The IMPC: Building the First Comprehensive Catalog of a Mammalian Genome

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Project Lead

Mouse Informatics at EMBL-EBI

Part of the MPI2 consortium

www.mousephenotype.org

IMPC

CREATE

20,000 knockout mouse strains – one null mutant mouse line for each protein coding gene

CHARACTERIZE

Systematically phenotype each strain

CATALOGUE

Make mutant strains publicly available
Publish data in near real time & provide analysis tools

CONNECT

Link phenotypic data to known biology
Disease models

Background: Building on IKMC Success

International Knockout Mouse Consortium

NIH:	EU:	Genome Canada:	Texas A&M :
Knockout Mouse Program **(KOMP1)**	European Conditional Mouse Mutagenesis Program **(EUCOMM)**	North American Conditional Mouse Mutagenesis Project **(NorCOMM)**	Texas A&M Institute for Genomic Medicine **(TIGM)**

EUCOMM - Tools for Functional Annotation of the Mouse Genome

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Background: Building on IKMC Success

>15,000 targeted mutant alleles created
in C57BL/6N ES cell lines
and more coming

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Background: The IMPC

International Mouse Phenotype Consortium

- Create and Characterize 20,000 knockout lines over 10 years
- Phase 1- 5000 strains by 2016
- Publish & Annotate Data in near Real-Time
- Integrate IMPC data with human mutation and disease repositories

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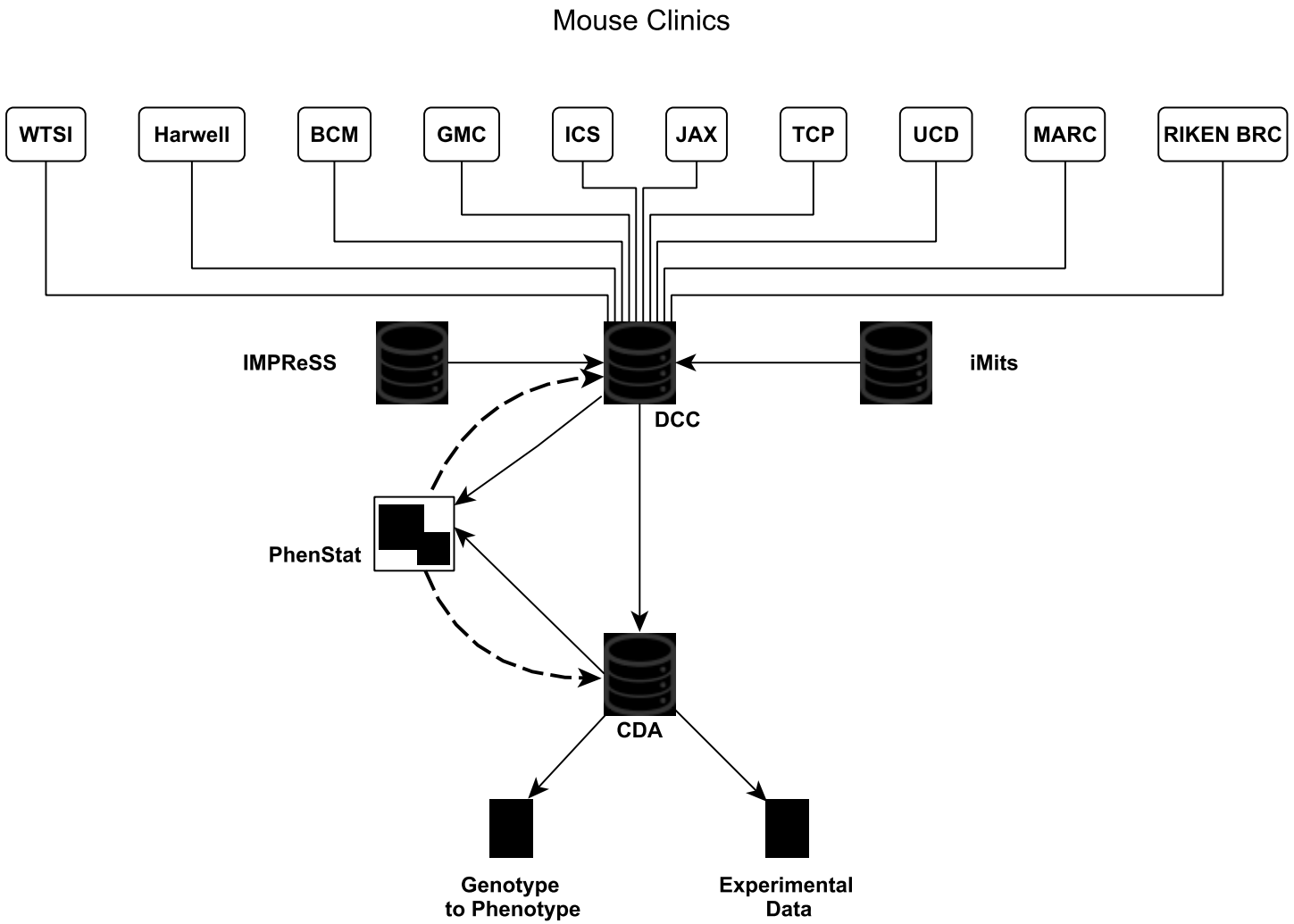
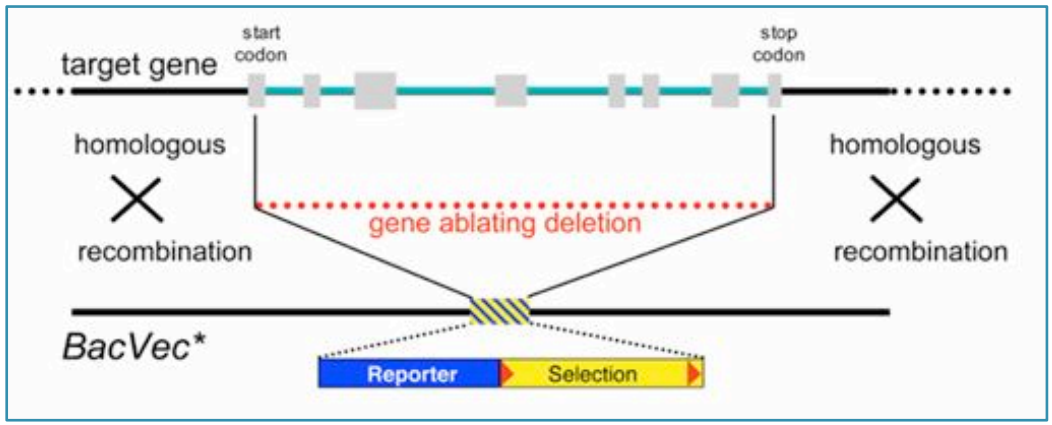
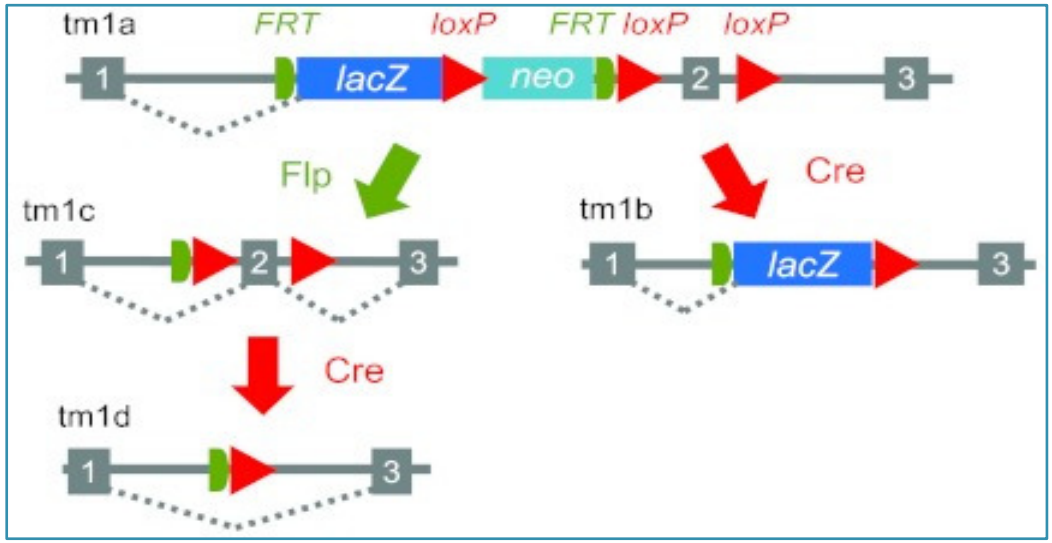
CHARACTERIZE- High quality data



CREATE: Knockout Line Production



KOMP
Velicogene



EUCOMM

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Brown, S and M.W. Moore. **Towards an encyclopaedia of mammalian gene function: the International Mouse Phenotyping Consortium.** *Dis. Model. Mech. May 2012, vol. 5 no. 3 289-292*

DEMO I

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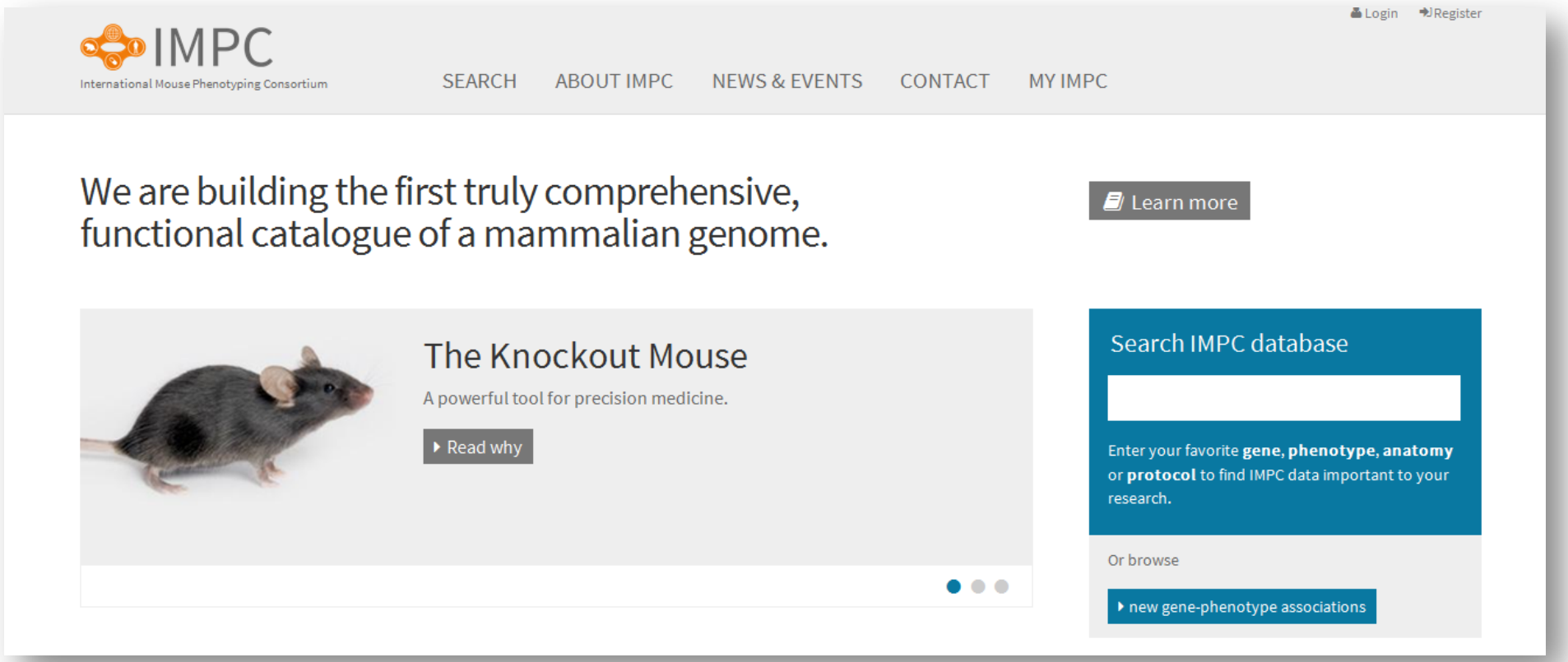
Home page



mousephenotype.org

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IMPC
International Mouse Phenotyping Consortium

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

The Knockout Mouse

A powerful tool for precision medicine.

Read why

International Mouse Phenotype Consortium

The goal of the International Mouse Phenotyping Consortium (IMPC) is to discover functional insight for every gene by generating and systematically phenotyping 20,000 knockout mouse strains.

One of the most important tools at our scientific disposal in understanding mammalian gene function is the laboratory mouse. The fundamental genetic similarity between mice and humans allows researchers to infer a human gene's function based on studies with laboratory mice. One powerful technique is to turn off, or "knockout", the activity of a mouse gene to assess what biological systems are impacted. This gives insights how a similar gene in humans may contribute to disease when its activity is altered.

The IMPC is generating a knockout mouse strain for every protein coding gene by using the embryonic stem cell resource generated by the International Knockout Mouse Consortium (IKMC). The production of mouse strains from these ES cells are tracked within the "international Micro-injection tracking system" (iMits) and are made available to the research community via public repositories.

Systematic broad-based phenotyping is performed by each IMPC center using standardized procedures found within the International Mouse Phenotyping Resource of Standardised Screens (IMPReSS) resource. Gene-to-phenotype associations are made by a versioned statistical analysis with all data freely available by this web portal and by several data download features.

Search IMPC database

Search

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

Find mouse models of rare disease by either shared gene or shared phenotype features.

Visit Disease Models

IMPReSS

IMPReSS contains standardized phenotyping protocols, essential for the characterization of mouse phenotypes.

visit IMPReSS

iMITS

iMITS is the designated planning and tracking resource for IMPC mutant mouse strain production.

Visit iMITS

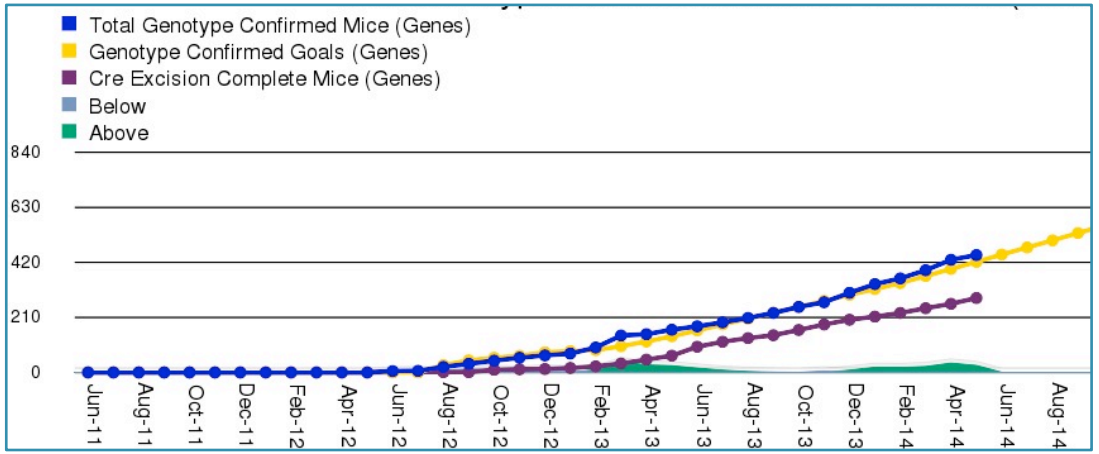
CREATE: Knockout Line Production

IMPC Mouse Production

iMits website reports real-time production status

Home | Gene Summary | Mouse Production | Phenotyping | Contacts for Production Centres | Download of all Production

Status	Current Total (up to and inc. May)	Last Complete Month (May)
All genes	1379	55
ES Cell QC (genes)	877	26
ES QC Confirmed (genes)	795	26
ES QC Failed (genes)	22	
Microinjections (genes)	831	27



To date:

- 7000 ES clones have been injected
- 3000 genotype confirmed
- 1600 cre excised

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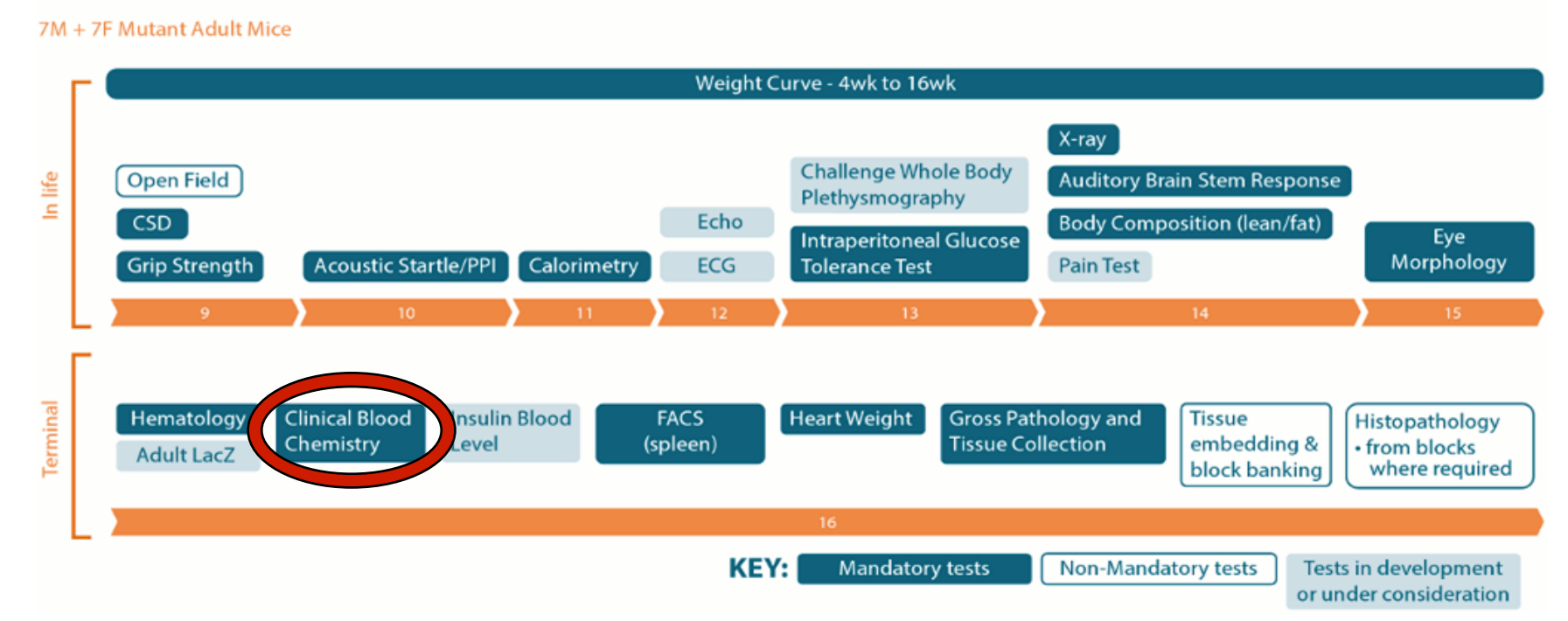
CHARACTERIZE
Adult phenotypes



- *IMPReSS:* (International Mouse Phenotyping Resource of Standardised Screens)
- Ascribe Biological Function to Each Gene
- Collaborate with phenotyping specialists

Characterize

- Protocol
- Data Parameter
- Ontology

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Clinical Blood Chemistry [IMPC_CBC_003]

View as PDF / Display Ontologies / Example XML Submission / Change History

Purpose | Experimental Design | Equipment | Procedure | Notes | Parameters | Metadata

Purpose

Clinical chemistry determines biochemical parameters in plasma including enzymatic activity, specific substrates and electrolytes.

Ontological description: MP:0001545 – blood physiology abnormalities.

Experimental Design

Minimum number of mutant animals: must maintain ≥ 7 size for male and female.

Age of animals: 16 weeks

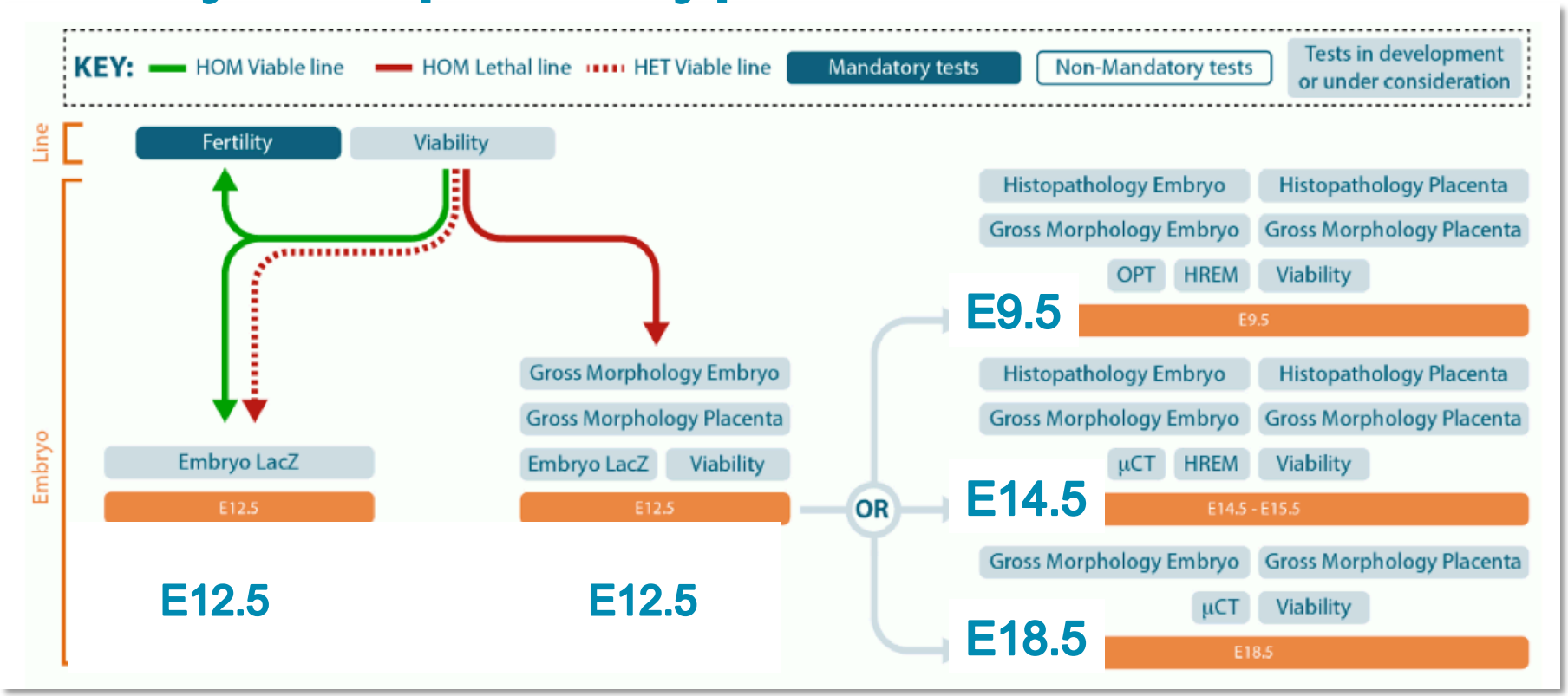
Sexual dimorphism: Yes for some of the parameters.

Parameter	Version	Type	Req. Upload	Req. Analysis	Annotation	Increment	Option	Ontology Options	Derived	Unit	Data Type
Sodium IMPC_CBC_001_001	1.3	simpleParameter			✓					mmol/l	FLOAT
Potassium IMPC_CBC_002_001	1.3	simpleParameter			✓					mmol/l	FLOAT
Chloride IMPC_CBC_003_001	1.4	simpleParameter			✓					mmol/l	FLOAT
Urea (Blood Urea Nitrogen - BUN) IMPC_CBC_004_001	1.5	simpleParameter	✓		✓					mg/dl	FLOAT

Parameter: Sodium IMPC_CBC_001_001

	Option	Increment	Ontology Term	Ontology ID	Sex
INCREASED			increased circulating sodium level	MP:0005633	
DECREASED			decreased circulating sodium level	MP:0005634	
ABNORMAL			abnormal circulating sodium level	MP:0001776	

CHARACTERIZE
Embryonic phenotypes



- A third of lines will be embryonic lethal
- Specialized pipeline created
- Cutting-edge imaging technologies being employed

IMPReSS API Access

- IMPReSS is accessible programmatically utilising a SOAP web service.
- This API access exposed all the Pipeline, Procedure, Parameter and Ontology term information held within IMPReSS
- The WSDL is available at https://www.mousephenotype.org/impress/soap/server?wsdl
- With full documentation available at https://www.mousephenotype.org/impress-web-services-technical-description

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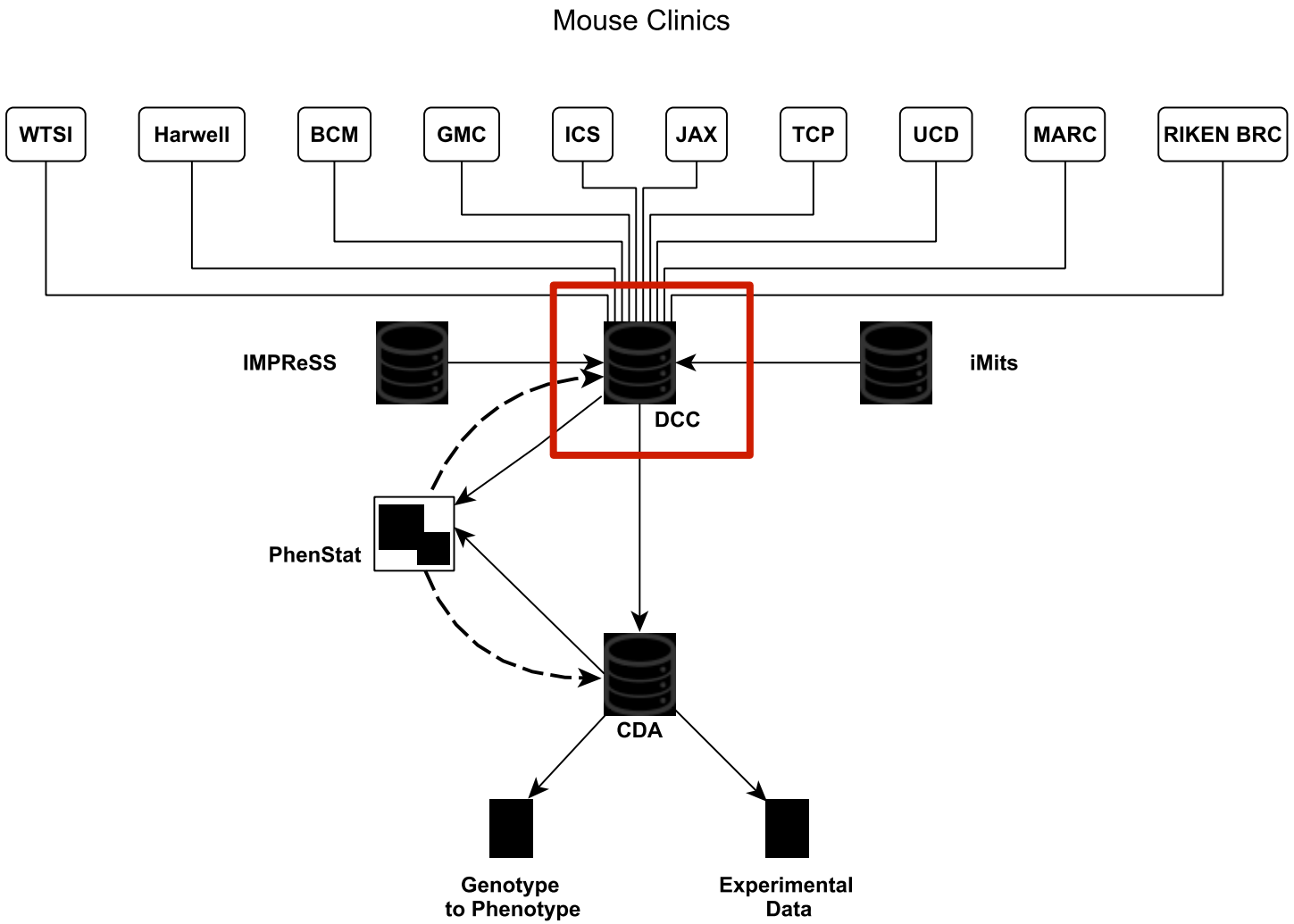
CHARACTERIZE- High quality data



CHARACTERIZE- Ensuring High quality Data

- All data **visually QCd** by the DCC Data Wranglers
  - Identify biologically impossible errors in data
  - Standardised protocols adhered to in each centre
- Monthly report to all centres:
  - Update on QC progress (number of issues raised vs resolved)
  - Draw attention to ongoing data problems, e.g. low cohort size
- Interactive QC system:
  - wranglers raise QC queries (“issues”) - centre responds

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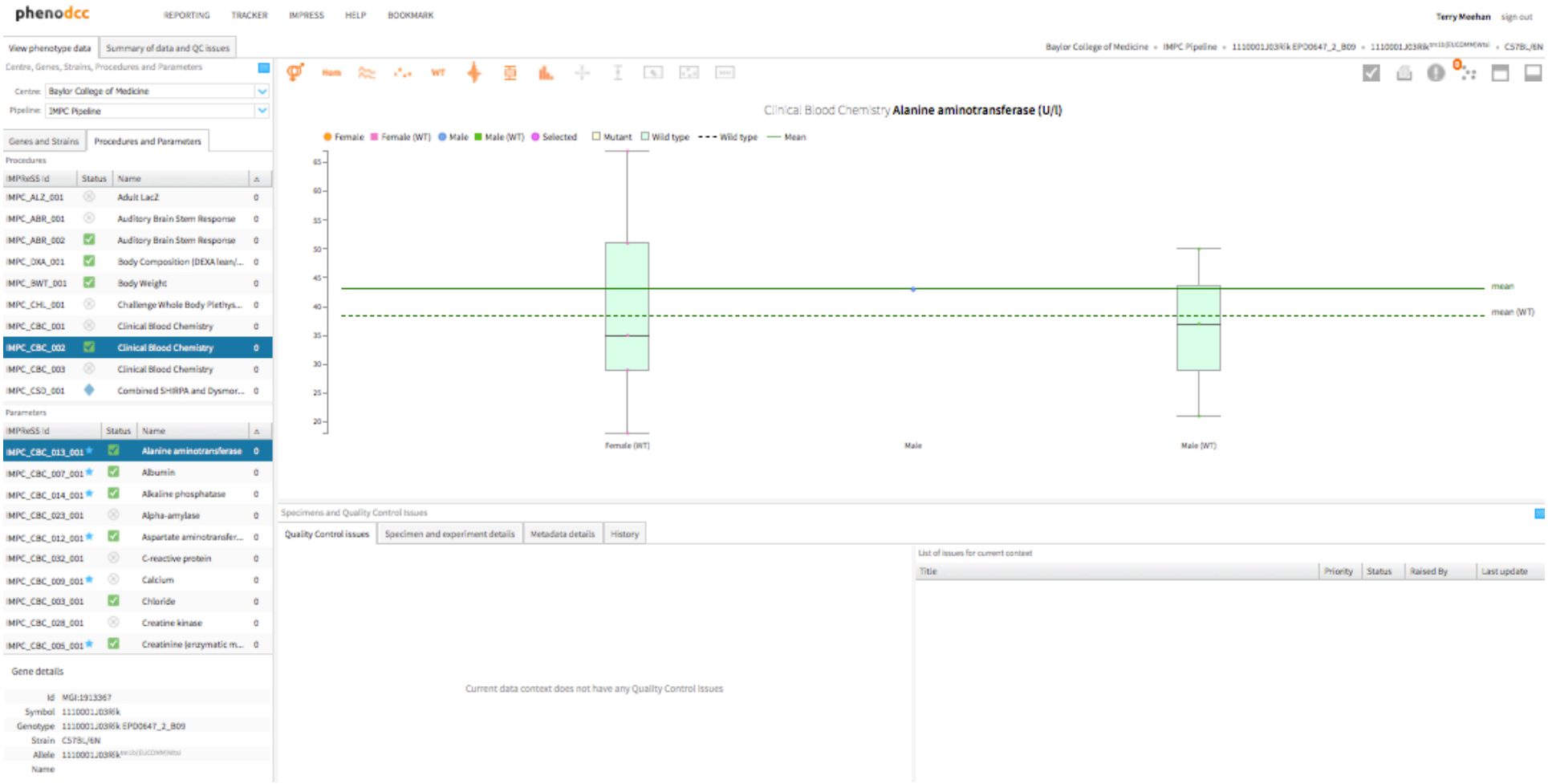
CHARACTERIZE- Shared QC interface



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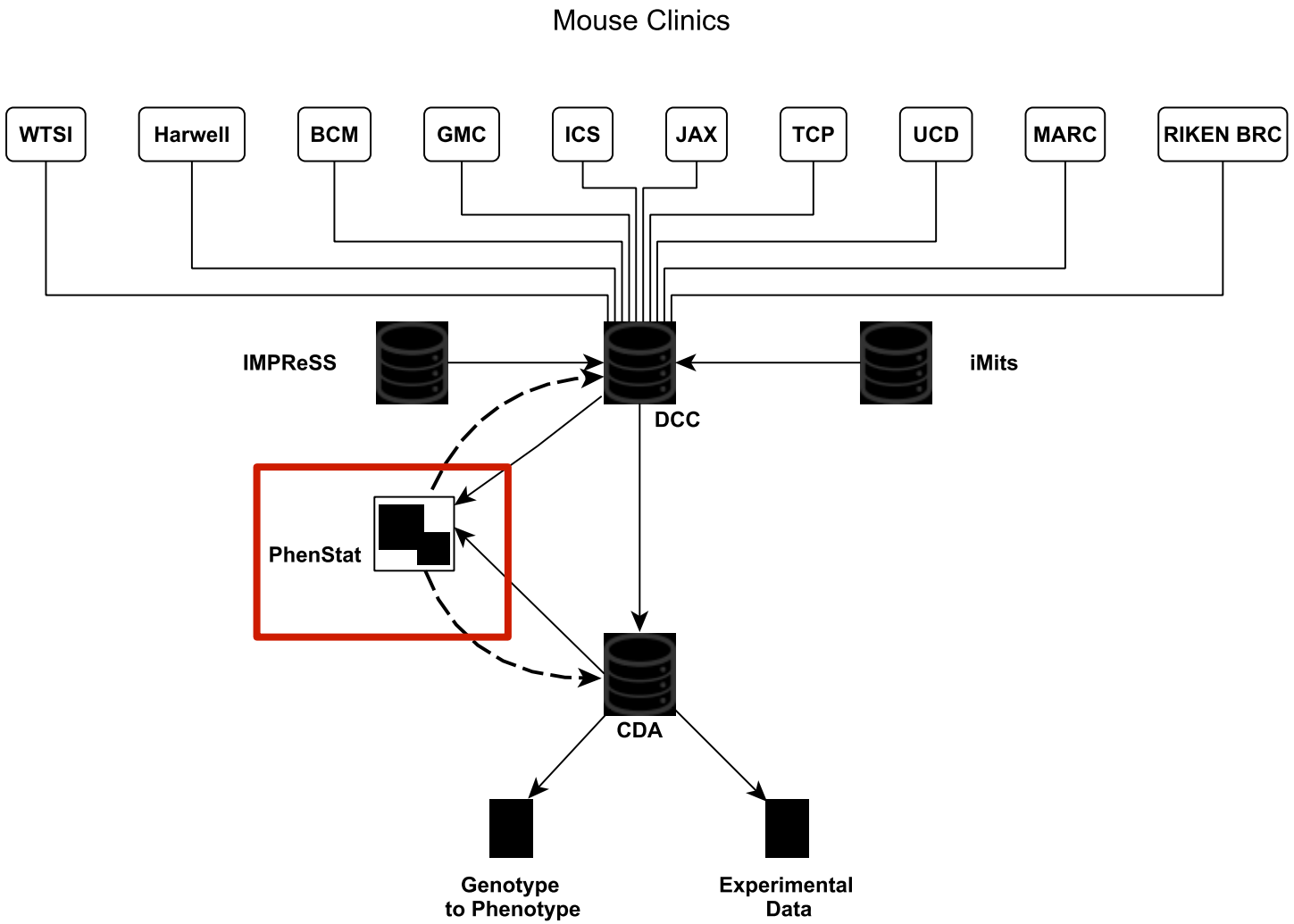
CHARACTERIZE- STATS Analysis



CHARACTERIZE- PhenStat
Our production statistical analysis

- Associate Genotype to Phenotype
  - Multiple workflows
  - Multiple data types
  - Built statistical analysis platform on expected workflows
    - Fisher Exact Test, Linear regression- Mixed Model

- The **PhenStat** package

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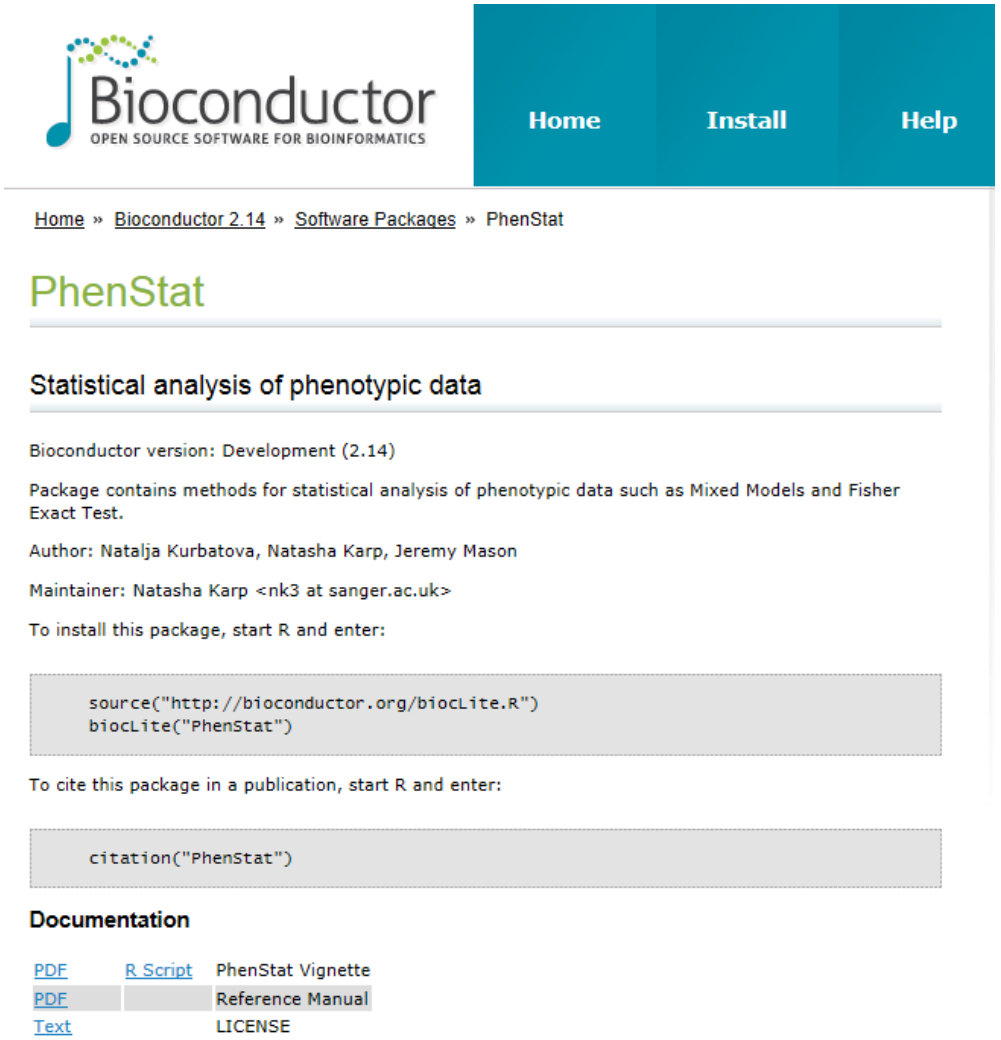
What is PhenStat?

- Freely available R Package
- Version controlled
- multiple workflows
- Can include a covariate e.g. body weight.
- Gives both a statistical and biological measure
- Assesses sexual dimorphism



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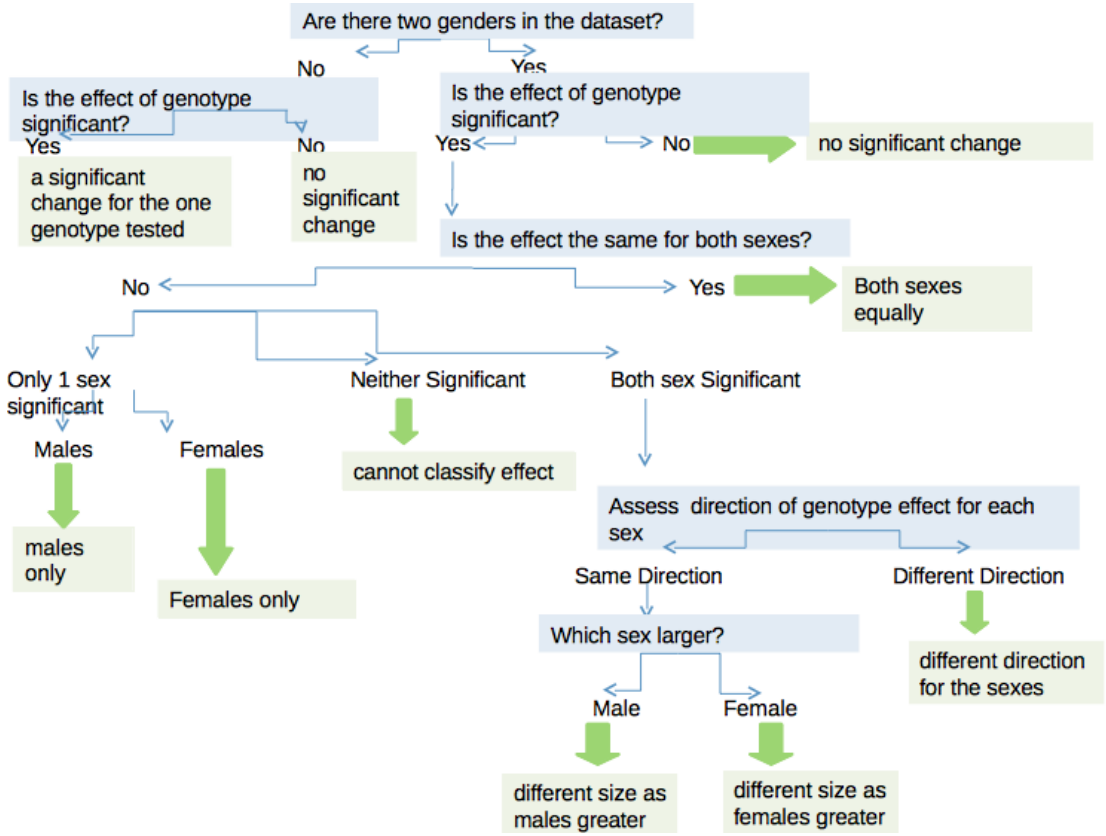
Statistical benefits include:

- Various statistical strategies implemented
- Can include a covariate e.g. body weight.
- Gives both a statistical and biological measure
- Assesses sexual dimorphism



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CHARACTERIZE- Other Approaches (BAYESIAN)

- Non-Gaussian response distributions
- Correlated observations (same litter, same day measured)
- Effects of measured variables
  - Biological variation e.g. sex or mouse strain.
  - Experimental effects, e.g. investigator
  - *model as covariates*
- Effects of unmeasured variables
  - Systematic drift over time in baseline mean or variance
  - Clustering of baseline response not explained by metadata
  - *Address systematic baseline drift by incorporating a smooth function of time in the model*

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CHARACTERIZE- Other Approaches (BAYESIAN) II

- Unified approach to quantitative and categorical data
  - Linear regression on transformed quantitative data
  - Logistic regression on categorical data
- Known sources of variation modelled as covariates
  - Day, litter, sex, strain, experimenter, metadata
- Effects of unmeasured variables
  - Address systematic baseline drift by incorporating a smooth function of time in the model

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DEMO II

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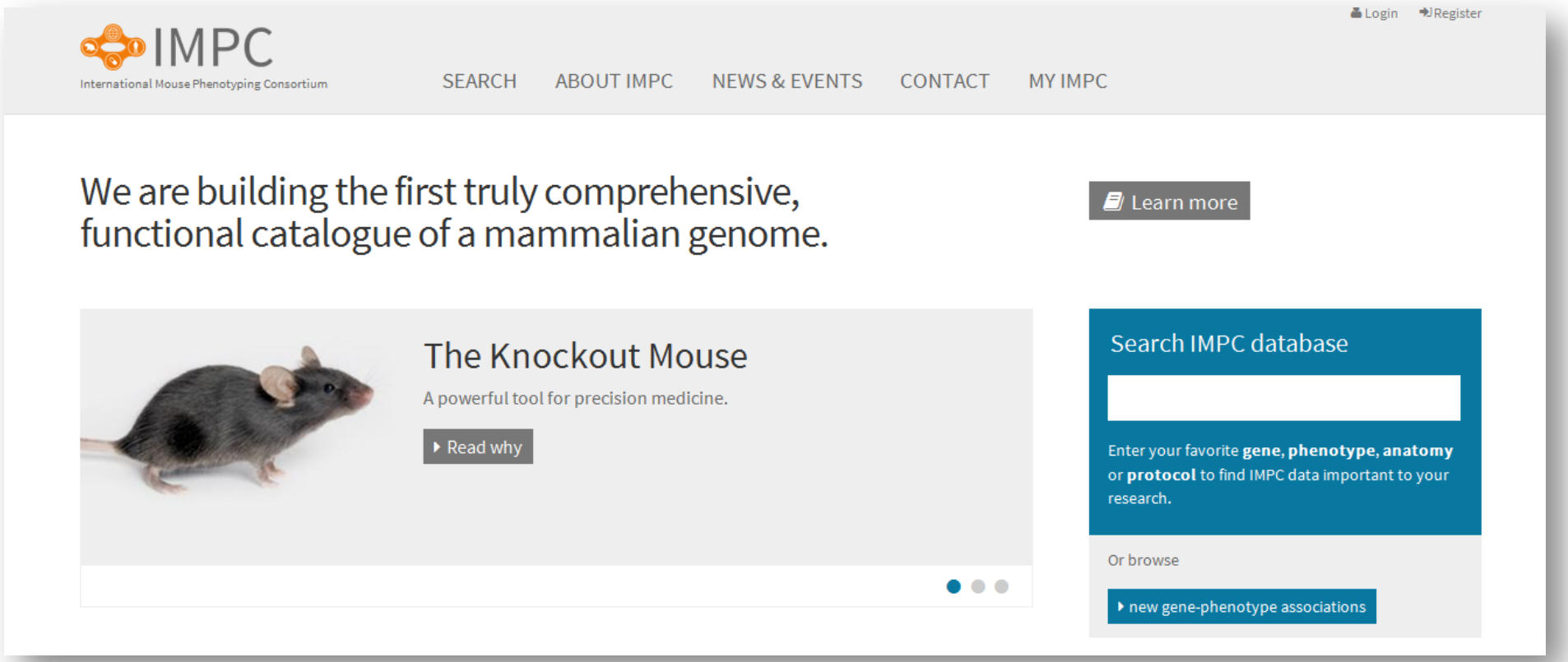
Home page



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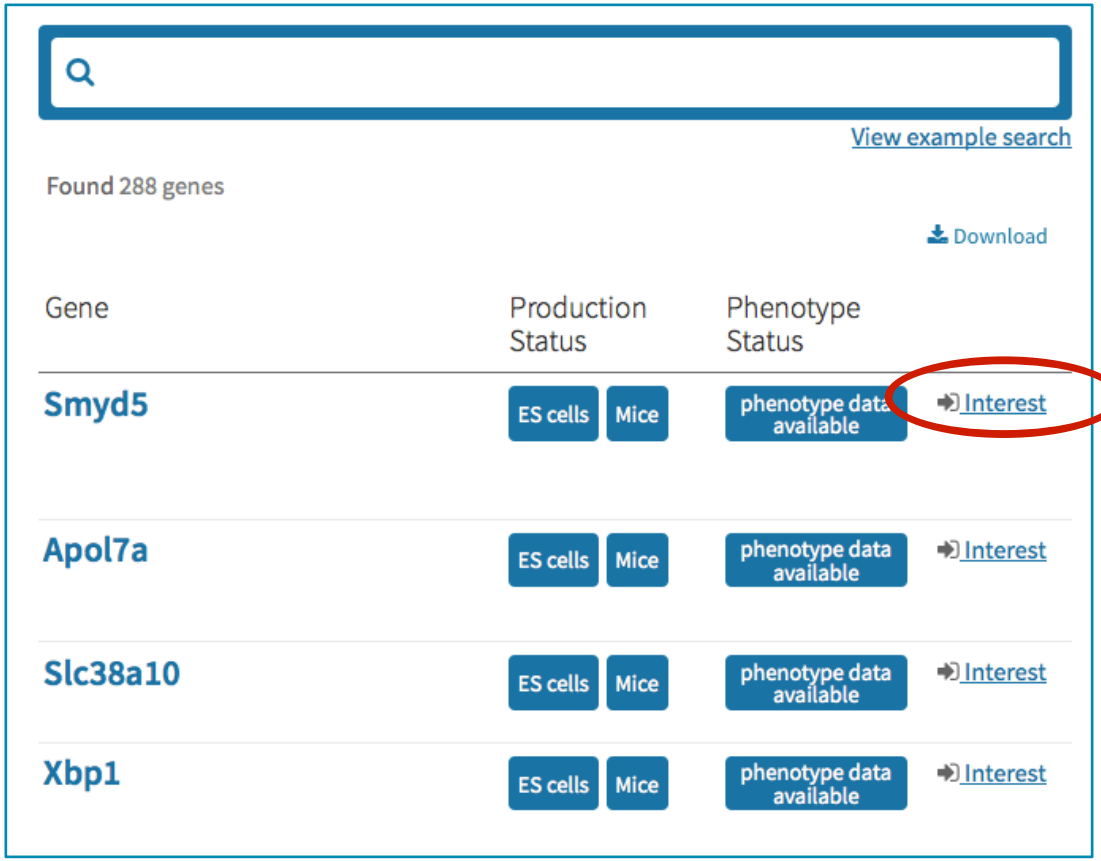
CATALOGUE

Follow genes you are interested in

IMPC will send an email when new data is published



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CONNECT

Example Searches

Sample queries for several fields are shown. Click the desired query to execute any of the samples. **Note that queries are focused on Relationships, leaving modifier terms to be applied as filters.**

Gene query examples

Akt2- looking for a specific gene, Akt2
*rik- looking for all Riken genes
hox*- looking for all hox genes

Phenotype query examples

abnormal skin morphology- looking for a specific phenotype
ear- find all ear related phenotypes

Procedure query Example

grip strength- looking for a specific procedure

Phrase query Example

zinc finger protein- looking for genes whose product is zinc finger protein

Search for a specific gene, type of gene, phenotype, procedure or phrase

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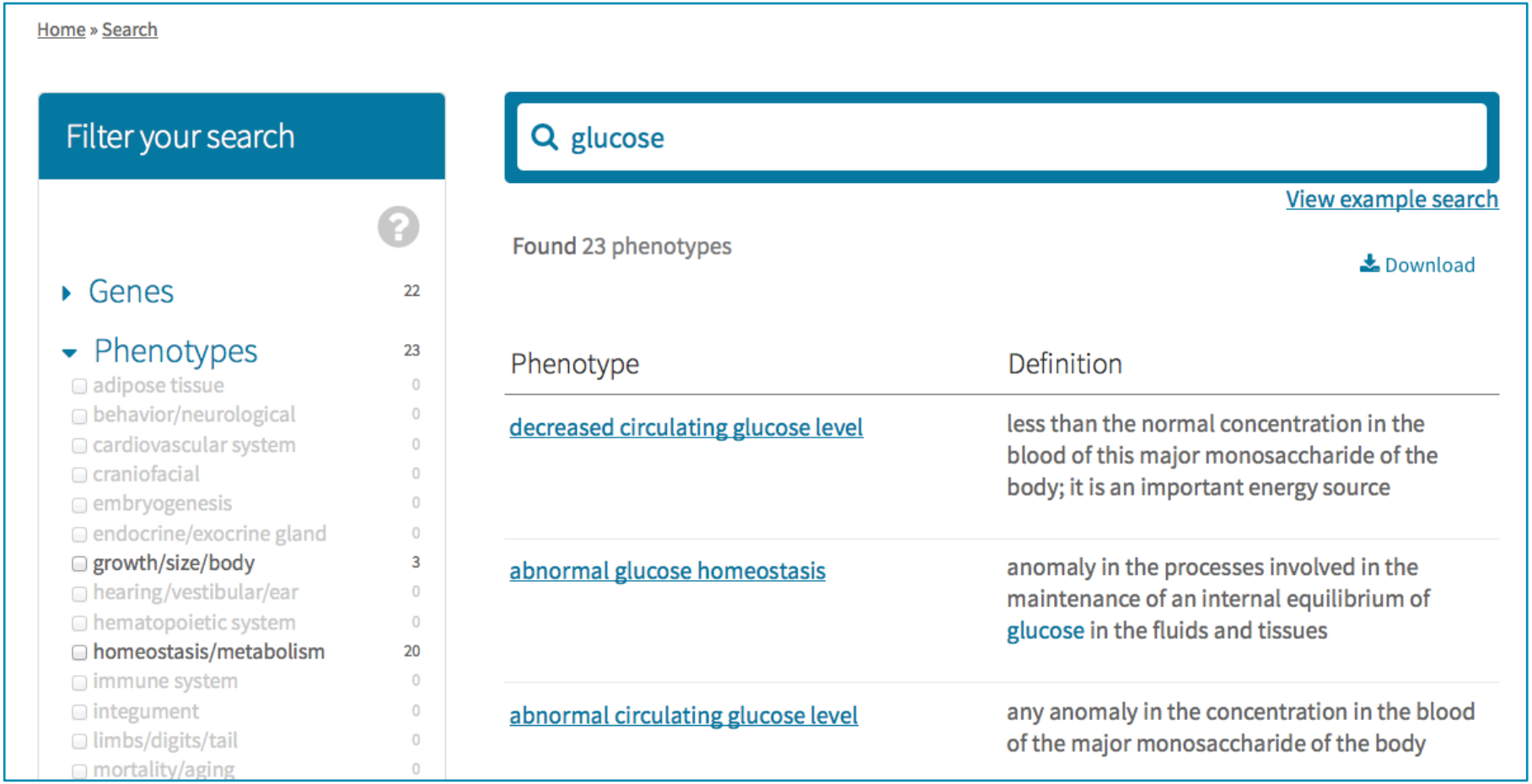
CONNECT- Search



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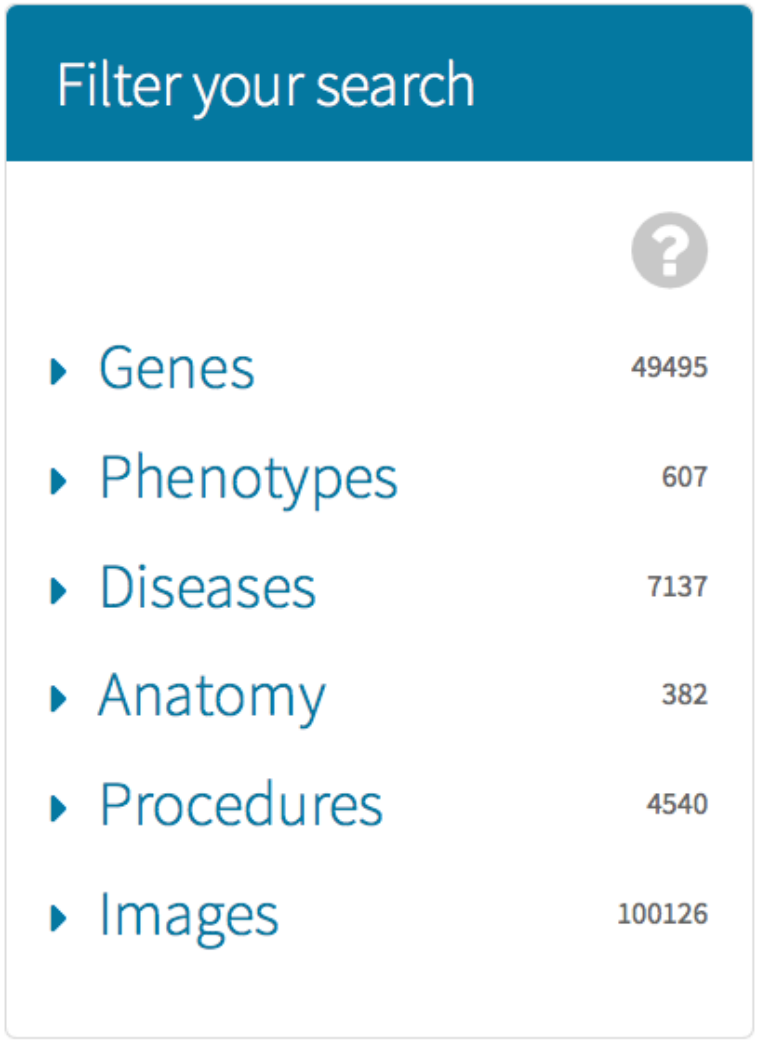
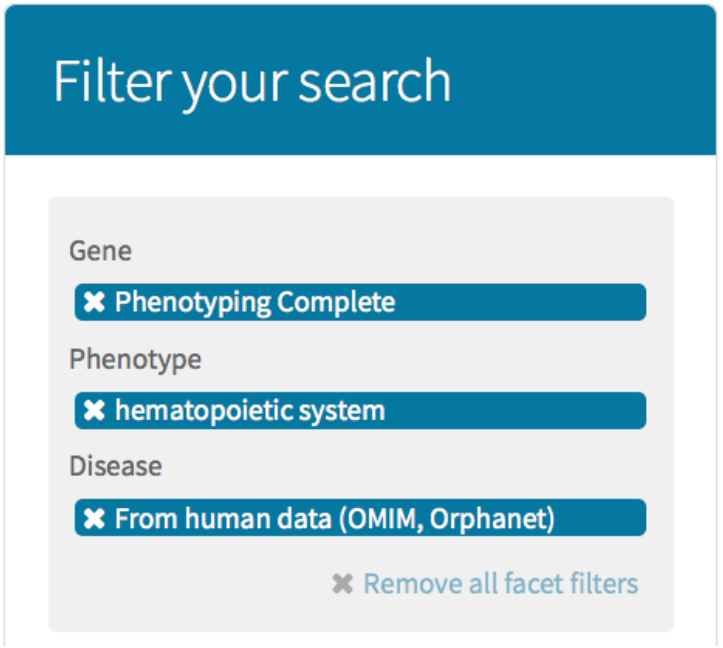
CONNECT- Filter



Filter by phenotype, source, or pathology.



Found 22 genes

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CONNECT- Gene page

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CONNECT- Gene to phenotype

Phenotype associations for Nbeal2

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

Both sexes have the following phenotypic abnormalities

- skeleton phenotype. Evidence from IMPC (3)
- hematopoietic system phenotype. Evidence from IMPC (5)

Following phenotypic abnormalities occured in **males** only

- immune system phenotype. Evidence from IMPC (1)

Phenotype overview

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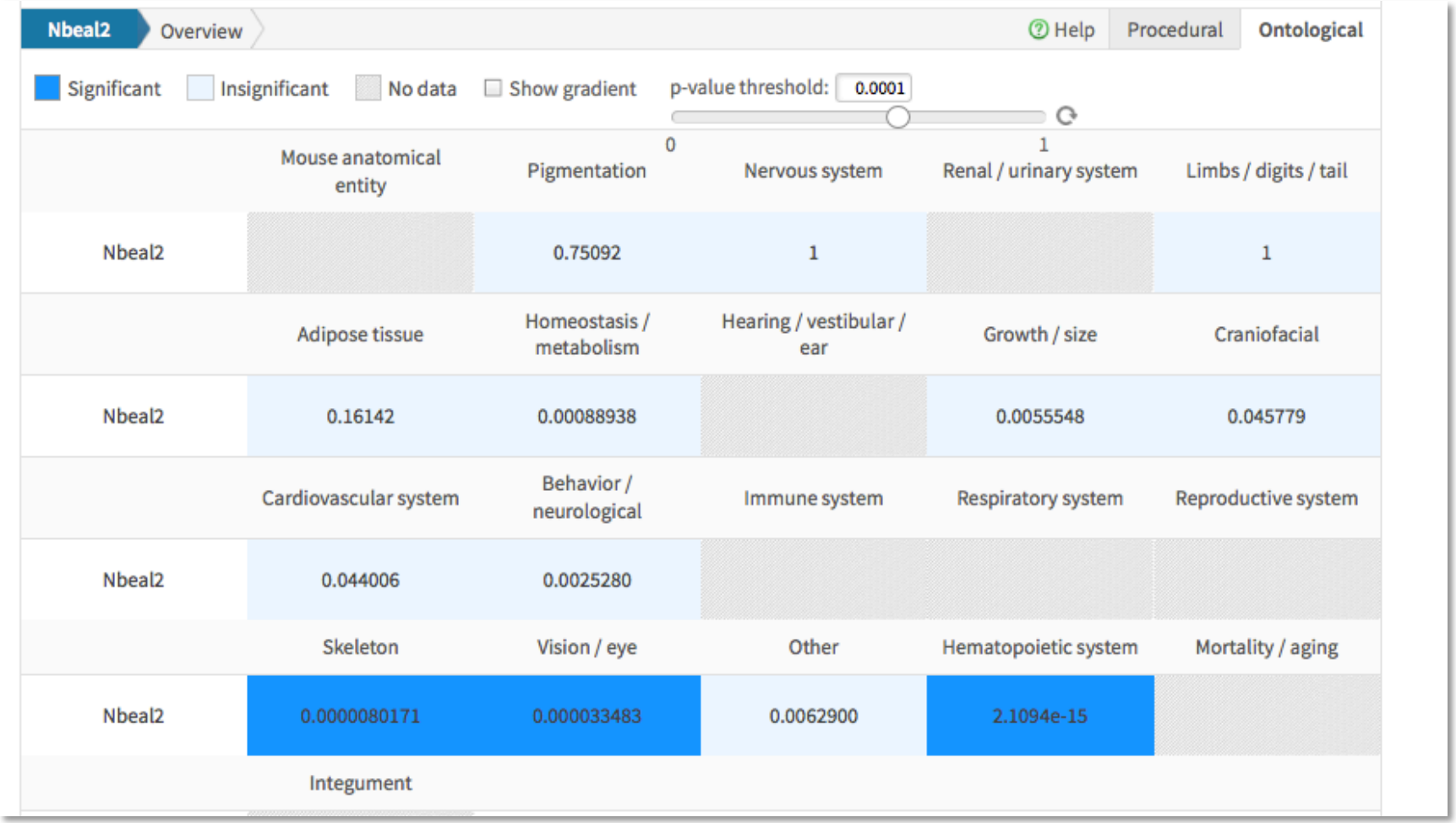
CONNECT- Gene to phenotype



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Phenotype heatmap

CONNECT- Gene to phenotype

Drill down further for detailed phenotype data

▸ Top level MP: All ▸ Source: All

Total number of results: 8

Phenotype	Allele	Zygosity	Sex	Procedure | Parameter	Phenotyping Center	Source	P Value	Graph
increased mean platelet volume	Nbeal2$^{tm1a(EUCOMM)Wtsi}$	homozygote	♀ ♂	Hematology | Mean platelet volume	WTSI	IMPC	0.0	
decreased platelet cell number	Nbeal2$^{tm1a(EUCOMM)Wtsi}$	homozygote	♀ ♂	Hematology | Platelet count	WTSI	IMPC	2.11E-15	
increased leukocyte cell number	Nbeal2$^{tm1a(EUCOMM)Wtsi}$	homozygote	♂	Hematology | White blood cell count	WTSI	IMPC	4.71E-8	
decreased bone mineral density	Nbeal2$^{tm1a(EUCOMM)Wtsi}$	homozygote	♀ ♂	Body Composition (DEXA lean/fat) | Bone Mineral Density (excluding skull)	WTSI	IMPC	4.18E-6	

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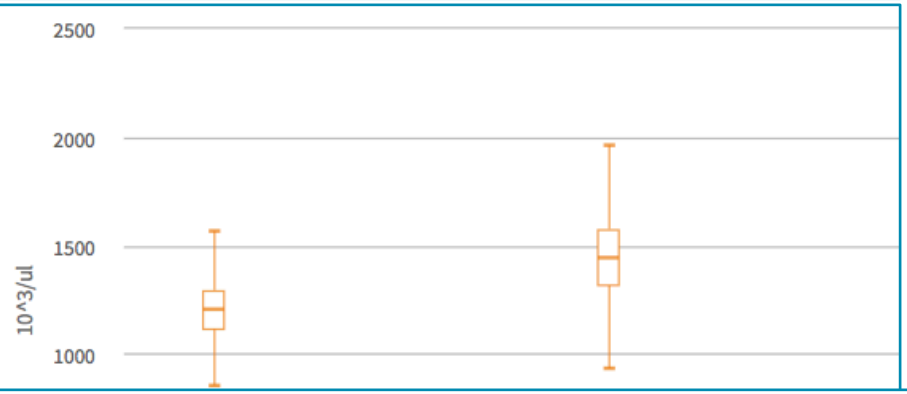
CONNECT- Display of data

Allele - Nbeal2$^{tm1a(EUCOMM)Wtsi}$



P Value	Classification
2.1094E-15	Different effect size, males greater

Sex	Sex*Genotype P Value	Effect size	Standard Error
Female	7.1758E-22	-534.08	± 54.458
Male	9.1166E-38	-737.84	± 55.404

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CONNECT- Data in near real time

Phenotype	Allele	Zygosity	Sex	Procedure | Parameter	Phenotyping Center	Source	P Value	Graph
abnormal bone structure	Dnase1l2$^{tm1.1(KOMP)Wtsi}$	heterozygote	♀ ♂	Body Composition (DEXA lean/fat) | Bone Area (BMC/BMD)	JAX	IMPC	0.0	
abnormal bone structure	Dnase1l2$^{tm1.1(KOMP)Wtsi}$	heterozygote	♀ ♂	Body Composition (DEXA lean/fat) | Bone Area (BMC/BMD)	UC Davis	IMPC	0.0	
decreased body length	Dnase1l2$^{tm1.1(KOMP)Wtsi}$	heterozygote	♀ ♂	Body Composition (DEXA lean/fat) | Body length	UC Davis	IMPC	0.0	
decreased body weight	Dnase1l2$^{tm1.1(KOMP)Wtsi}$	homozygote	♀ ♂	Grip Strength | Body weight	MRC Harwell	IMPC	0.0	

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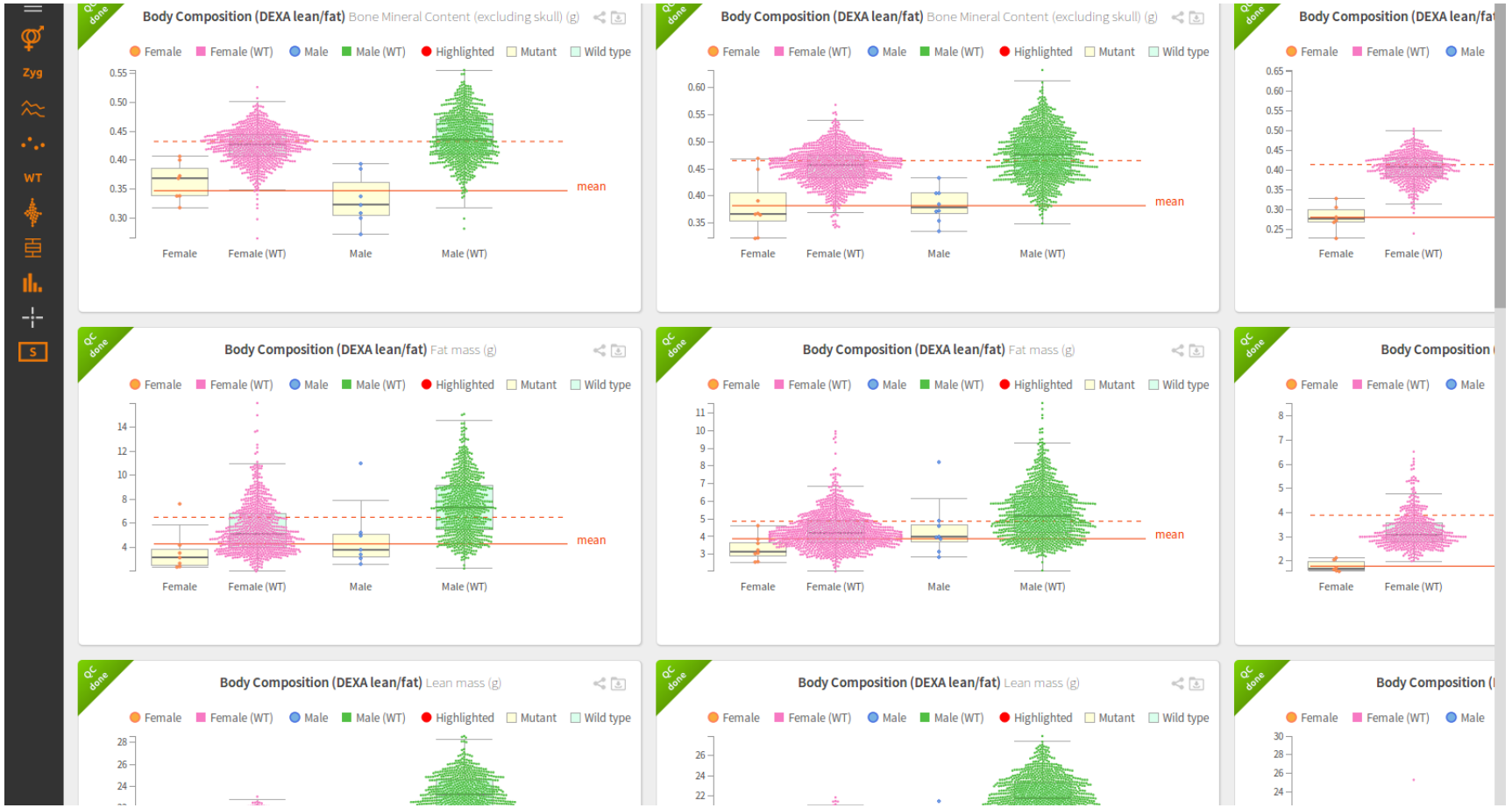
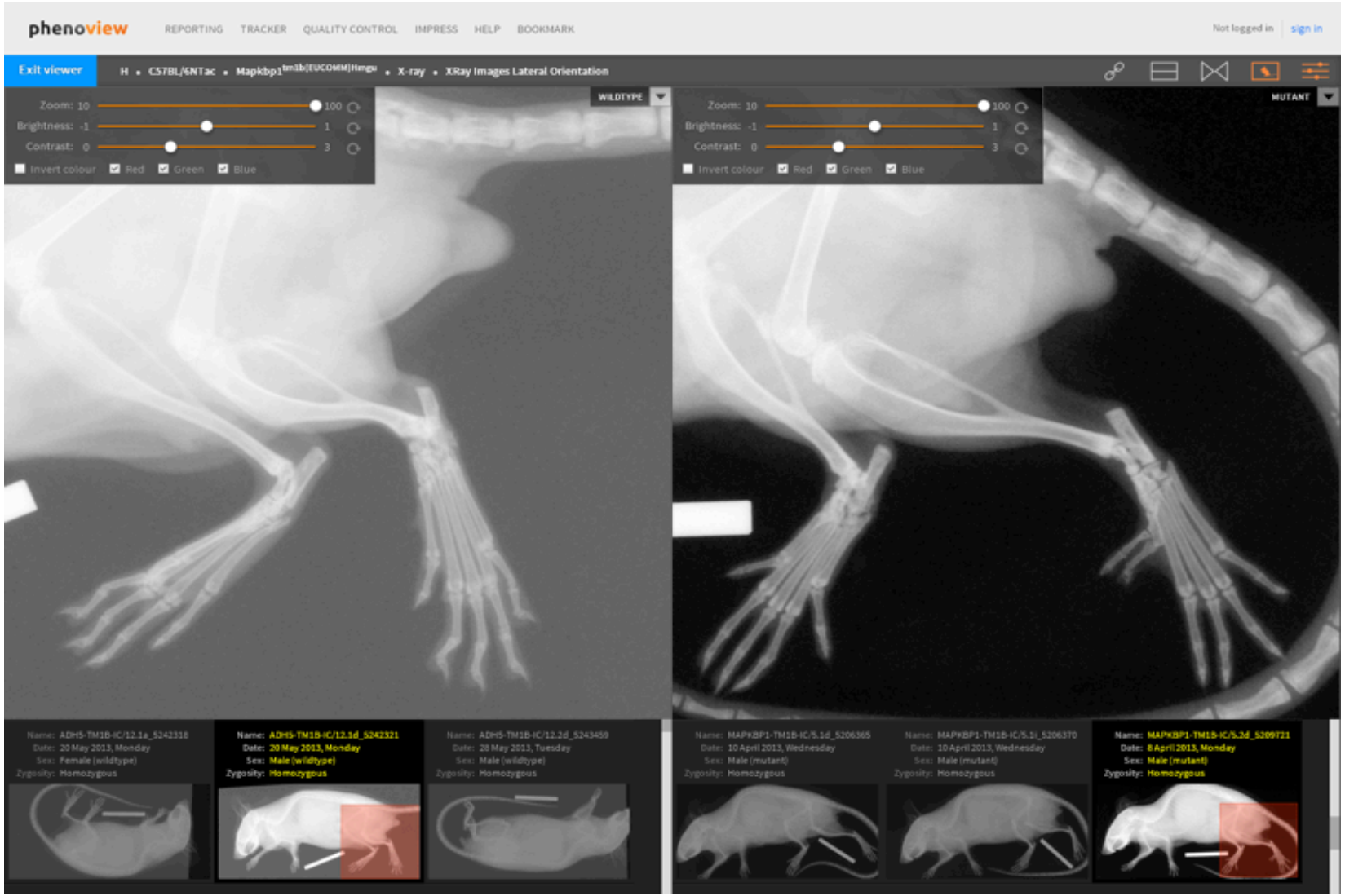
Pheno-DCC- Pre QC view



X-Ray Images Lateral



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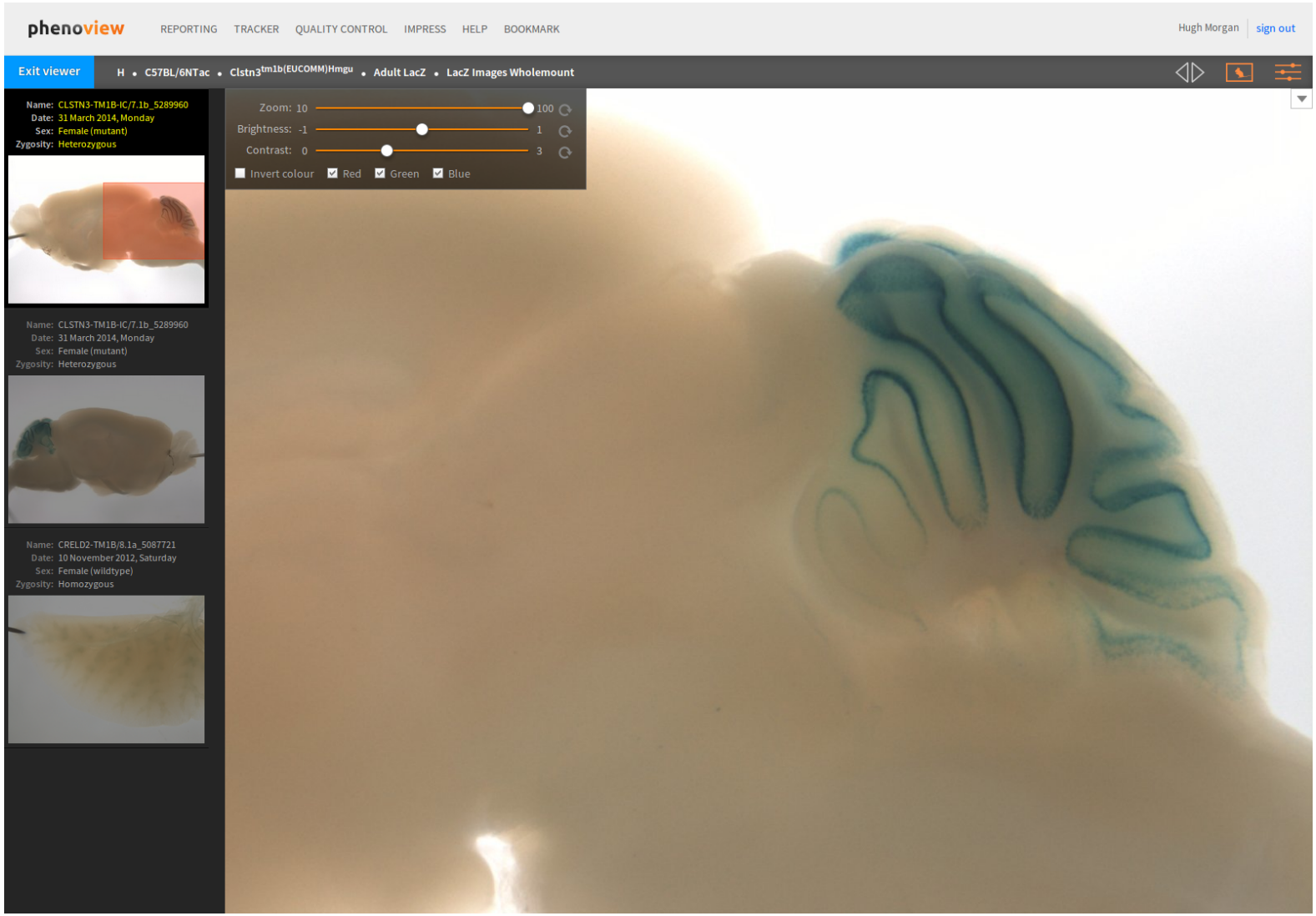
LacZ Images



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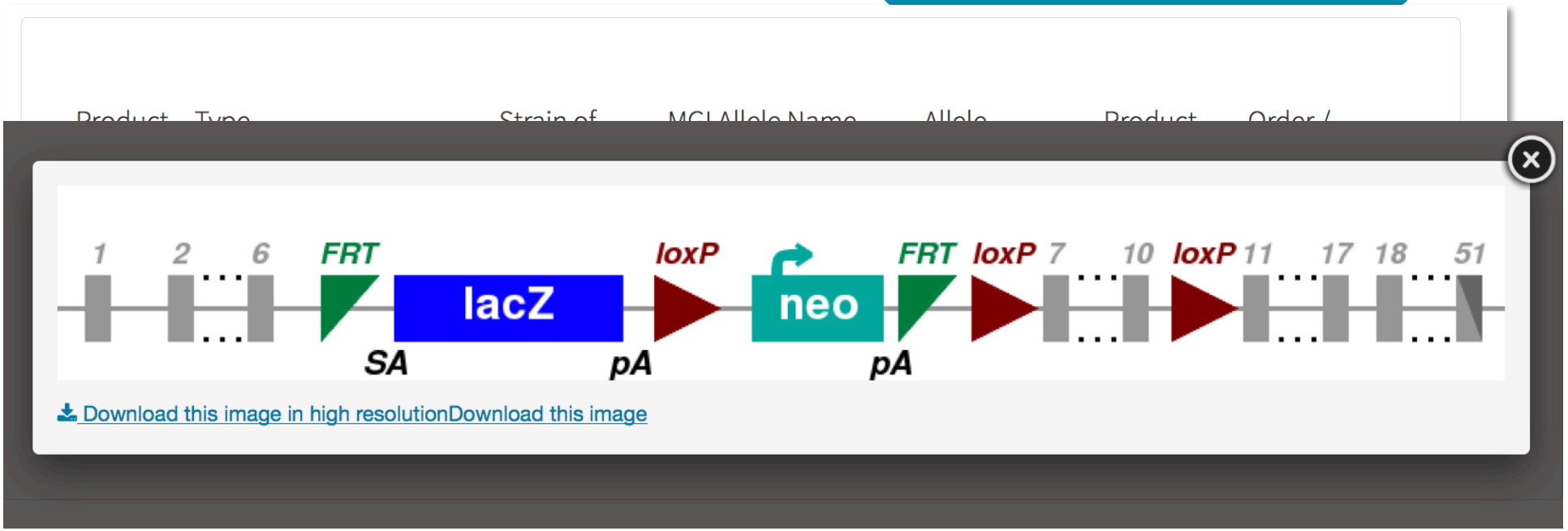
CONNECT- Find resources

Order Mice & ES Cells directly from website



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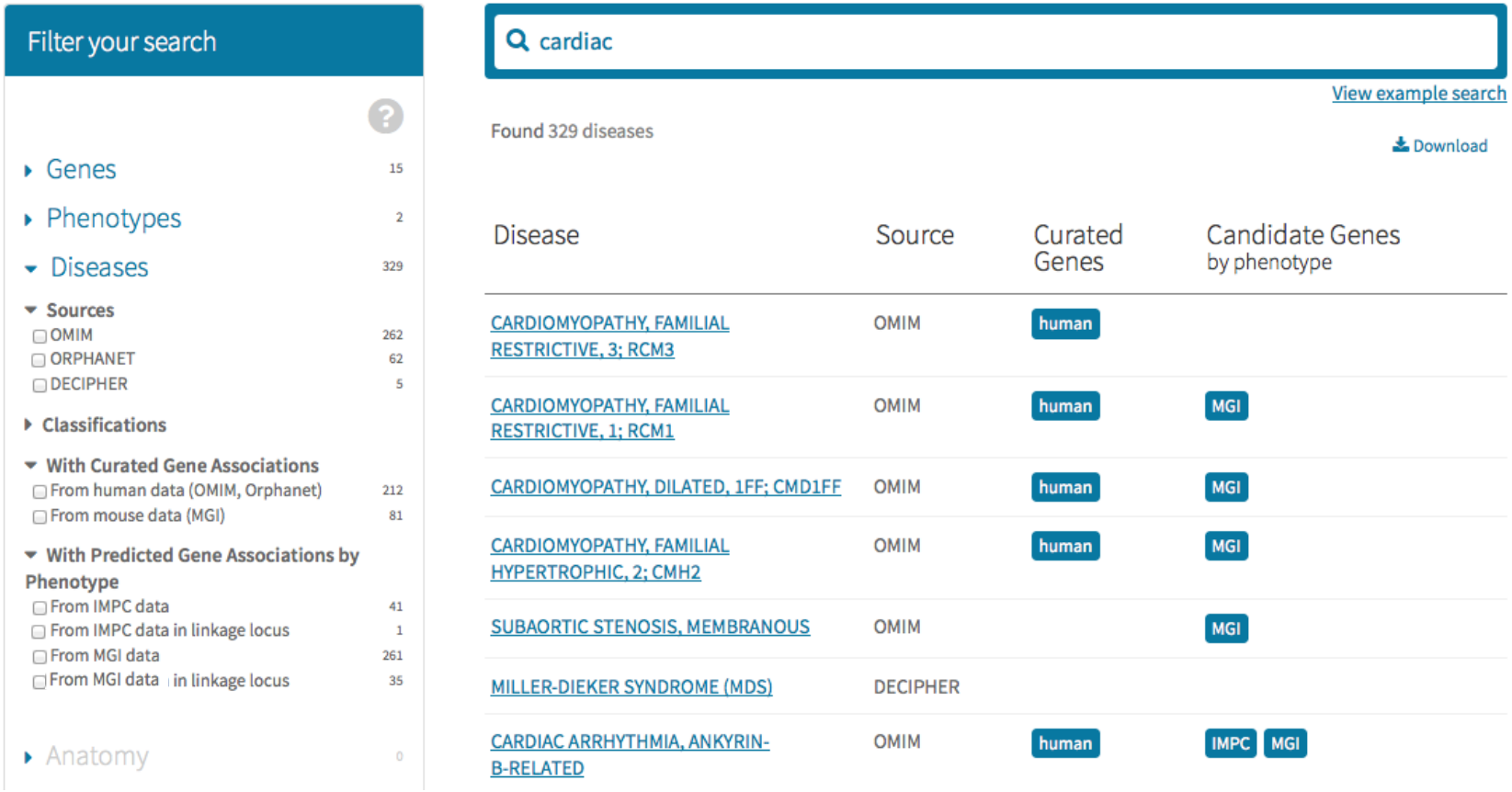
CONNECT- Phenotype Pages

Total number of results: 109

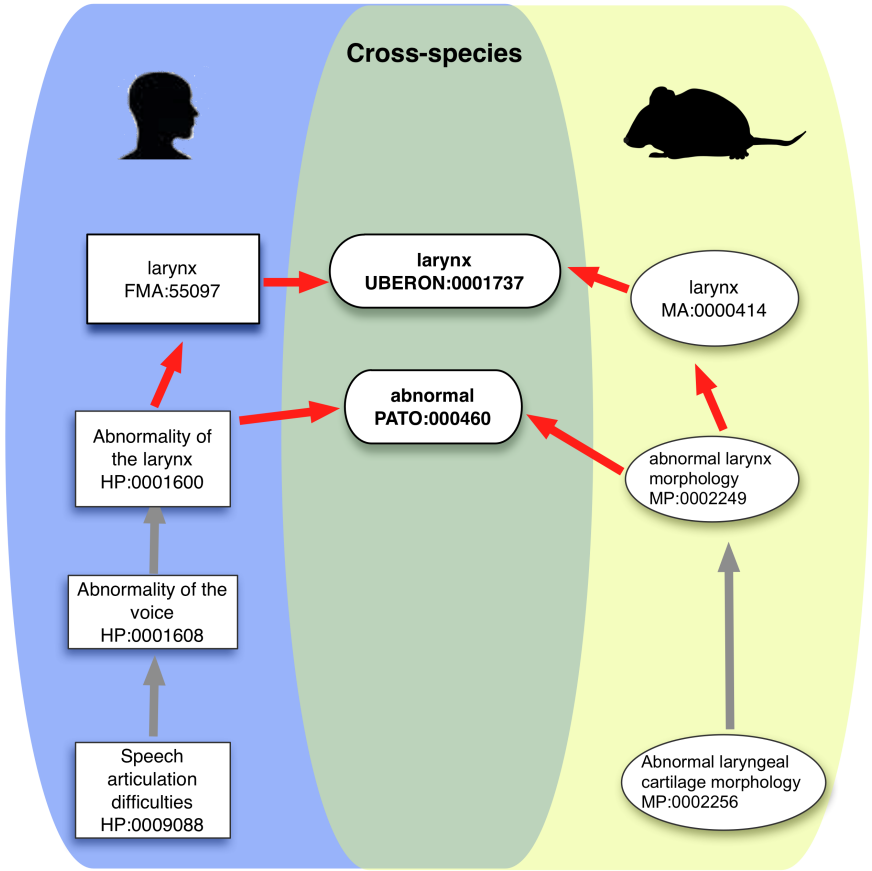
Gene / Allele	Zygosity	Sex	Phenotype	Procedure | Parameter	Phenotyping Center	Source	P Value	Graph
Ankrd13a Ankrd13a$^{Gt(RRH308)Byg}$	homozygote	♀ ♂	increased platelet cell number	Haematology | Platelets count	WTSI	EuroPhenome	0.0	
Ghrhr Ghrhr$^{tm1.1(KOMP)Vlcg}$	homozygote	♀ ♂	decreased platelet cell number	Hematology | Platelet count	JAX	IMPC	0.0	
Nbeal2 Nbeal2$^{tm1a(EUCOMM)Wtsi}$	homozygote	♀ ♂	increased mean platelet volume	Hematology | Mean platelet volume	WTSI	IMPC	0.0	
Knstrn Knstrn$^{tm1b(KOMP)Wtsi}$	homozygote	♀ ♂	decreased platelet cell number	Hematology | Platelet count	ICS	IMPC	1.11E-16	
Nbeal2 Nbeal2$^{tm1a(EUCOMM)Wtsi}$	homozygote	♀ ♂	decreased platelet cell number	Hematology | Platelet count	WTSI	IMPC	2.11E-15	
Fbxo7 Fbxo7$^{tm1a(EUCOMM)Wtsi}$	homozygote	♂	increased platelet cell number	Hematology | Platelet count	WTSI	IMPC	6.46E-12	
Crlf3 Crlf3$^{tm1a(KOMP)Wtsi}$	homozygote	♀ ♂	decreased platelet cell number	Haematology test | Platelets-count	WTSI	EuroPhenome	6.72E-12	

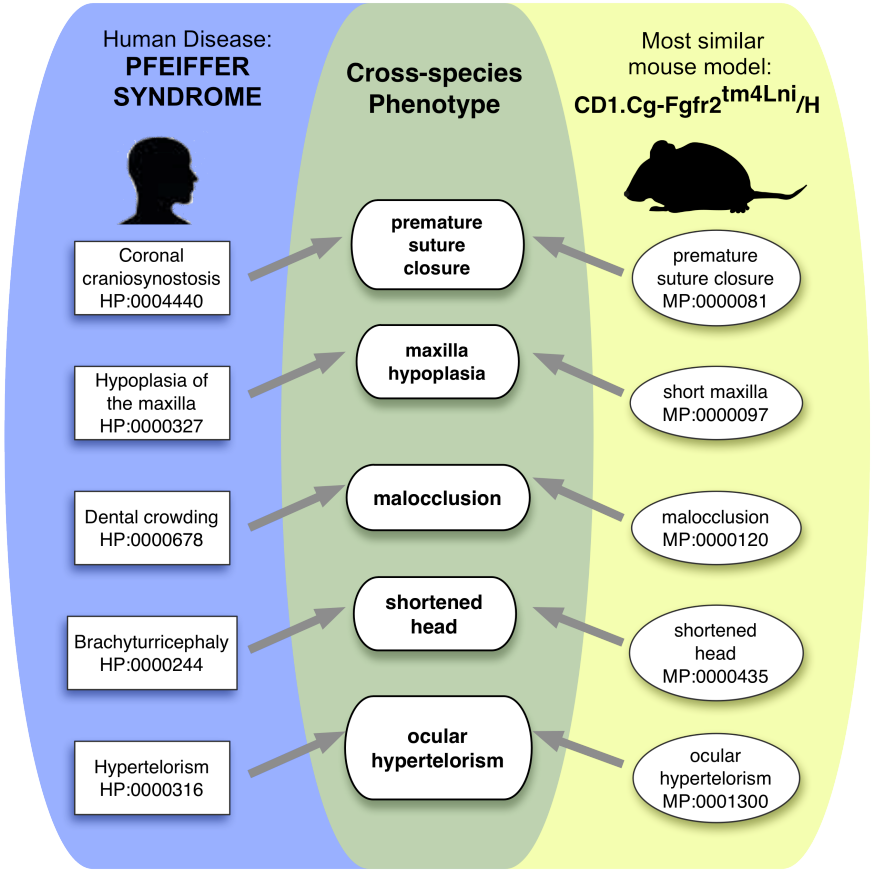
CONNECT- Disease



IMPC

CONNECT- Cross-species phenotype comparisons by semantic similarity





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CONNECT- Disease

Allele - Nbeal2$^{tm1a(EUCOMM)Wtsi}$

Potential Disease Models

Disease Name	Source	Disease Gene Ortholog	Syntenic Disease Locus	Mouse Literature Evidence (MGI)	MGI Mouse Phenotype Evidence (Phenodigm)	IMPC Mouse Phenotype Evidence (Phenodigm)	
Gray Platelet Syndrome	OMIM:139090	Yes	Yes	Yes	90.31	62.24	⊕
Gray Platelet Syndrome	ORPHANET:721	Yes			74.61	55.79	⊕
Platelet Signal Processing Defect	OMIM:173590				91.37	67.05	⊕

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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^{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

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		+

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CONNECT-Disease gene discovery

Disease: Malignant Hyperthermia, Susceptibility To, 3

Name	Malignant Hyperthermia, Susceptibility To, 3
Synonyms	MHS3
Locus	7q21-q22
Associated Human Genes	-
Mouse Orthologs	-
Source	OMIM:154276

OMIM:154276 Disease Phenotype Terms

- Hypertonia
- Fever
- Malignant hyperthermia
- Hyperkalemia
- Hyperphosphatemia
- Lactic acidosis
- Myopathy
- Elevated serum creatine phosphokinase
- Viral infection-induced rhabdomyolysis
- Exercise-induced rhabdomyolysis
- Anesthetic-induced rhabdomylosis
- Alcohol-induced rhabdomyolysis

Associated Mouse Models (PhenoDigm predicted)

77.67: Gpc2$^{tm1.1(KOMP)Vlcg}$/+ C57BL/6NCrl (Source:

- increased circulating phosphate level
- increased circulating chloride level
- decreased circulating chloride level
- increased circulating bilirubin level
- decreased blood urea nitrogen level
- increased circulating sodium level
- decreased circulating sodium level

57.12: Gpc2$^{tm1.1(KOMP)Vlcg}$/Gpc2$^{tm1.1(KOMP)Vlcg}$ C57

- decreased neutrophil cell number
- decreased body weight
- decreased basophil cell number
- decreased eosinophil cell number
- decreased circulating potassium level
- decreased mean platelet volume

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)
Gpr22		Yes			71.39
Gpc2		Yes			77.67

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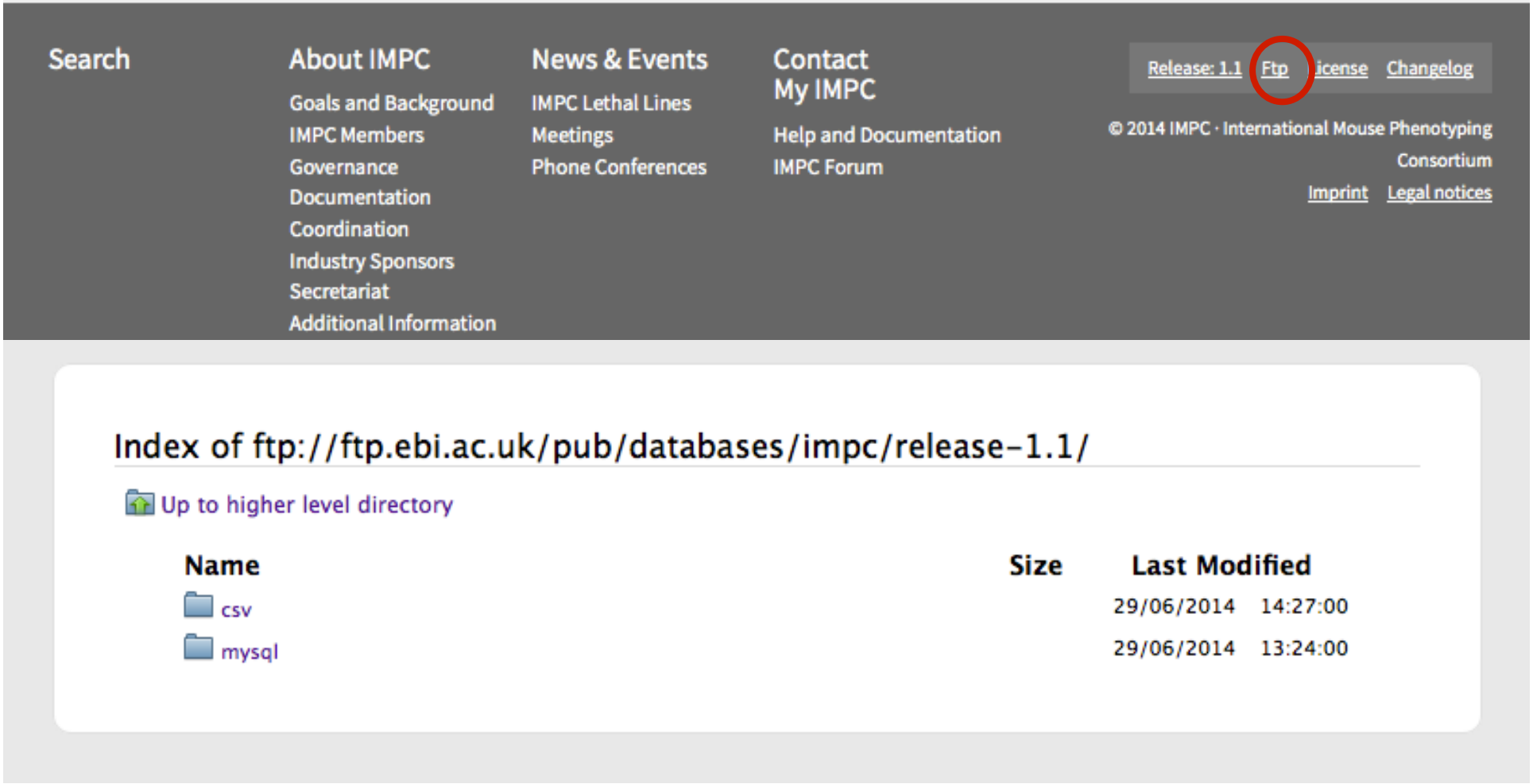
CONNECT-Data download



IMPC

CONNECT- RESTFUL API

https://github.com/mpi2/PhenotypeArchive/wiki/REST-APIs

The IMPC offers the following RESTful APIs for consuming data:

Genotype-Phenotype API

Please see the Genotype-Phenotype API documentation

Experimental observation API

Please see the Experimental observation API documentation

Statistical results API

Please see the Statistical results API documentation

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CONNECT- Gene-Phenotype API

Genotype associated phenotype calls

There are many ways to get information about the MP terms associated to the different KO genes. You can select data per:

- phenotyping center (UCD, Wellcome Trust Sanger Institute, JAX, etc.)
- phenotyping program (legacy MGP, EUMODIC, etc.)
- phenotyping resource (EuroPhenome, MGP, IMPC)
- phenotyping pipeline (EUMODIC1, EUMODIC2, MGP, IMPC adult, IMPC embryonic, etc.)
- phenotyping procedure or parameter
- allele name or MGI allele ID
- strain name or MGI strain ID
- gene symbol or MGI gene ID
- or a combination of all these fields

Retrieve all genotype-phenotype associations for a specific MP term

We will constrain the results by adding a condition to the **q** (query) parameter using the specific **mp_term_name** field. To retrieve genotype associated to "decreased total body fat amount", simply specify **q=mp_term_name:"decreased total body fat amount"**

```
curl \
    --basic  \
    -X GET \
    'http://www.ebi.ac.uk/mi/impc/solr/genotype-phenotype/select?q=mp_term_name:"d
```

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CONNECT- Experimental data & Stats API

- There are many ways to select and filter
- all data points for a parameter
- all data points for a gene for one experiment
- all data for a specific pipeline
- all stats results below a pvalue
- all stats results with sexual dimorphism

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Disseminate statistical results - API

API documentation: https://github.com/mpi2/PhenotypeArchive/wiki/REST-APIs


```
– <doc>
    <double name="intercept_estimate">5.752570152282715</double>
    <double name="group_2_residuals_normality_test">0.613398015499115</double>
    <double name="genotype_effect_stderr_estimate">0.3152709901332855</double>
    <double name="group_1_residuals_normality_test">0.39963701367378235</double>
    <int name="male_control_count">8</int>
    <bool name="variance_significant">true</bool>
    <str name="zygosity">homozygote</str>
    <str name="data_type">unidimensional</str>
    <int name="female_mutant_count">8</int>
    <str name="status">Success</str>
    <bool name="batch_significant">false</bool>
    <double name="sex_effect_stderr_estimate">0.3152709901332855</double>
    <double name="interaction_effect_p_value">0.12988199293613434</double>
    <str name="dependent_variable">ESLIM_009_001_703</str>
    <int name="control_biological_model_id">2</int>
    <str name="doc_id">ESLIM_009_001_703_1</str>
    <double name="sex_effect_p_value">0.07062750309705734</double>
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    <double name="genotype_effect_parameter_estimate">-0.6093779802322388</double>
    <double name="null_test_p_value">0.04863490164279938</double>
    <int name="db_id">1</int>
    <str name="metadata_group">b114ce3ef8bb816cc6b14ec12f0314c8</str>
    <str name="group_2_genotype">HEPD0528_4_A08</str>
```


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Lets Explore

- Try searching for your favourite gene
- Now try favorite phenotype
- Disease

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