

IMPC Web Portal and Data Dissemination

8 May 2014

INFRAFRONTIER / IMPC
workshop

Gautier Koscielny

MPI2 Consortium

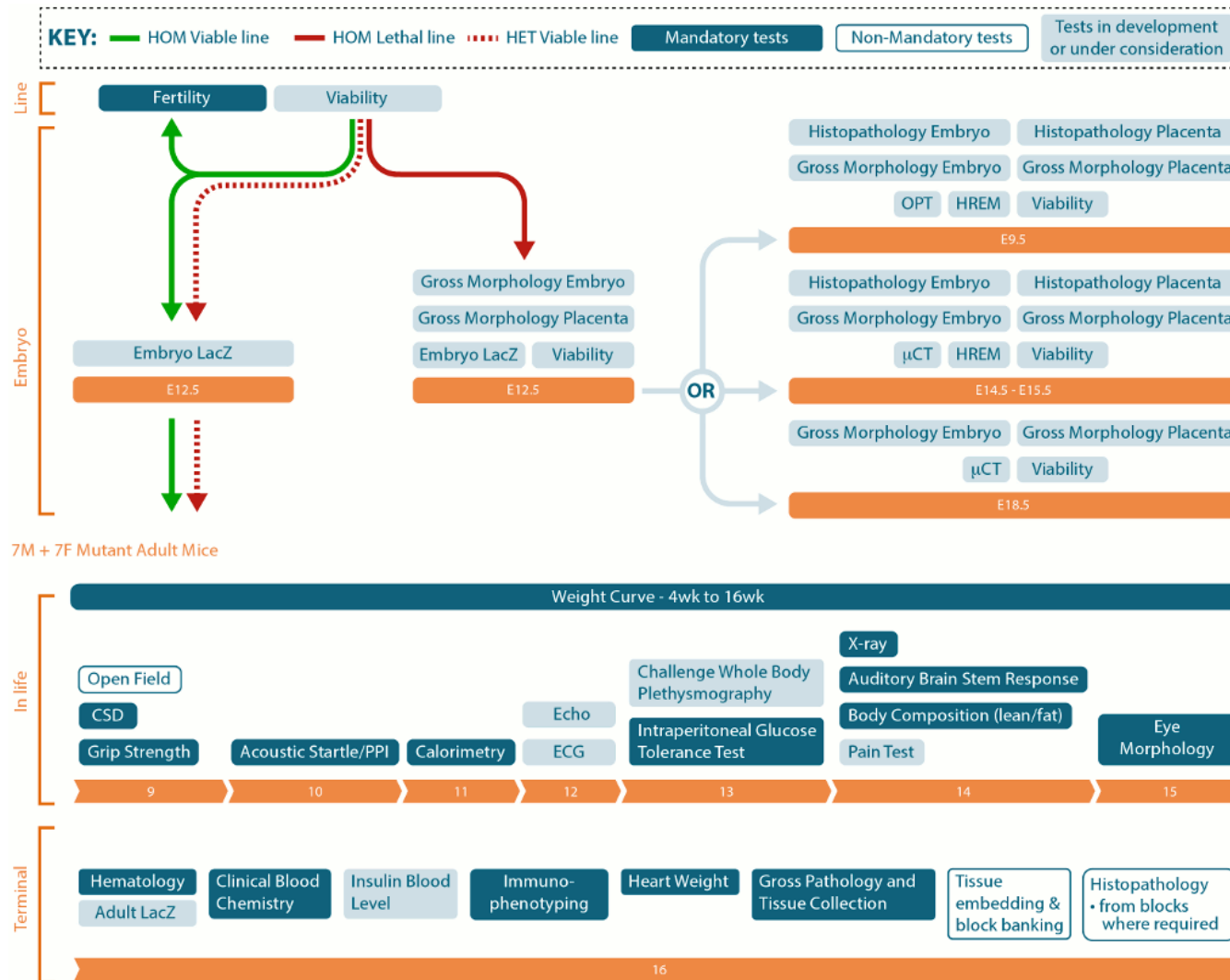
EMBL-EBI
www.mousephenotype.org



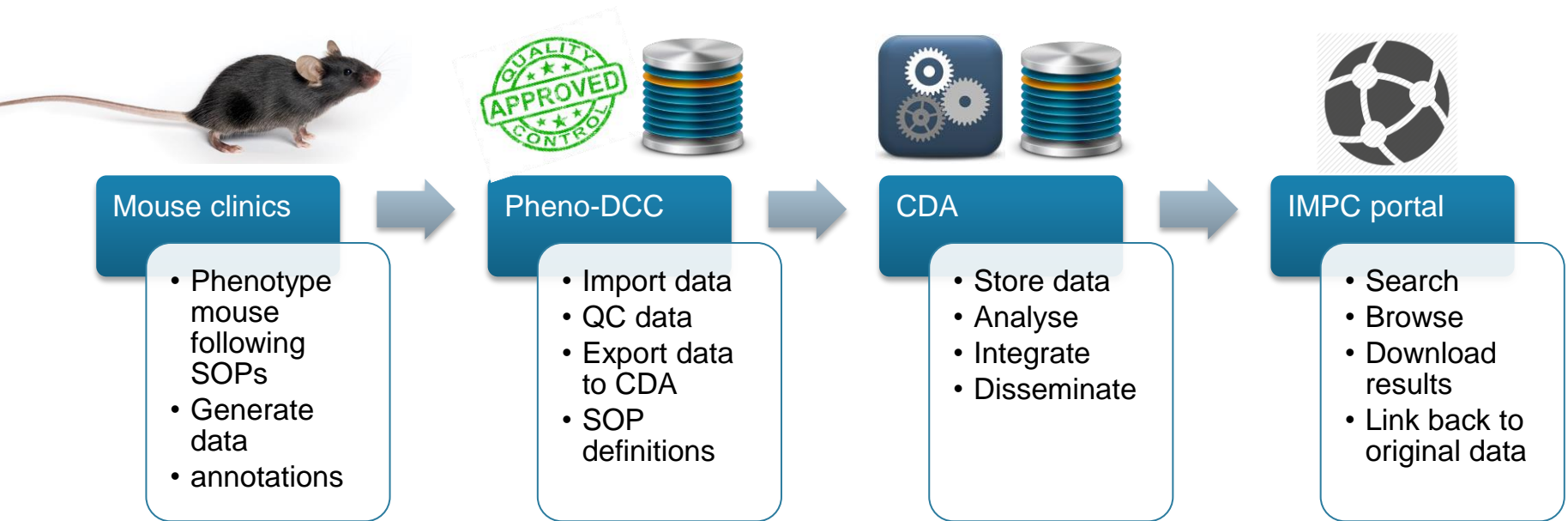
IMPC Goals

- Encyclopedia of mammalian gene function
- Create and phenotype over 20,000 mutant mouse lines
- Build collaborative "networks" for more focused phenotyping efforts
- Industry outreach
- **Provide a centralized data center and portal for free, unrestricted access to primary and secondary data**

IMPC Core Phenotyping Pipeline

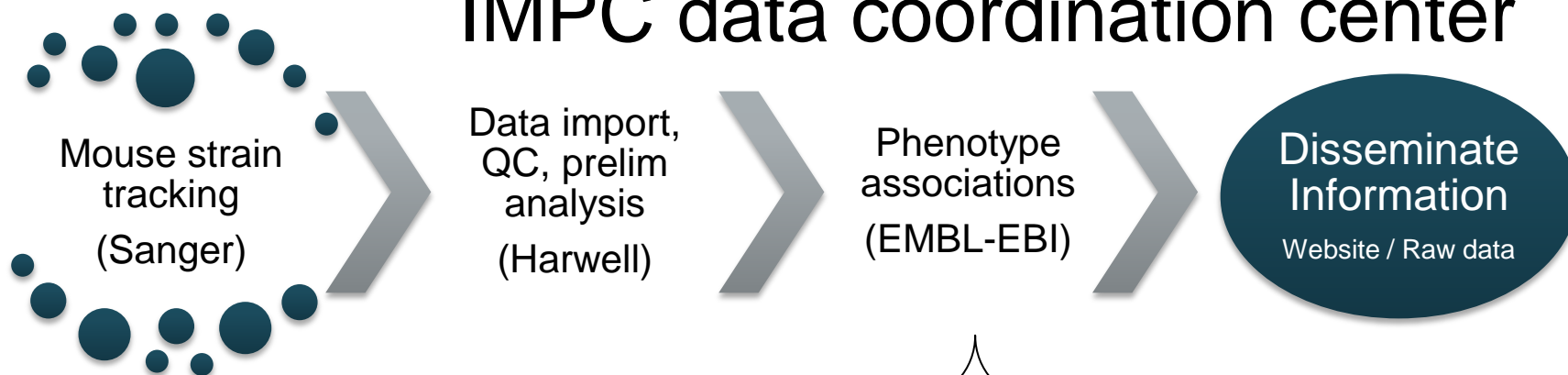


High throughput phenotyping workflow

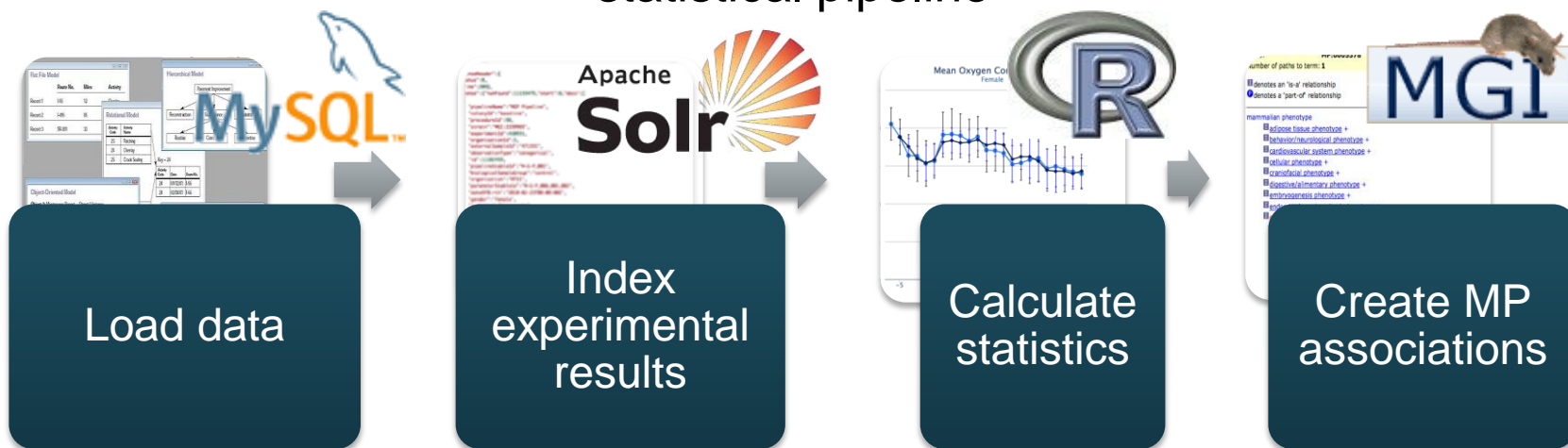


Standardised Statistical Pipeline

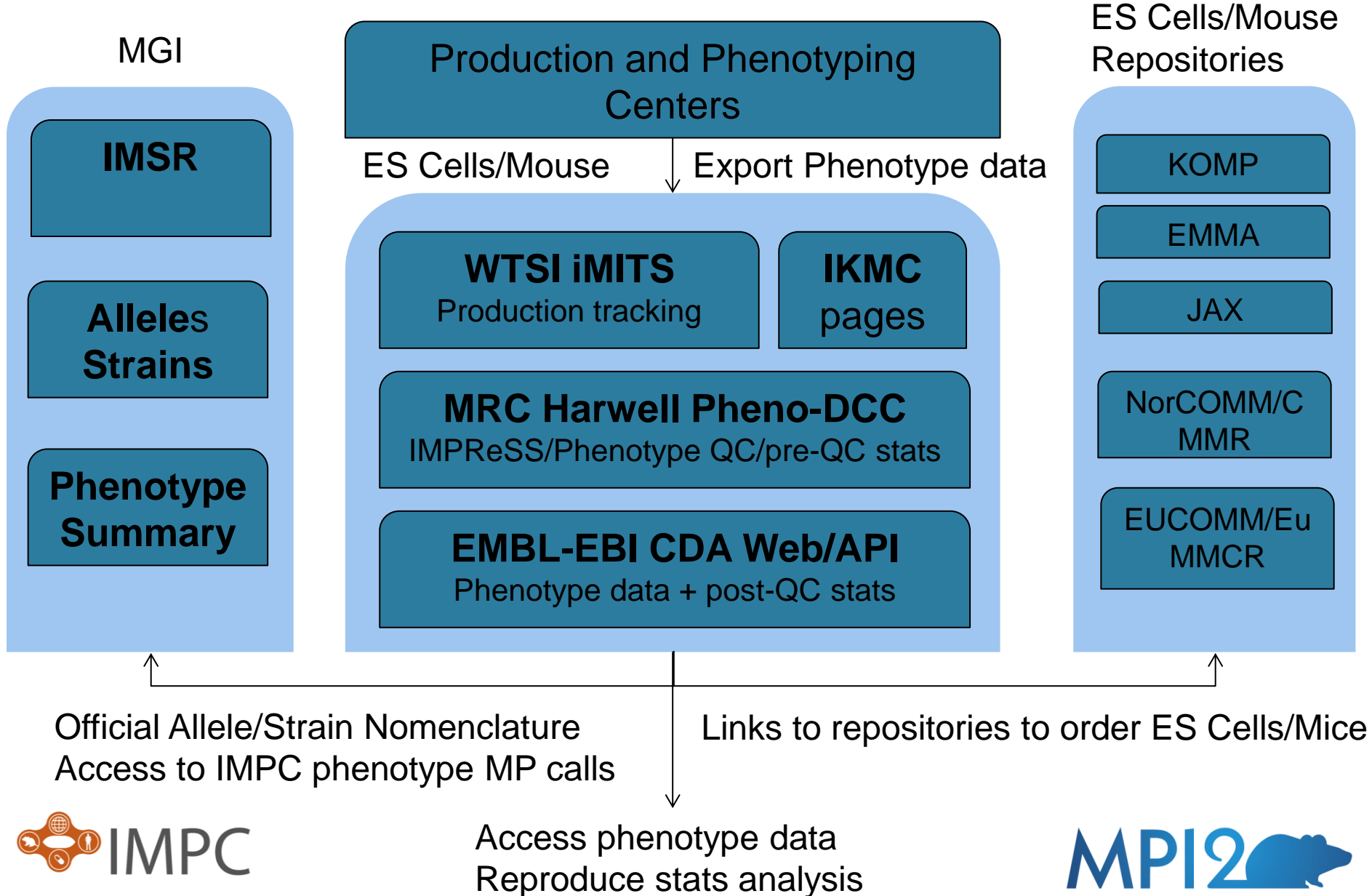
IMPC data coordination center



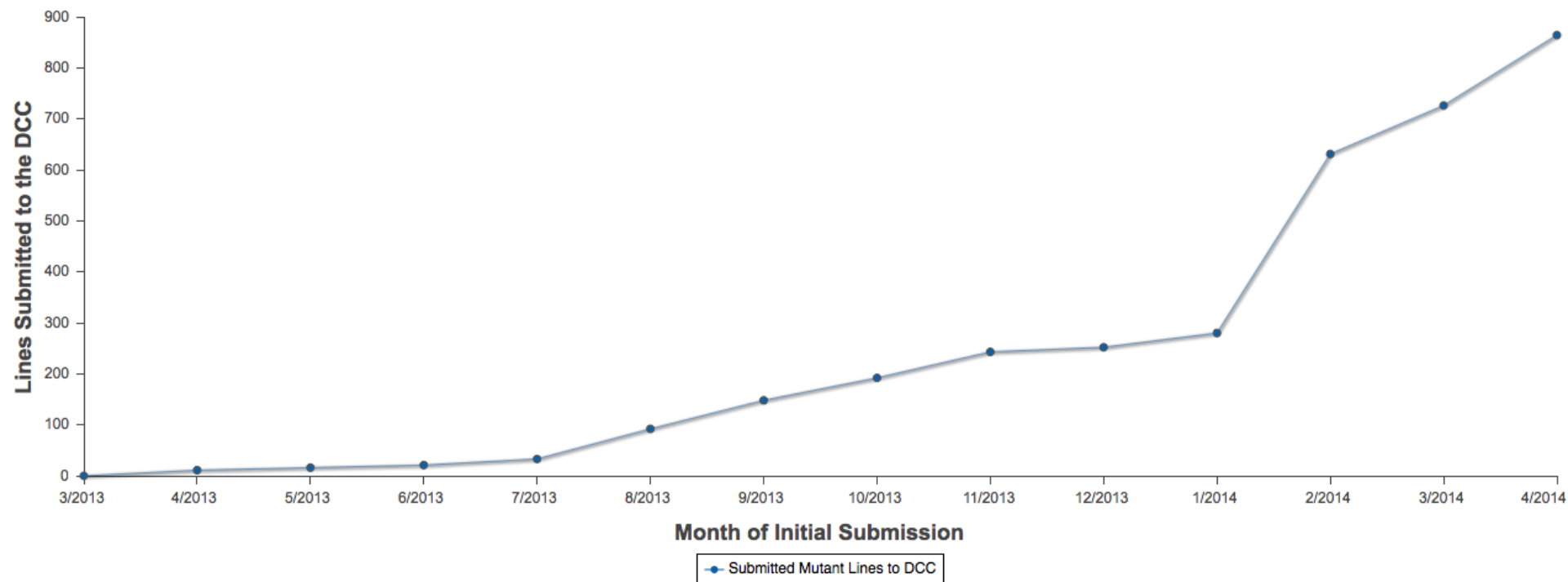
statistical pipeline



IMPC Ecosystem



846 Strains submitted to the Pheno-DCC



Phenotyping Centre	Project	Lines	Total Lines to date	Specimens	Total Specimens to date	Procedures	Total Procedures to date
Baylor College of Medicine	BaSH	0	35	0	930	0	8224
Helmholtz Zentrum Munchen	Helmholtz GMC	0	40	0	979	0	19577
MRC Harwell	BaSH	0	99	0	3628	0	77488
Institut Clinique de la Souris	Phenomin	0	42	0	1028	0	11753
The Jackson Laboratory	JAX	0	125	0	3079	0	60042
RIKEN Tsukuba Institute, BioResource Center	RIKEN BRC	0	5	0	177	0	3623
The Toronto Centre for Phenogenomics	DTCC	0	58	0	1354	0	17291
The Toronto Centre for Phenogenomics	NorCOMM2	0	40	0	651	0	12137
University of California, Davis	DTCC	0	101	0	3736	0	34967
Wellcome Trust Sanger Institute	BaSH	0	34	0	596	0	10014
Wellcome Trust Sanger Institute	MGP	0	267	0	5336	0	92020
IMPC	IMPC	0	846	0	21494	0	347136

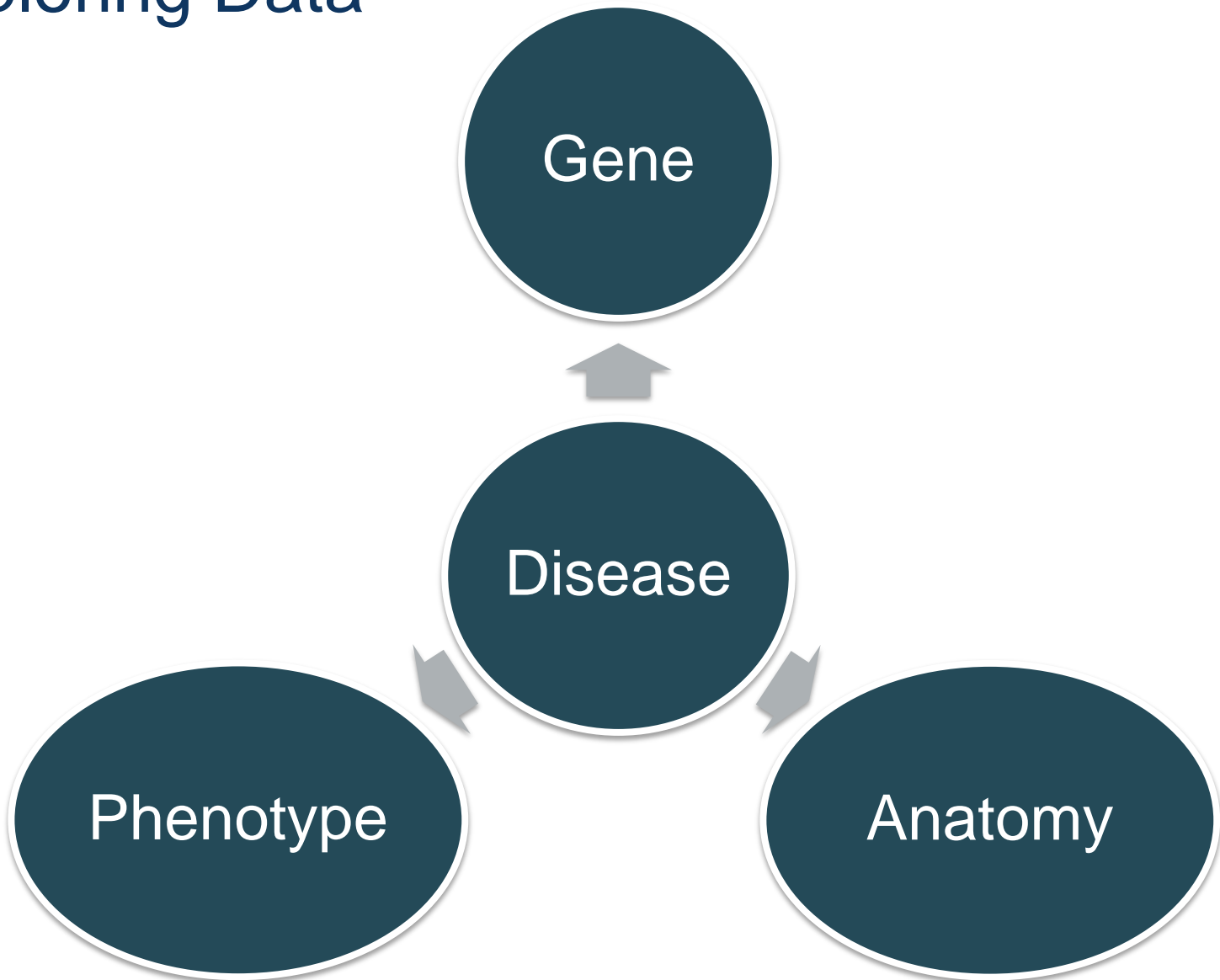
Data Available on the IMPC Portal

- Preliminary results from statistical analysis available for **846** submitted knockout strains (QC in progress)
- **293** knockout strains QC'ed with complete data:
 - > **12M** data points measuring parameters from standardised operating procedures defined in IMPReSS
 - Normal fertility and viability
- > **98,000** images from the Wellcome Trust Mouse Genetics Program


Summary of Results

- Of 293 knockout strains:
 - 176 have at least one MP annotation at p value ≤ 0.0001
 - 84 overlap with orthologous genes in OMIM
 - 30 overlap with Orphanet
 - 6 genes from NIH IDG list
 - Tnik, Scn3b, Gprc5b, Cdk14, Kcnv2, Pdk3, Pth2r
 - 24 with 1 or more MP annotations have no known molecular function or biological process (Gene Ontology)

Exploring Data



New Web Portal – beta.mousephenotype.org


 **IMPC**
International Mouse Phenotyping Consortium

[Login](#) [Register](#)

[SEARCH](#) [ABOUT IMPC](#) [NEWS & EVENTS](#) [CONTACT](#) [MY IMPC](#)

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](#)

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](#)



News and Events

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

March 5, 2014
[IMPC members give two presentations at the RE\(ACT\) Rare Disease Meeting in Basel, Switzerland](#)

February 11, 2014

Rare Disease Models

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

[Visit Disease Models](#)

KO strains are produced and phenotyped

Filter your search

Gene

phenotyping started

mice phenotyped at WTSI

Disease

OMIM

Remove all facet filters

?

Genes

60

IMPC Phenotyping Status

60

Started

0

Attempt Registered

0

IMPC Mouse Production Status

IMPC Mouse Production Center

IMPC Mouse Phenotyping Center

Subtype

Phenotypes

130

Diseases

85

Anatomy

0

Procedures

0

Images

0

Search

View example search

Found 60 genes

Download

Gene	Production Status	Phenotype Status
Ush1c	<div>ES cells</div> <div>Mice tm1a</div> <div>Mice tm1e</div>	<div>phenotype data available</div> <div>Interest</div>
Tmc6	<div>ES cells</div> <div>Mice tm1a</div>	<div>phenotype data available</div> <div>Interest</div>
Ift80	<div>ES cells</div> <div>Mice tm1a</div> <div>Mice tm2a</div> <div>Mice tm1e</div> <div>Mice tm2e</div>	<div>phenotype data available</div> <div>Interest</div>
Gldc	<div>ES cells</div> <div>Mice tm1a</div> <div>Mice tm1e</div>	<div>phenotype data available</div> <div>Interest</div>
Il10rb	<div>ES cells</div> <div>Mice tm1a</div> <div>Mice tm1e</div>	<div>phenotype data available</div> <div>Interest</div>

Filter your search

Gene

☒ mice produced

[Remove all facet filters](#)

Genes

3443

IMPC Phenotyping Status

- ☐ Started 728
- ☐ Attempt Registered 97

IMPC Mouse Production Status

- ☒ Mice Produced 3443
- ☐ Assigned for Mouse Production and Phenotyping 0
- ☐ ES Cells Produced 0
- ☐ Assigned for ES Cell Production 0
- ☐ Not Assigned for ES Cell Production 0

IMPC Mouse Production Center

- ☐ UCD 1056
- ☐ WTSI 426
- ☐ JAX 335
- ☐ Harwell 262
- ☐ BCM 157
- ☐ HMGU 130
- ☐ TCP 183
- ☐ ICS 45
- ☐ Monterotondo 53
- ☐ MARC 20
- ☐ RIKEN BRC 2
- ☐ CIPHE 0
- ☐ IMG 2
- ☐ SEAT 2
- ☐ EMBL-Rome 0

IMPC Mouse Phenotyping Center

- ☐ WTSI 362
- ☐ UCD 330
- ☐ JAX 349
- ☐ Harwell 114
- ☐ HMGU 110
- ☐ BCM 78
- ☐ TCP 74
- ☐ ICS 48
- ☐ MARC 20
- ☐ RIKEN BRC 20

Subtype

Phenotypes

217

Search

[View example search](#)

Found 3443 genes

[Download](#)

Gene	Production Status		Phenotype Status	
Dennd1c	ES cells	Mice tm1b	phenotype data available	Interest
	Mice tm1a	Mice tm1e		
Marc2	ES cells	Mice tm2a	phenotype data available	Interest
	Mice tm1a	Mice tm1e		
	ES cells	Mice tm1a		Interest
	Mice tm2a	Mice tm1e		
2310022B05Rik	ES cells	Mice tm1a		Interest
	Mice tm1e			
Hdac1	ES cells	Mice tm1b		Interest
	Mice tm1a	Mice tm1e		
Polr1e	ES cells	Mice tm1a		Interest
Myo5a	ES cells	Mice tm1e		Interest
	Mice tm2a	Mice tm2e		
Wbp2	ES cells	Mice tm2a		Interest
	Mice tm1a	Mice tm1e	Mice tm1	
Snip1	ES cells	Mice tm1a		Interest
	Mice tm1e	Mice tm1		

Production centers

Phenotyping centers


Register Interest

ES Cells and Mice on Gene Page

Gene: Ush1c

Name	Usher syndrome 1C
Synonyms	harmonin
MGI Id	MGI:1919338
Status	<div><div>ES cells</div><div>Mice tm1a</div><div>Mice tm1e</div><div>phenotype data available</div></div>
ENSEMBL Links	Gene View Location View Compare View
	Gene Browser ENU(9)

[Login to register interest](#)
[Order](#)



Click on the cart icon to
order ES cells and mice

Phenotype associations for Ush1c


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 (2)
- [adipose tissue phenotype](#). Evidence from IMPC (4)
- [behavior/neurological phenotype](#). Evidence from IMPC (4)
- [hearing/vestibular/ear phenotype](#). Evidence from IMPC (12)
- [homeostasis/metabolism phenotype](#). Evidence from IMPC (15)
- [hematopoietic system phenotype](#). Evidence from IMPC (2)
- [growth/size/body phenotype](#). Evidence from IMPC (14)



Order Mouse and ES Cells

Product	Type	Strain of Origin	MGI Allele Name	Allele Description	Product Details	Order
Mouse	Knockout First, Reporter-tagged insertion with	C57BL/6NTac	Aff3 ^{tm1a(EUCOMM)Wtsi}	 image  genbank file		 EMMA

Product	Type	Strain of Origin	MGI Allele Name	Allele Description	Product Details	Order
Mouse	Knockout First, Reporter-tagged insertion with conditional potential	C57BL/6N	Dnmt3a ^{tm1a(KOMP)Wtsi}	 image  genbank file		 KOMP
Mouse	Knockout First, Reporter-tagged insertion with conditional potential	C57BL/6NTac	Dnmt3a ^{tm1a(KOMP)Wtsi}	 image  genbank file		 EMMA
Mouse	Cre-excised deletion (tm1b)	C57BL/6NJ	Dnmt3a ^{tm1b(KOMP)Wtsi}	 image  genbank file		 JAX  KOMP

Product Details	Order
	 KOMP
	 KOMP
	 KOMP

s: [31203](#)

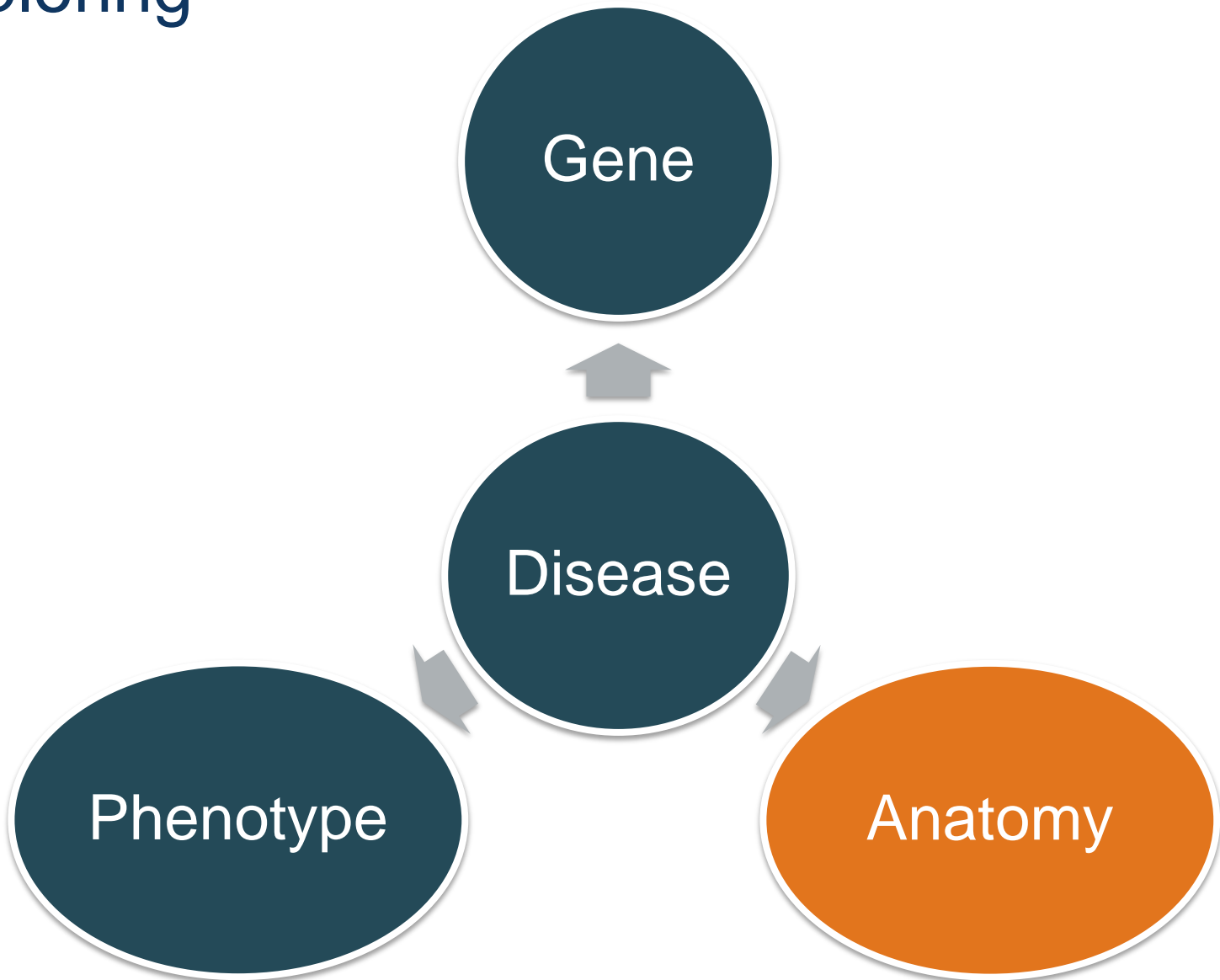
IKMC incorporation



- International knockout mouse consortium
- ES cells still being generated
- Find all relevant information at mousephenotype.org

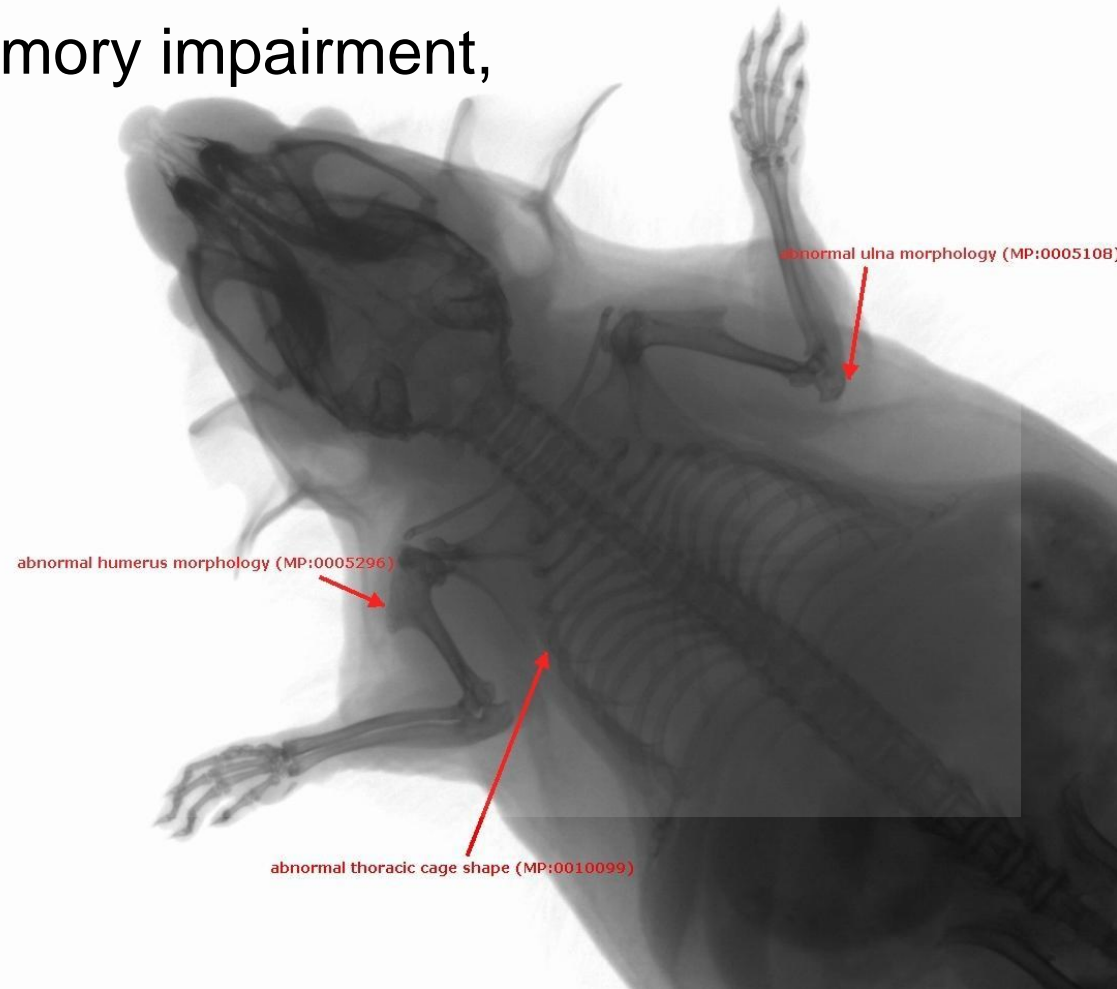


Exploring



Cenpj^{-/-} Phenotypes – Seckel Syndrome

- intrauterine dwarfism,
- microcephaly with memory impairment,
- ossification defects,
- ocular and
- skeletal abnormalities



Disruption of mouse Cenpj, a regulator of centriole biogenesis, phenocopies Seckel syndrome
Rebecca McEntyre et al. PLoS Genet. 2012;8(11)

Retrieving information on Cenpj

Filter your search

▶ Genes 1

▶ Phenotypes 64

▶ Diseases 3

▶ Anatomy 0

▶ Procedures 0

▼ Images 230

▼ Phenotype

- ☐ cardiovascular system 6
- ☐ craniofacial 74
- ☐ endocrine/exocrine gland 1
- ☐ hearing/vestibular/ear 74
- ☐ integument 1
- ☐ limbs/digits/tail 16
- ☐ pigmentation 1
- ☐ renal/urinary system 1
- ☐ reproductive system 6
- ☐ skeleton 7
- ☐ vision/eye 6

▼ Anatomy

- ☐ extremity 113
- ☐ integumental system 1

Q "cenpj"

[View example search](#)

Show Image View

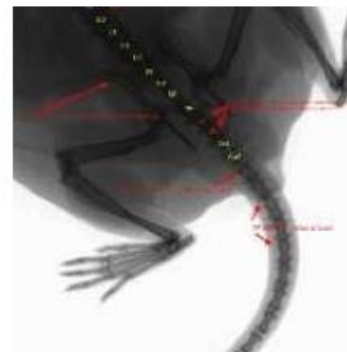
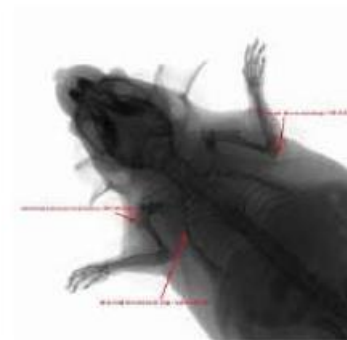
Annotation View: groups images by annotation

Found 27 annotations / [230 images](#)

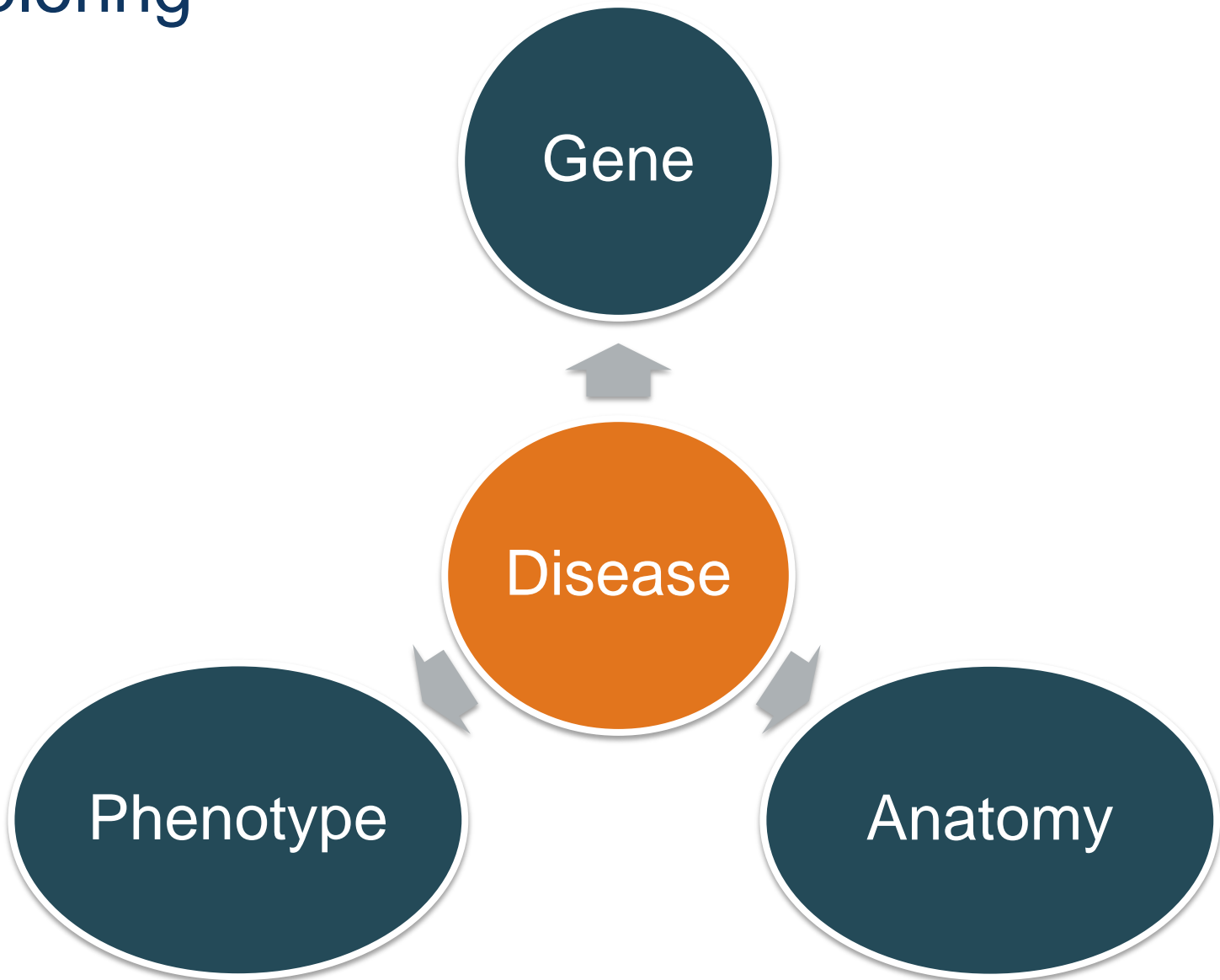
[Download](#)

Name	Example Images
------	----------------

Gene: [Cenpj](#) ([229 images](#))



Exploring



Gene to Diseases

Filter your search

Gene

✕ mice phenotyped at WTSI

✕ phenotyping started

✕ [Remove all facet filters](#)

?

▼ Genes283

▶ IMPC Phenotyping Status

▶ IMPC Mouse Production Status

▶ IMPC Mouse Production Center

▼ IMPC Mouse Phenotyping Center

☒ WTSI283

☐ UCD0

Gene: Nbeal2

Name

neurobeachin-like 2

MGI Id

[MGI:2448554](#)

Status

Mice
tm1a

Mice
tm1e

phenotype data available

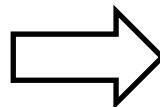
ENSEMBL Links

[Gene View](#)

[Location View](#)

[Compara View](#)

[Gene Browser](#)



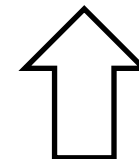
▼ Diseases110

▼ Sources

☐ OMIM84

☐ ORPHANET26

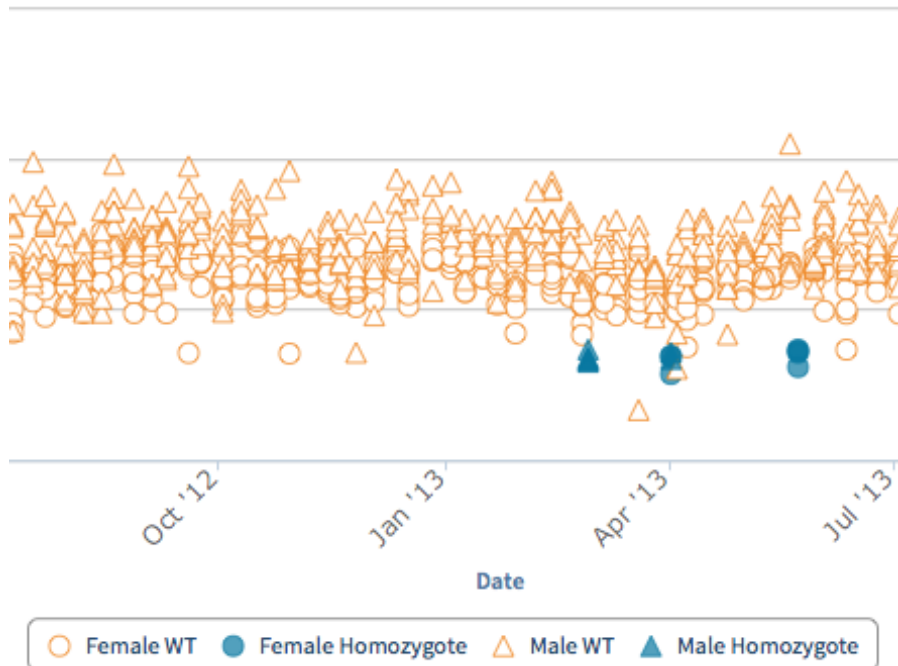
☐ DECIPHER0



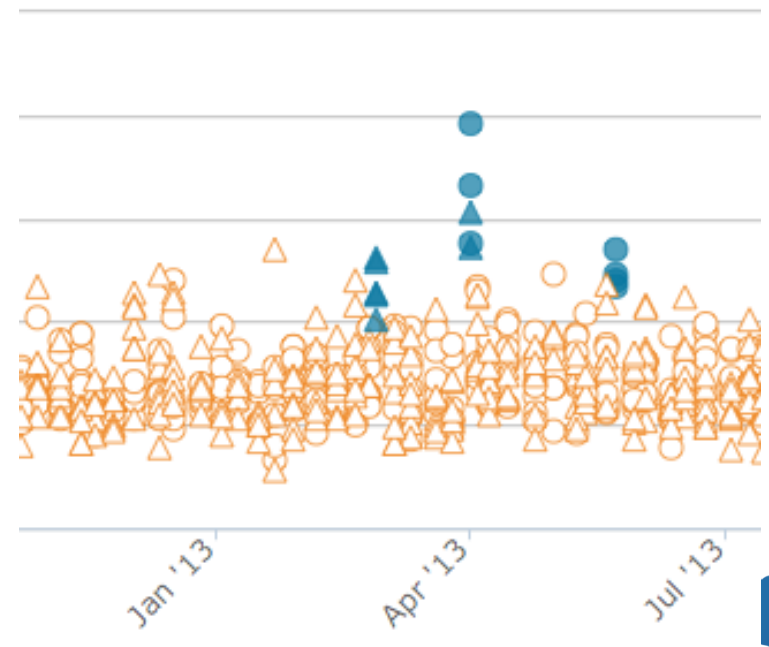
OMIM#139090- Grey Platelet Syndrome

The gray platelet syndrome is a rare inherited disorder characterized by mild to moderate bleeding tendency, **moderate thrombocytopenia**, and a marked decrease or absence of platelet alpha-granules and of the proteins contained in alpha-granules. **The platelets are enlarged, but not giant**, and have a gray appearance on light microscopy

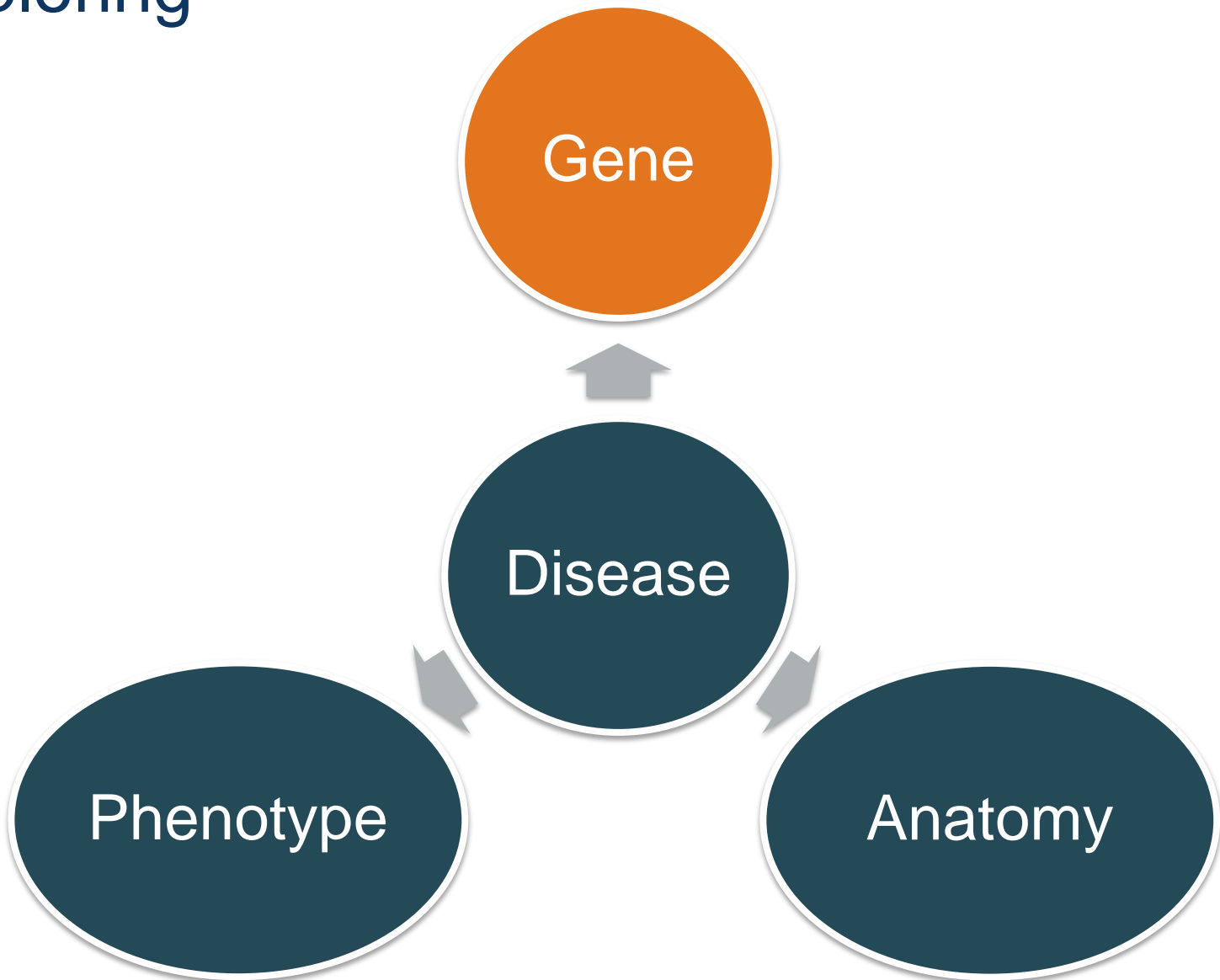
Platelet count
IMPC_HEM_008_001



Mean platelet volume
IMPC_HEM_019_001



Exploring



From Gene to Phenotype (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 occurred in males only






- [immune system phenotype](#). Evidence from IMPC (1)

Filter this table

► Top level MP: All

► Analysis: All

Total number of results: 8

Phenotype	Allele	Zygosity	Sex	Procedure / Parameter	Phenotyping Center	Analysis	Graph
decreased bone mineral content	Nbeal2^{tm1a(EUCOMM)Wtsi}	homozygote	♂	Body Composition (DEXA lean/fat) / Bone Mineral Content (excluding skull)	WTSI	IMPC	
decreased bone mineral density	Nbeal2^{tm1a(EUCOMM)Wtsi}	homozygote	♀ ♂	Body Composition (DEXA lean/fat) / Bone Mineral Density (excluding skull)	WTSI	IMPC	
decreased platelet cell number	Nbeal2^{tm1a(EUCOMM)Wtsi}	homozygote	♀ ♂	Hematology / Platelet count	WTSI	IMPC	
increased leukocyte cell number	Nbeal2^{tm1a(EUCOMM)Wtsi}	homozygote	♂	Hematology / White blood cell count	WTSI	IMPC	
increased mean platelet volume	Nbeal2^{tm1a(EUCOMM)Wtsi}	homozygote	♀ ♂	Hematology / Mean platelet volume	WTSI	IMPC	



- High level summary
- Sex specific differences
- Filter the results

- Graph data

Summarising Statistical Analysis (pre-QC)

#	Descriptor	Gene symbol	Background strain	Allele	Phenotyping center
1	Nbeal2	Nbeal2	C57BL/6N	Nbeal2 ^{tm1a(EUCOMM)Wtsi}	Wellcome Trust Sanger Institute
<div> <div>Nbeal2</div> <div>Overview</div> <div>Help</div> <div>Procedural</div> <div>Ontological</div> </div>					
<div> <div>Significant</div> <div>Insignificant</div> <div>No data</div> <div>Show gradient</div> <div>p-value threshold: 0.0001</div> </div>					
<div> <div>Nervous system</div> <div>Renal / urinary system</div> <div>Limbs / digits / tail</div> <div>Adipose tissue</div> <div>Homeostasis / metabolism</div> </div>					
Nbeal2				0.15556	0.00034816
<div> <div>Hearing / vestibular / ear</div> <div>Growth / size</div> <div>Cardiovascular system</div> <div>Behavior / neurological</div> <div>Immune system</div> </div>					
Nbeal2		0.0060883	0.046582	0.0025744	
<div> <div>Respiratory system</div> <div>Reproductive system</div> <div>Skeleton</div> <div>Vision / eye</div> <div>Other</div> </div>					
Nbeal2			0.0000041777		
<div> <div>Hematopoietic system</div> <div>Mortality / aging</div> <div>Integument</div> </div>					
Nbeal2		0.0000			
<div> <div>Procedure</div> <div>Parameter</div> <div>MP annotation</div> <div>p-value</div> </div>					
Hematology		Mean platelet volume	↑ Increased mean platelet volume	0.0000	

Summarising Statistical Analysis (pre-QC)

#	Descriptor	Gene symbol
1	Ush1c	Ush1c
Ush1c Overview		
Significant Insignificant No data		
Nervous system		
Ush1c		
Hearing / vestibular /		
Ush1c		
Respiratory system		
Ush1c		
Hematopoietic system		
Ush1c		0.000099934

Graph D

phenoview

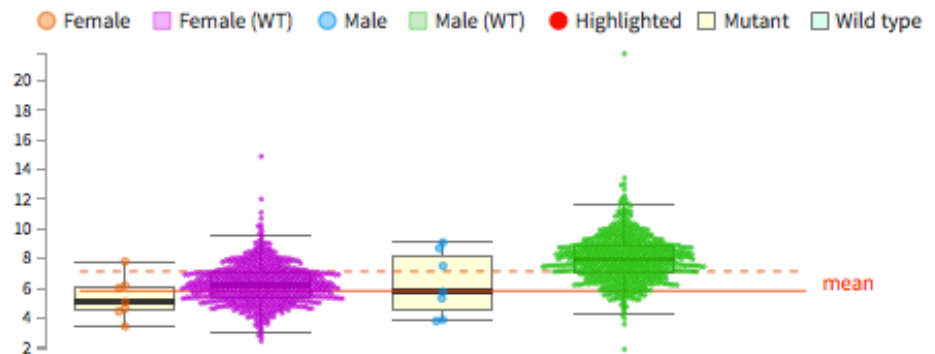
Reporting • Tracker • Quality Control • IMPReSS • Help • Bookmark



Wtsi • MGI:1919338 • C57BL/6N • Ush1c^{tm1a(KOMP)Wtsi}

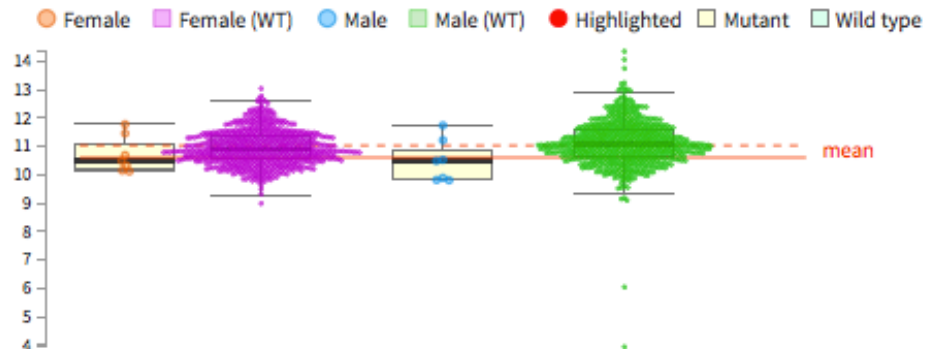
QC pending

Hematology White blood cell count (10³/ul)

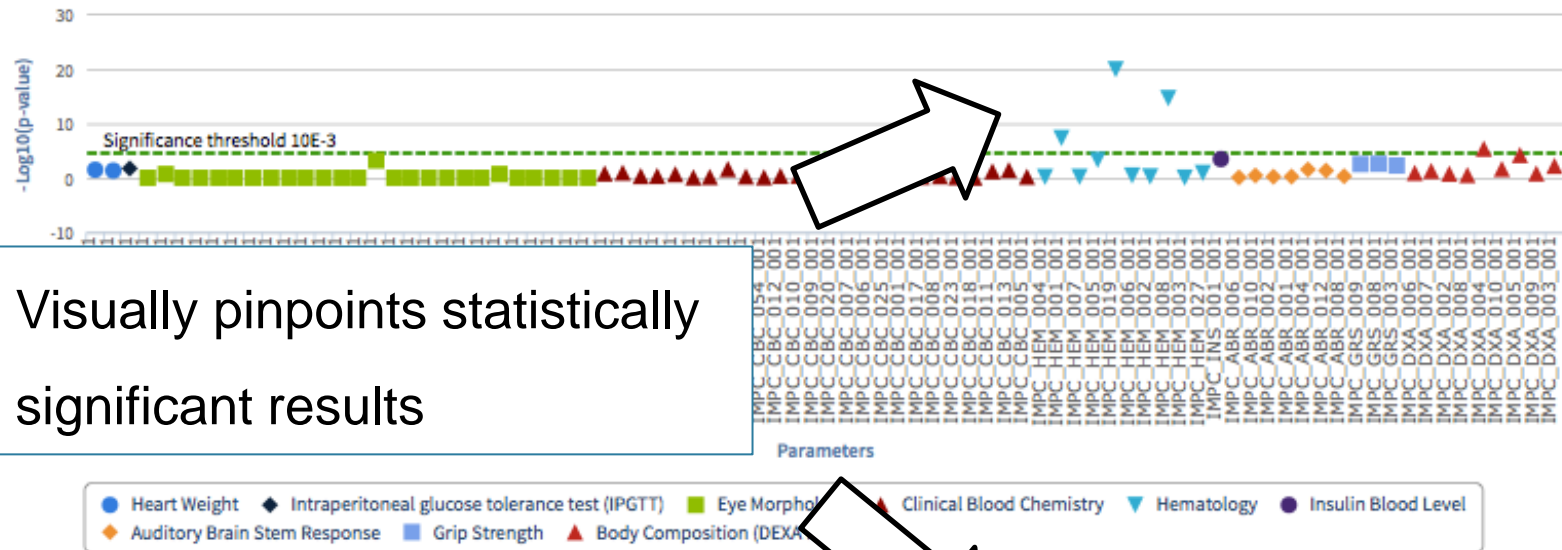


QC pending

Hematology Red blood cell count (10⁶/ul)



Statistical Analysis Overview (post-QC)



Visually pinpoints statistically significant results

Total number of results: 94

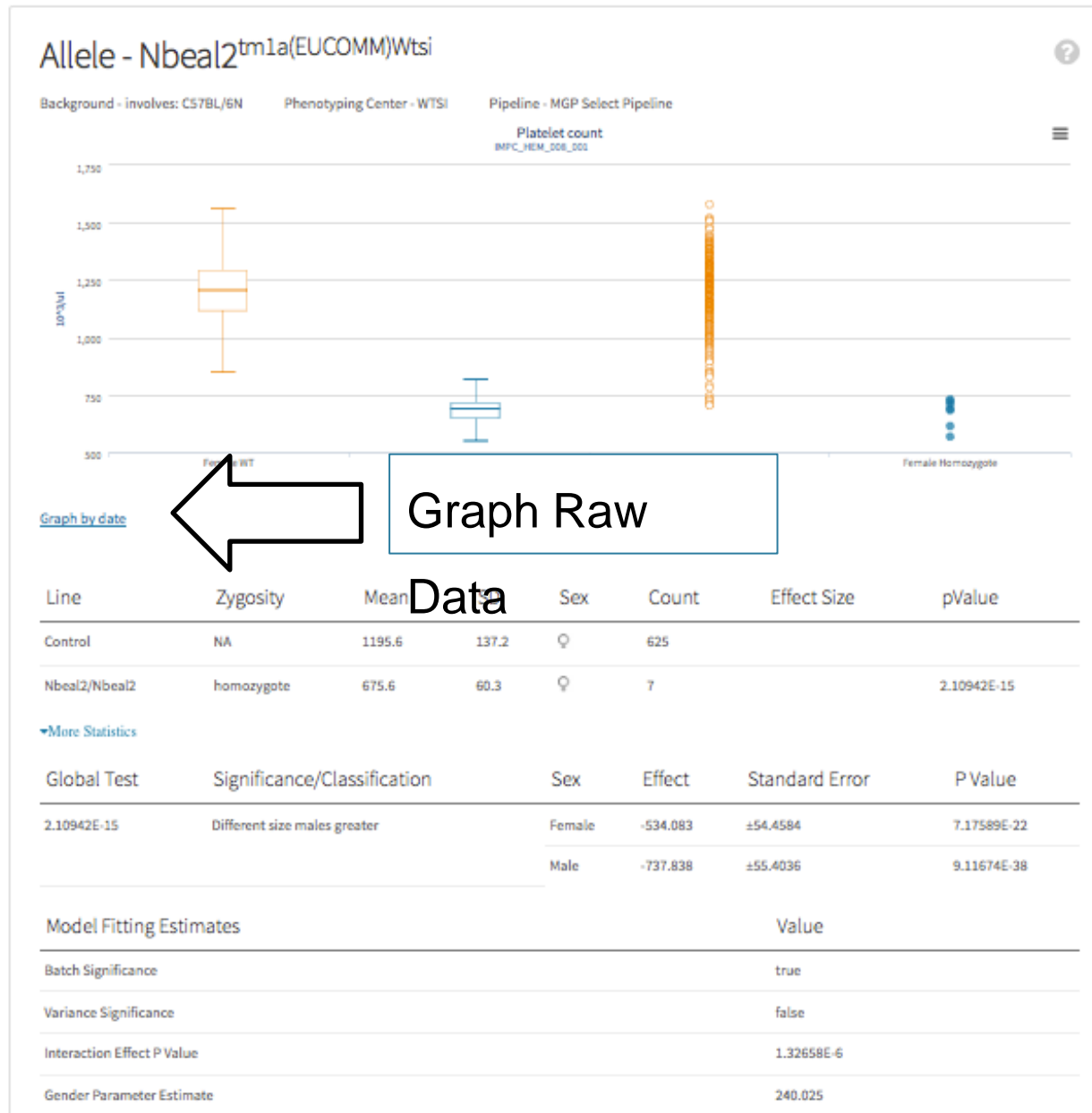
Procedure	Parameter	Data type	Zygotity	P-value	Status	Graph
Hematology	Mean platelet volume	unidimensional	homozygote	0.0	Success	
Hematology	Platelet count	unidimensional	homozygote	2.10942E-15	Success	
Hematology	White blood cell count	unidimensional	homozygote	4.71196E-8	Success	
Body Composition (DEXA lean/fat)	Bone Mineral Density (excluding skull)	unidimensional	homozygote	4.17771E-6	Success	
Body Composition (DEXA lean/fat)	Bone Mineral Content (excluding skull)	unidimensional	homozygote	6.11604E-5	Success	
Insulin Blood Level	Insulin	unidimensional	homozygote	3.48163E-4	Success	



IMM C



Graphs and Statistical Method Details



Graph by Date

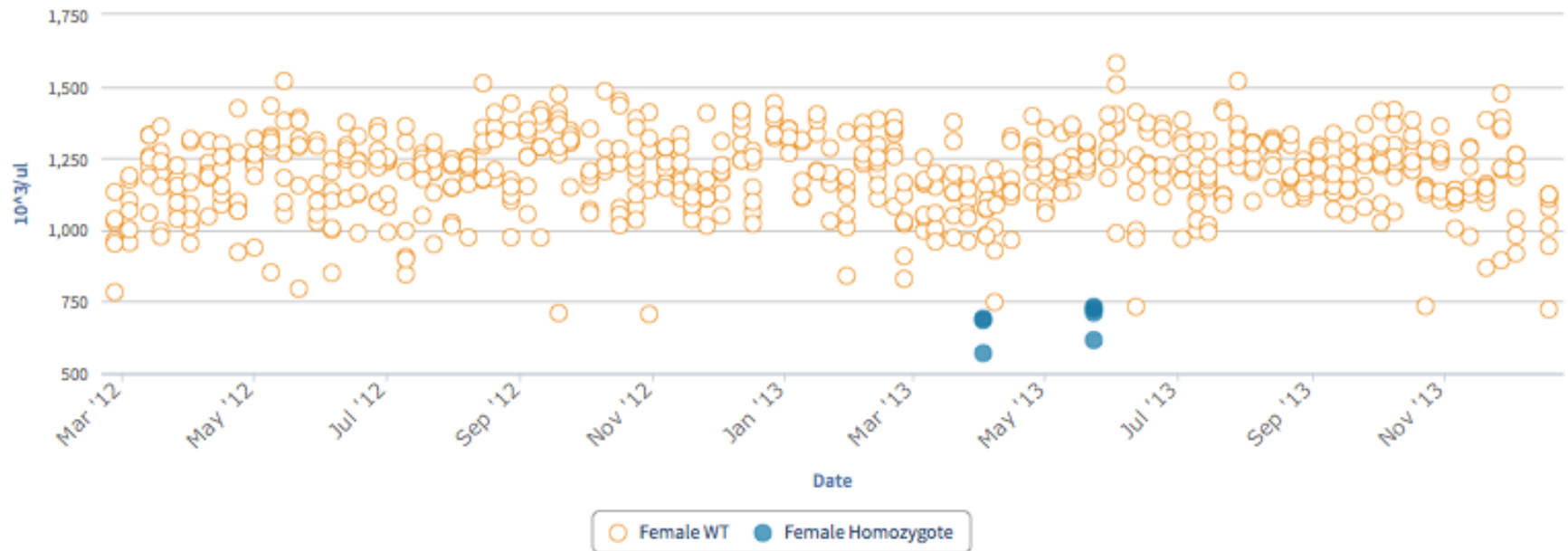
Allele - Nbeal2^{tm1a(EUCOMM)Wtsi}

Background - involves: C57BL/6N

Phenotyping Center - WTSI

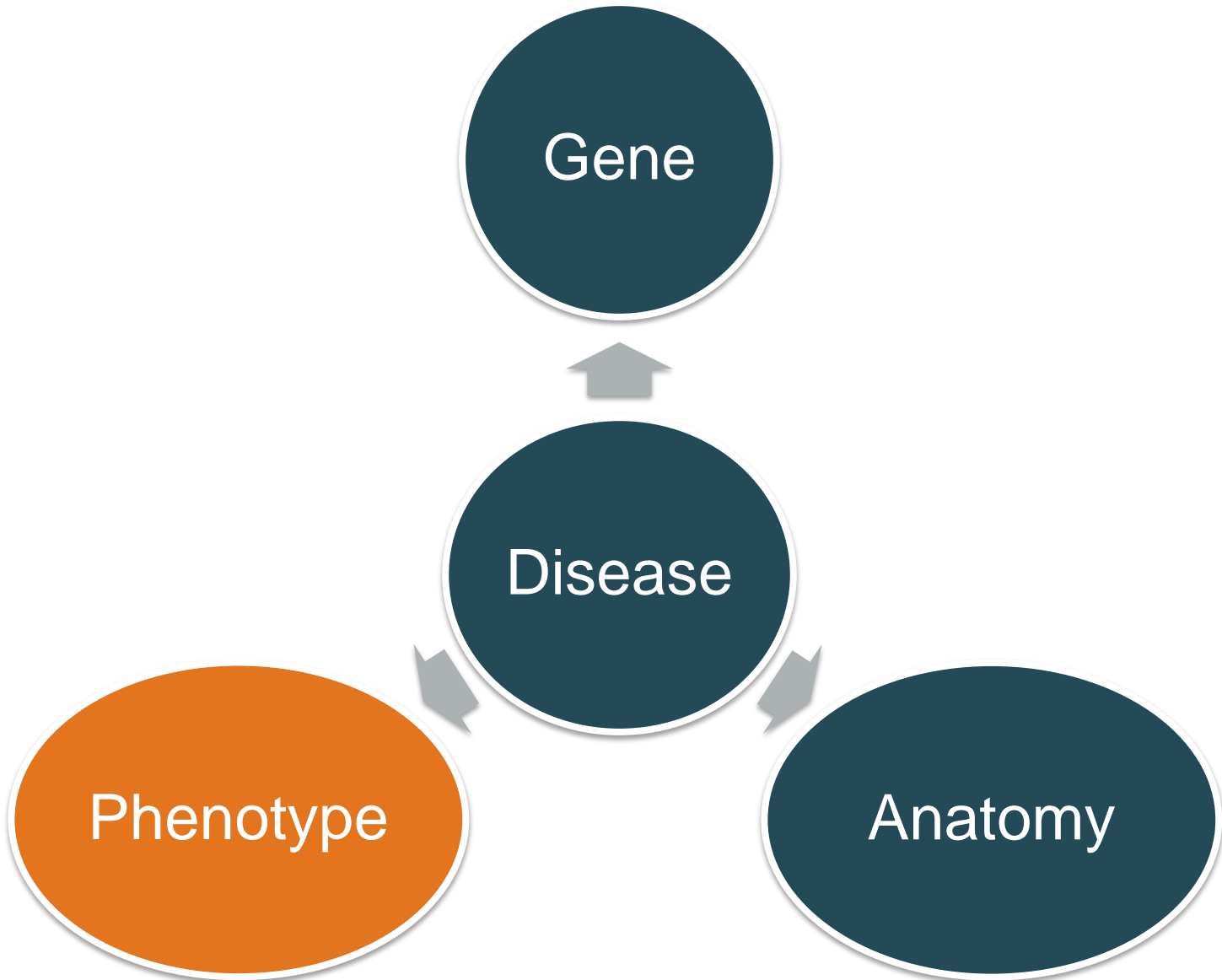
Pipeline - MGP Select Pipeline

Platelet count
IMPC_HEM_008_001



[Box Plot / Time Series Graphs](#)

Portal Search



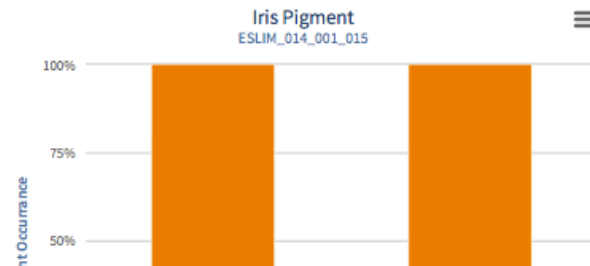
From Phenotype to Genes

Phenotype associations stats

0.32% of tested genes with null mutations on a B6N genetic background have a phenotype association to abnormal iris pigmentation (source: EuroPhenome) (2/622)

0.00% females (0/553)

0.32% males (2/621)



Gene variants with abnormal iris pigmentation

► Phenotype: All

► Gene: All

► Procedure: All

► Analysis: All

Total number of results: 3

Gene / Allele	Zygosity	Sex	Phenotype	Procedure / Parameter	Phenotyping Center	Analysis	Graph
Kdm8 Kdm8 ^{tm1a} (EUCOMM)/Wtsi	heterozygote	♂	abnormal iris pigmentation	Slit Lamp / Iris pigment	ICS	EuroPhenome	
Kdm8 Kdm8 ^{tm1a} (EUCOMM)/Wtsi	heterozygote	♂	abnormal iris pigmentation	Slit Lamp / Iris pigment	ICS	IMPC	
Tmc8 Tmc8 ^{tm1a} (EUCOMM)/Wtsi	homozygote	♂	abnormal iris pigmentation	Slit Lamp / Iris pigment	ICS	EuroPhenome	

Export table as: [TSV](#) or [XLS](#)

From Phenotype to Genes

Phenotype associations stats

0.90% of tested genes with null mutations on a B6N genetic background have a phenotype association to decreased bone mineral content (source: EuroPhenome) (4/444)

0.90% females (4/444)

0.00% males (0/443)

Select a parameter 

BMC/Body weight

BMC/Body weight

Bone Mineral Content

Bone Mineral Content (excluding skull)

60



Gene variants with decreased bone mineral content

► Phenotype: All

► Gene: All

▼ Body Compositi...

► International ...





☒ Body Composition (DEXA lean/fat)

☐ Body Composition (DEXA)

☐ DEXA

☐ Dexa-scan analysis

Total number of results: 27

Gene / Allele	Zygotity	Sex	Phenotype	Parameter	Center	Analysis	Graph
Nbeal2 Nbeal2 ^{tm1a(EUCOMM)Wtsi}	homozygote	♂	decreased bone mineral content	Body Composition (DEXA lean/fat) / Bone Mineral Content (excluding skull)	WTSI	IMPC	
Klh21 Klh21 ^{tm1a(KOMP)Wtsi}	heterozygote	♀	decreased bone mineral content	Body Composition (DEXA lean/fat) / Bone Mineral Content (excluding skull)	WTSI	IMPC	
Daam2 Daam2 ^{tm1a(KOMP)Wtsi}	homozygote	♀	decreased bone mineral content	Body Composition (DEXA lean/fat) / Bone Mineral Content (excluding skull)	WTSI	IMPC	
Entpd6 Entpd6 ^{tm1a(KOMP)Wtsi}	homozygote	♀	decreased bone mineral content	Body Composition (DEXA lean/fat) / Bone Mineral Content (excluding skull)	WTSI	IMPC	

Programmatic Interfaces

RESTful APIs:

- Genotype-Phenotype associations
- Experimental Data
- Interest in using this as “news feed” to phenotype specialist groups

Statistics:

- PhenStat statistical package developed in R and available from Bioconductor
- <http://www.bioconductor.org/packages/devel/bioc/html/PhenStat.html>

Summary

- A translational resource linking gene to diseases
- ES Cells and Mouse can be ordered
- Provides estimations of genotype to phenotype significant associations using:
 - Data from standardised procedures
 - Reproducible statistical methods
 - Mammalian phenotype ontology
- Statistical analysis successfully deployed

Future Directions

- Statistical analysis and phenotype calls will be versioned
- Beta will move to production end of May
- Automate data analysis processes:
 - Gene to disease associations (mostly done)
 - GO enrichment
 - Protein families
 - Pathway analysis
- Special Interest Group pages (e.g. Immunology, IDG)

Acknowledgements-

Funding: U54 HG006370-02

- **MRC Harwell:**

- Ahmad Retha
- Andrew Blake
- Armida Di Fenza
- Duncan Sneddon
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- **Welcome Trust Sanger Institute:**

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- Richard Easty
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- Jeanne Estabel,
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- **DMMD:**

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- **European Bioinformatics Institute:**

- Chao-Kung Chen
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- Gautier Koscielny
- Natalja Kurbatova
- Ilinca Tudose
- Terry Meehan
- Helen Parkinson
- Paul Flicek

- **NIH**

- Mark Moore
- Colin Fletcher

Tell us what you want

- Suggestions for new ideas / improvements
- Volunteers to test the beta site are welcomed

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