examine the extent to which Mendelian variation contributes to complex 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

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 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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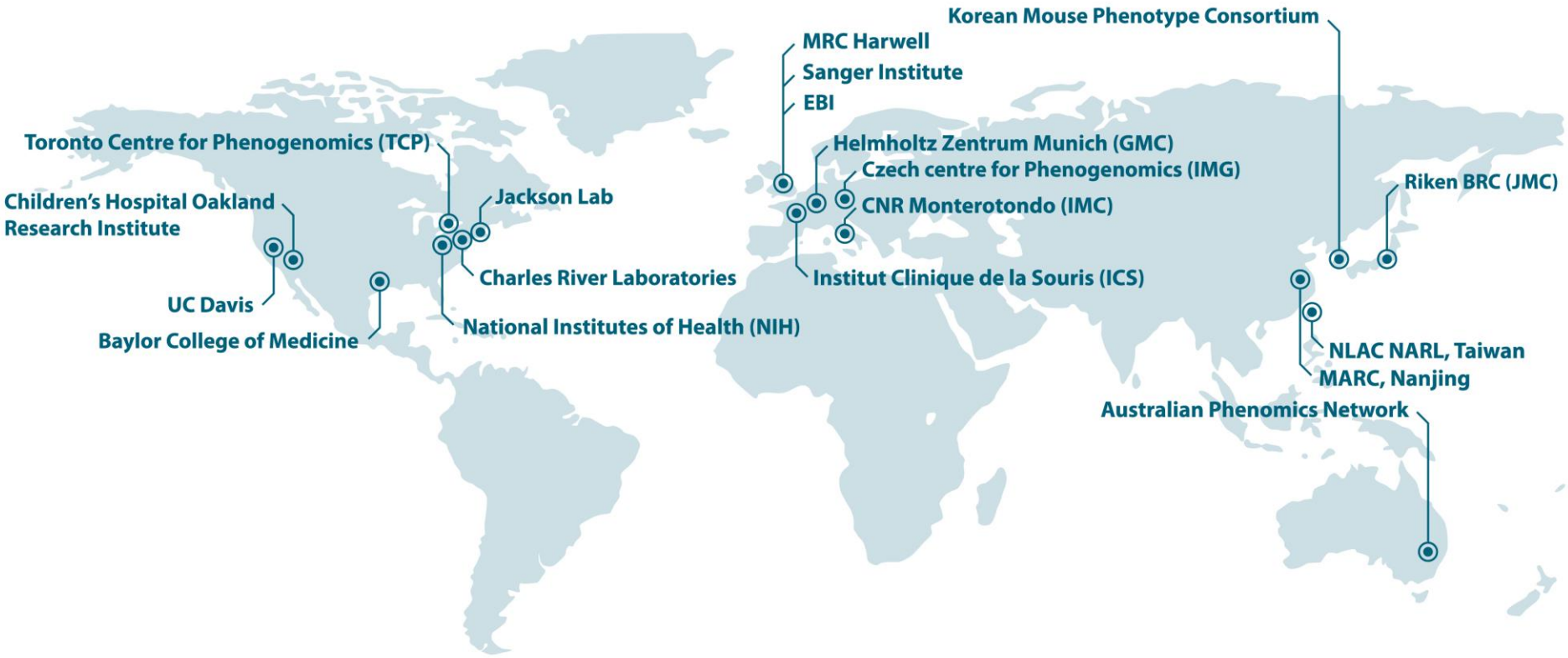

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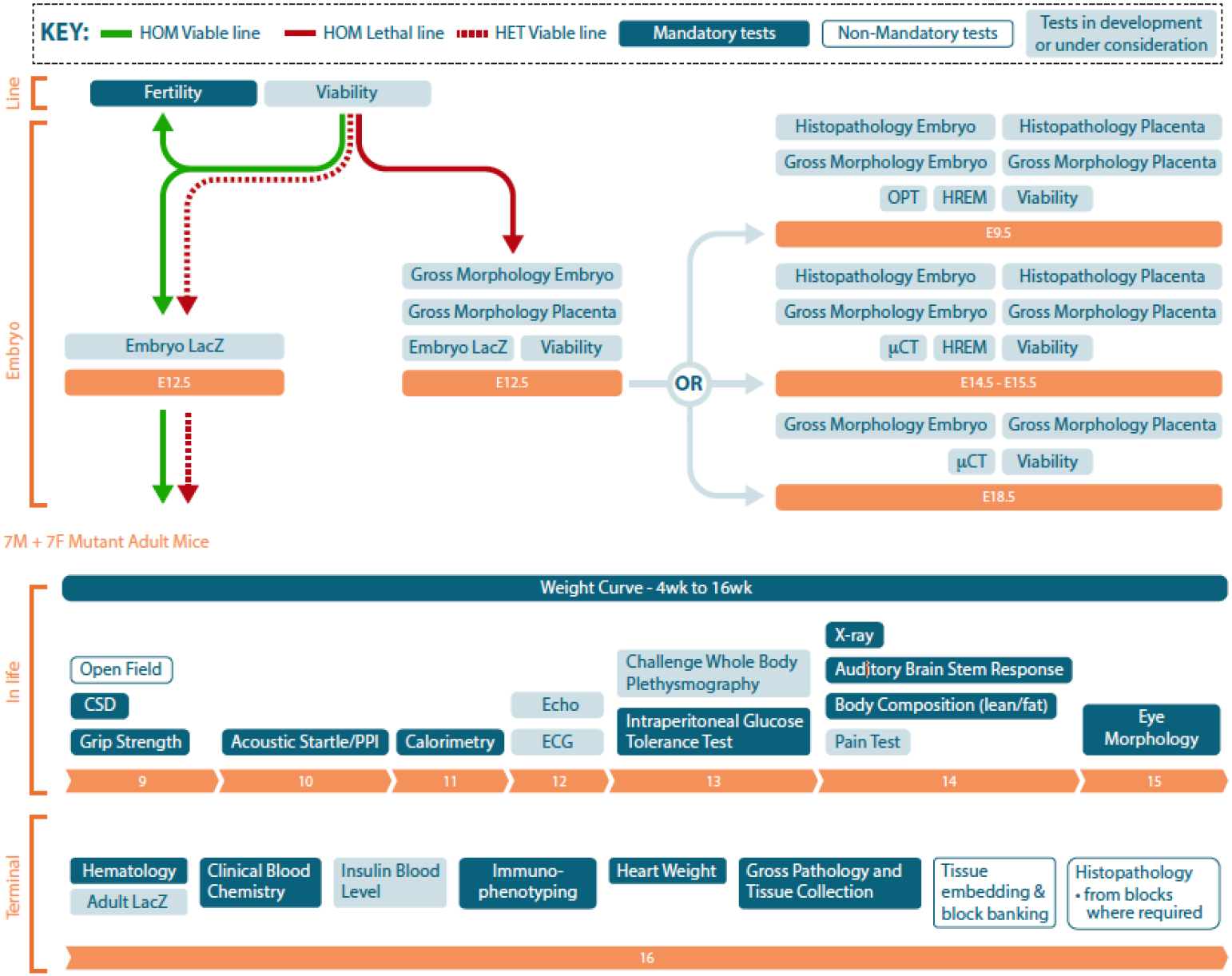
IMPC phenotyping pipeline



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)

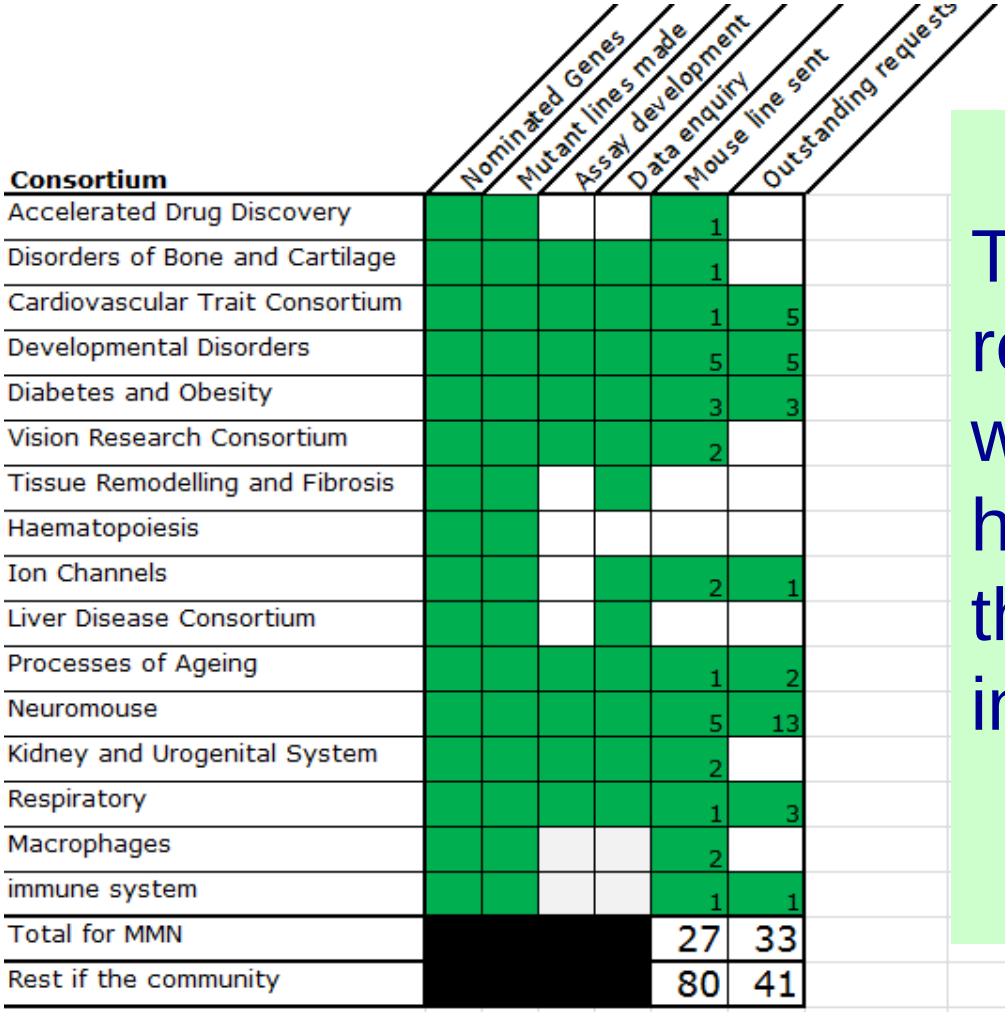
Immune
- Hematology
- FACS analysis – blood/spleen

General
- Modified SHIRPA/Dysmorphology
- Gross Pathology & Tissue Collection (2+2)
- Tissue embedding &Block Banking (2+2)
- Histopathology (2+2) - from blocks where required

IMPC status:
Current iMits (March 2014)

Centre	Total Clones Injected	Genotype Confirmed	Cre excision	Phenotype started (Data in the DCC)
Baylor	622	268	82	36
Harwell	502	219	150	90
HMGU	429	127	109	34
ICS	118	93	73	34
JAX	852	384	245	85
MARC	67	53	3	44
Monterotondo	36	11		
RIKEN	59	16	8	5
TCP	305	148	76	34
UCD	1586	391	218	85
WTSI	1458	642	125	378
TOTAL	**6034**	**2352**	**1089**	**825**

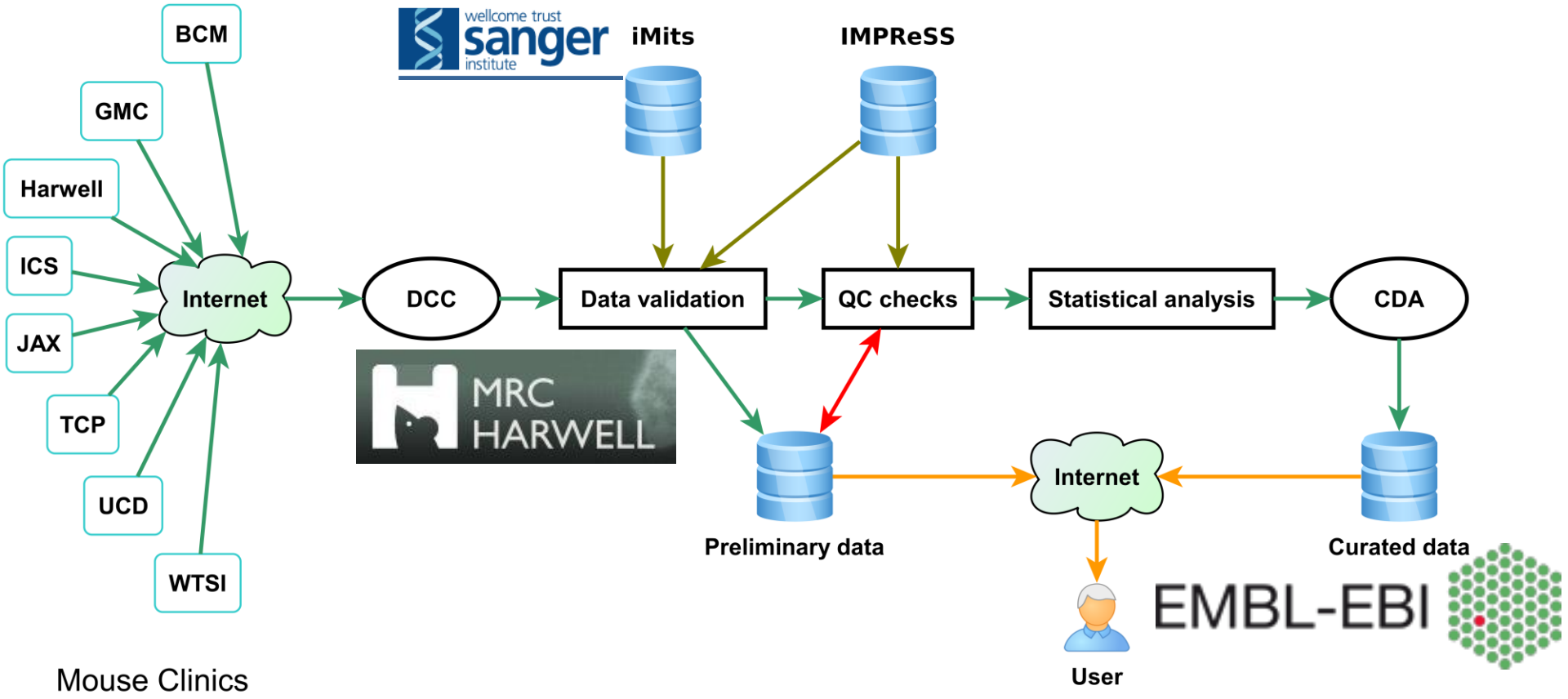
MRC Mouse Networks



Consortium	Nominated Genes	Mutant lines made	Assay development	Data enquiry	Mouse line sent	Outstanding requests
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 if the community					80	41

The value of these resources to the wider community has already repaid the MRC investment in IMPC

IMPC Informatics Team



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DCC Monthly Data Submission update

Phenotyping Centre	Project	Lines	Total Lines to date
Baylor College of Medicine	BaSH	0	35
Helmholtz Zentrum Munchen	Helmholtz GMC	0	40
MRC Harwell	BaSH	0	99
Institut Clinique de la Souris	Phenomin	0	42
The Jackson Laboratory	JAX	0	125
RIKEN Tsukuba Institute, BioResource Center	RIKEN BRC	0	5
The Toronto Centre for Phenogenomics	DTCC	0	58
The Toronto Centre for Phenogenomics	NorCOMM2	0	40
University of California, Davis	DTCC	0	101
Wellcome Trust Sanger Institute	BaSH	0	34
Wellcome Trust Sanger Institute	MGP	0	267
IMPC	IMPC	0	846

- 846 Lines in total to date submitted to the DCC

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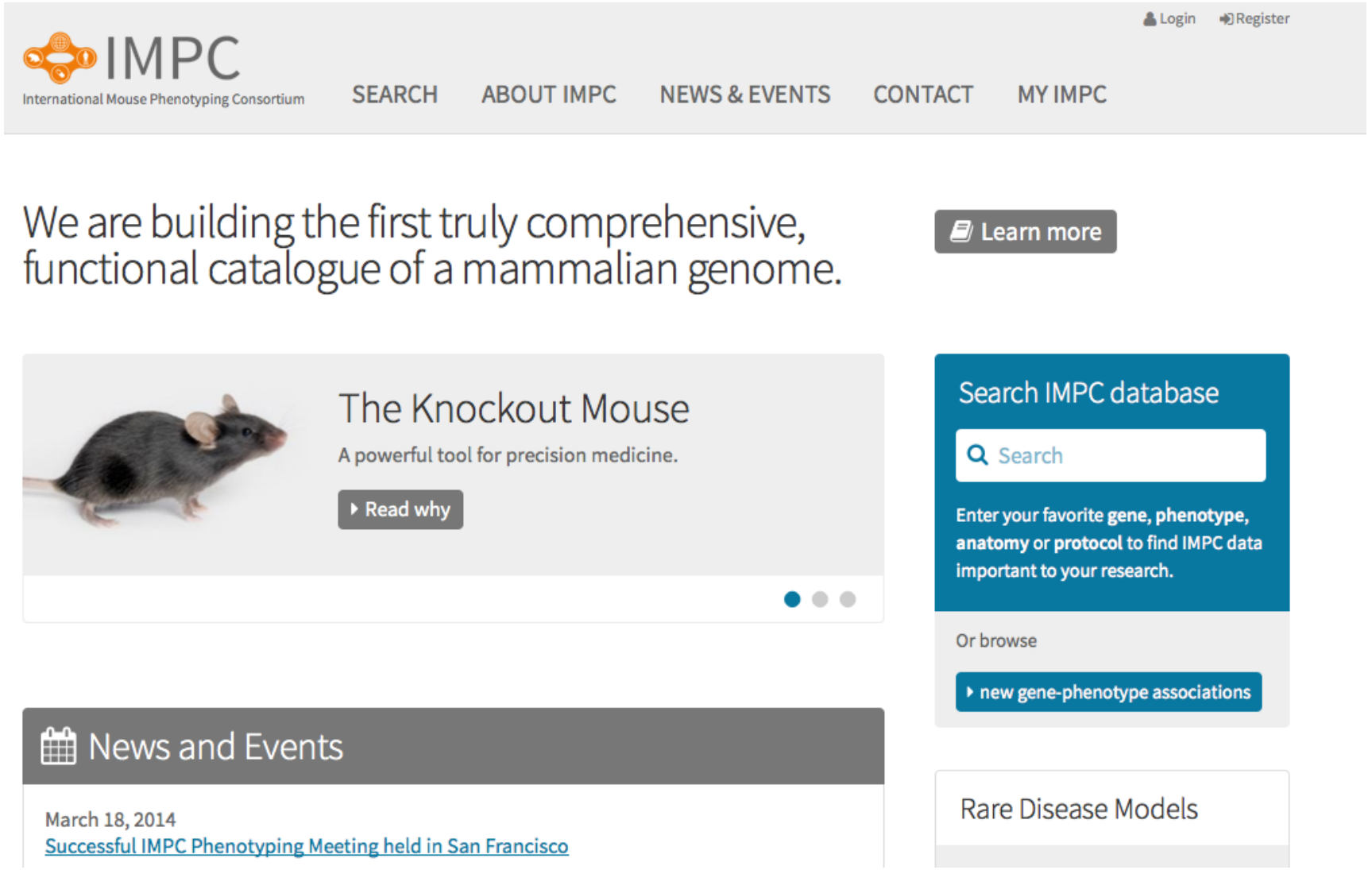
MPI2

IMPC portal



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beta.mousephenotype.org

MPI2

Filter your search

Gene
phenotyping started
Remove all facet filters

- Genes 728
- IMPC Phenotyping Status
  - Started 728
  - Attempt Registered 0
- IMPC Mouse Production Status
- IMPC Mouse Production Center
- IMPC Mouse Phenotyping Center
- Subtype

- Phenotypes 272
- Diseases 248
- Anatomy 41
- Procedures 413
- Images 31490

Search

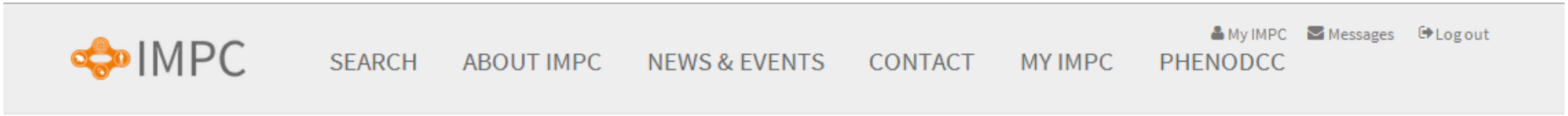
View example search

Found 728 genes

Download

Gene	Production Status	Phenotype Status	
Ell2	Mice tm1a, Mice tm1b, Mice tm1a, Mice tm1e, Mice tm1e	phenotype data available	Interest
Fam175b	Mice tm1a, Mice tm1e	phenotype data available	Interest
Wdr37	Mice tm1a	phenotype data available	Interest
Dynlrb1	Mice tm1a, Mice tm1e	phenotype data available	Interest
Nacad	Mice tm1	phenotype data available	Interest
Jmjd1c	Mice tm1a, Mice tm1e	phenotype data available	Interest

Gene Page



Home » Search » Genes » Cib2

Gene: Cib2

Name	calcium and integrin binding family member 2
Synonyms	calcium binding protein Kip2
MGI Id	MGI:1929293
Status	ES cells · Mice tm1b · phenotype data available
ENSEMBL Links	Gene View · Location View · Compara View

Gene Browser

Register interest

Order

Pre-QC phenotype heatmap - Cib2$^{tm1b(EUCOMM)Wtsi}$

Caution

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

Pre-QC phenotype heatmap - Cib2$^{tm1b(EUCOMM)Wtsi}$

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	Cib2	Cib2	C57BL/6NTac	Cib2$^{tm1b(EUCOMM)Wtsi}$	MRC Harwell

Cib2 | 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
Cib2		1	6.6272e-7	0.0000031464	0.039490
	Adipose tissue	Homeostasis / metabolism	Hearing / vestibular / ear	Growth / size	Craniofacial
Cib2	0.39803	0.0000052945	7.7628e-12	0.037543	0.14015
	Cardiovascular system	Behavior / neurological	Immune system	Respiratory system	Reproductive system
Cib2	0.0000032635	0.0000	0.0074618		1
	Skeleton	Vision / eye	Other	Hematopoietic system	Mortality / aging
Cib2	0.061017	0.11221		0.048526	1
	Integument				
Cib2	1				

H • MGI:1929293 • C57BL/6NTac • Cib2$^{tm1b(EUCOMM)Wtsi}$

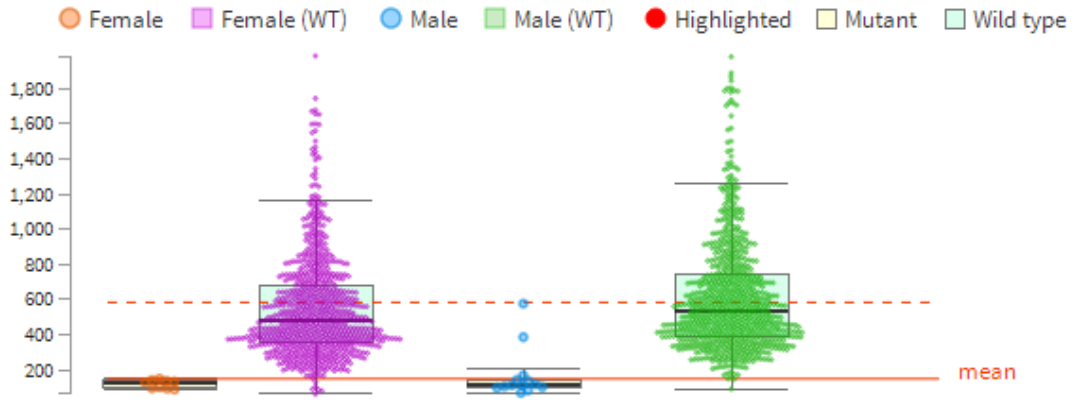
Hom

WT

S

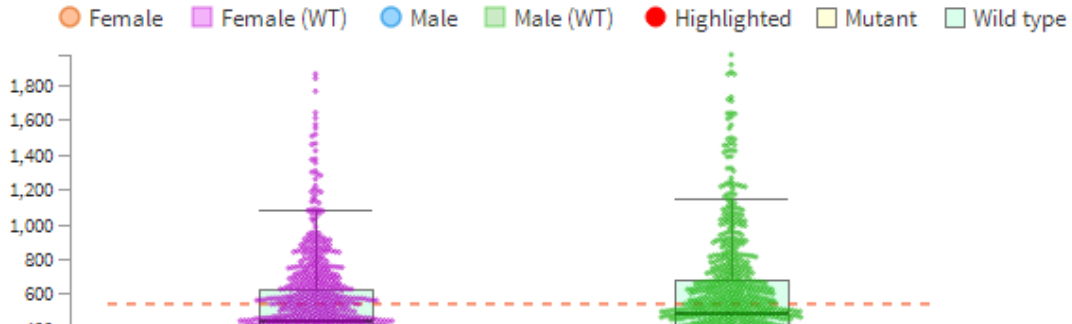
QC pending

Acoustic Startle and Pre-pulse Inhibition (PPI) Response amplitude - S



QC pending

Acoustic Startle and Pre-pulse Inhibition (PPI) Response amplitude - PP1_S



Phenotype Page – abnormal locomotor activation

Phenotype: abnormal locomotor activation

Definition	altered ability or desire of an animal to initiate locomotor activity
Procedure	• Combined SHIRPA and Dysmorphology (IMPC Pipeline) • Combined SHIRPA and Dysmorphology (Harwell) • Combined SHIRPA and Dysmorphology (JAX Pipeline) ▸ more procedures
MGI MP browser	MP:0003313

Phenotype Page – abnormal locomotor activation

▸ Phenotype: All ▸ Gene: All ▸ Procedure: All ▸ Analysis: All

Total number of results: 34

Gene / Allele	Zygosity	Sex	Phenotype	Procedure / Parameter	Phenotyping Center	Analysis	Graph
Acp2 $Acp2^{tm1a(EUCOMM)Wtsi}$	homozygote	♂	abnormal locomotor activation	Modified SHIRPA / Body position	MRC Harwell	EuroPhenome	
Atp8a1 $Atp8a1^{tm1a(EUCOMM)Wtsi}$	homozygote	♀	abnormal locomotor activation	Modified SHIRPA / Body position	MRC Harwell	EuroPhenome	
Ccnyl1 $Ccnyl1^{tm1a(EUCOMM)Wtsi}$	homozygote	♂	abnormal locomotor activation	Modified SHIRPA / Body position	MRC Harwell	EuroPhenome	
Clk1 $Clk1^{tm1a(EUCOMM)Wtsi}$	homozygote	♂	abnormal locomotor activation	Modified SHIRPA / Body position	ICS	EuroPhenome	

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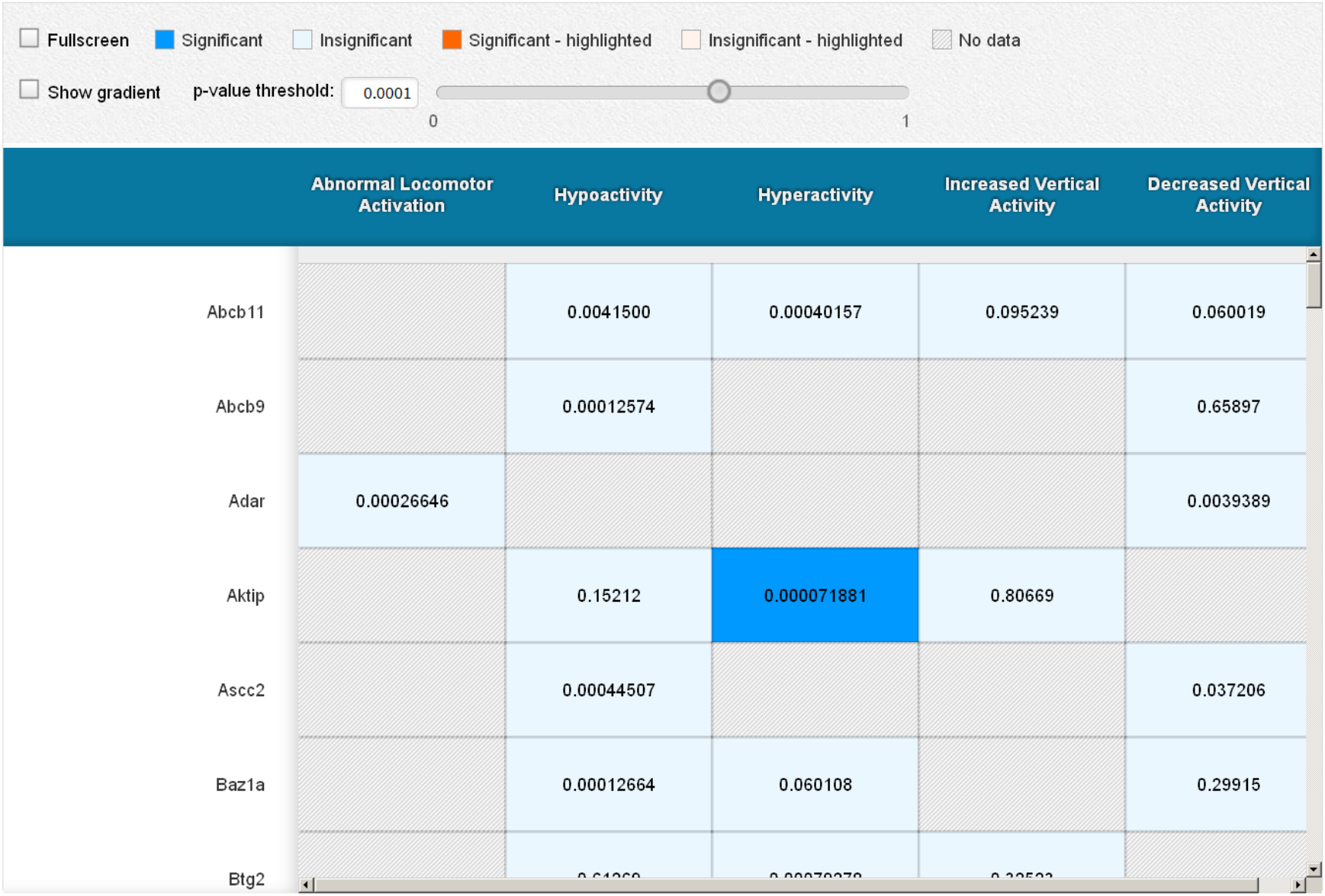
MPI2

Phenotype Page – abnormal locomotor activation



	Abnormal Locomotor Activation	Hypoactivity	Hyperactivity	Increased Vertical Activity	Decreased Vertical Activity
Abcb11		0.0041500	0.00040157	0.095239	0.060019
Abcb9		0.00012574			0.65897
Adar	0.00026646				0.0039389
Aktip		0.15212	0.000071881	0.80669	
Ascc2		0.00044507			0.037206
Baz1a		0.00012664	0.060108		0.29915
Btg2					

IMPC Production

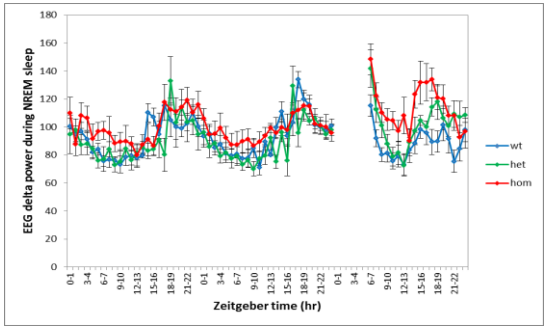
- **5000 microinjections achieved by end year 2**
- **Significant progress in technical developments speeding mouse production**
  - 2i media
  - Cell permeable cre
- **Significant outreach and dissemination of mouse mutants to the community**
- **Future Developments: CRISPR/Cas9**
  - Pilots underway at IMPC centres to inform future planning
  - Pronuclear injection, followed by breeding of F0
  - Exon deletions; introduction of loxP sites
  - **Development of a STANDARDISED, HIGH QUALITY ALLELE**

IMPC Phenotyping

- **IMPC adult core pipelines established and operational at IMPC centres**
- **Significant baseline control data uploaded to DCC**
- **Preliminary QC'd data on 846 mutant lines in DCC**
- **Future Developments**
  - A step change in phenotyping for Phase 2
  - Use of home cage monitoring, telemetry, biomarkers, imaging approaches, histopathology, ageing
  - More data per animal, complex longitudinal data, lower cost

IMPC Phenotyping Subgroups

Development of Phase 2 pipeline



Subgroup 1 **Behaviour**
Subgroup 2 **Metabolism & markers**
Subgroup 3 **Morphology**
Subgroup 4 **Challenges**
Subgroup 5 **Ex vivo**
Subgroup 6 **Sick mouse (existing group)**
Subgroup 7 **Telemetry**
Subgroup 8 **Automated image analysis (existing group)**
Subgroup 9 **Immune phenotyping**

IMPC Conclusions

- **IMPC is set to deliver 5,000 mouse lines and associated phenotype information by 2016**
- **Phenotype data from the first phenotyped lines is available at www.impc.org or www.mousephenotype.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**

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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

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