IMPC: Using the mouse phenotyping portal

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- Systems
- Ontologies
- Beginner
- 1 hour

The International Mouse Phenotyping Consortium (IMPC) portal allows you to search for phenotypes, disease models and knockout mouse strains for your gene of interest. This course will show you how to use the IMPC portal and what data is available.

Learning objectives:

- Learn what the IMPC is and what you can do with the portal
- Determine whether there are phenotypes and potential disease models for your gene of interest
- Establish whether there are knockout mouse strains available for your chosen gene and know how to order them
- Search for phenotypes and diseases you are interested in

What is the IMPC?

The International Mouse Phenotyping Consortium (IMPC) [2] is building the first truly comprehensive catalogue of a mammalian genome by creating and characterising 20,000 knockout [3] mouse strains - one for every protein-coding gene in the mouse genome (Figure 1).
Figure 1 The main goals of the International Mouse Phenotyping Consortium.

The IMPC has developed a free to access portal which provides data on phenotypes, disease models and protocols, as well as links to repositories where you can order these newly created mouse strains.

When to use the IMPC portal

The IMPC portal allows you to:

- Determine what phenotypes and diseases are associated with your gene of interest;
- Search for available knockout mouse strains and order them;
- Evaluate mouse models that exhibit a specific phenotype [4] or disease;
- Find information on a range of different phenotyping protocols.

Why do we need the IMPC portal?

A powerful organism for studying human disease

The laboratory mouse has become one of the most important research tools to enhance our understanding of mammalian gene function. The genetic, physiological and anatomical similarity to humans, coupled with our ability to directly manipulate the mouse genome, has made the mouse an extremely powerful organism to study human disease.

By creating a knockout mouse line for each protein-coding gene and performing high-throughput phenotyping of these lines, the IMPC is aiming to determine the function of every gene in the mouse genome. This will help drive new ideas and underpin future research into biological systems.
Making strains publicly available

In addition to providing phenotypic data, these mouse strains are preserved in repositories and made available to the scientific community - providing a valuable resource for basic scientific research and for generating new models of human diseases.

Where does the data come from?

Generating knockouts from ES cells

The IMPC is generating knockout mice by using a combination of gene trapping and gene targeting in C57BL/6 [5] mouse embryonic stem (ES) cells. These were originally created by the International Knockout Mouse Consortium (IKMC) [6].

Phenotyping the mice

The IMPC has developed a standardised high-throughput phenotyping pipeline called IMPReSS [7], which focuses on all the major organ systems and most areas of major human disease.

Mice from nine weeks old are subjected to a series of procedures to determine a range of phenotypes such as grip, hearing, metabolism, etc. Each test is done in sequence so that the previous tests don't influence the results of subsequent tests.

This project will last 10 years, with approximately 5,000 mouse lines being phenotyped in the first five years, rising to 20,000 upon completion of the project.

Members of the IMPC

The IMPC comprises some of the world's largest mouse model research programmes in order to integrate with human mutation and disease knowledge (Figure 2).

Figure 2 There are currently 18 international research institutions and 5 nationals funders who make up the IMPC
Navigating the IMPC homepage

The main features of the IMPC homepage are shown below in Figure 3.

![Figure 3](image_link)

**Figure 3** Navigating and using the IMPC portal.

How to search the IMPC portal

There are two main ways to search the IMPC portal (Figure 4):

A) Use the search box to enter simple search terms e.g. a gene name, phenotype, anatomy, disease or a protocol;
B) Click on the search link on the top menu bar. This will take you to an advanced search where you can filter your results (Figure 5).

![Image 4](image4.png)

**Figure 4** Searching from the homepage.

### Filtering your search results

Once you have entered a search term, you can narrow down your results using different filters such as phenotype, anatomy, pathology, etc (Figure 5).

![Image 5](image5.png)

**Figure 5** Filtering your search results.
[A] - Enter a search term into the search box.
[B] - Use the list of filters to narrow down your search.
[C] - Click on the 'view example search' link to see some tips on different types of search.

In this tutorial, we will show you how to search by gene, phenotype and disease and explore what data is available from these searches.

Searching for a gene

Performing a simple gene search

Let's start with a simple gene search from the IMPC homepage. We will use Nbeal2 (neurobeachin-like 2) as an example.

![Search IMPC database](image)

Figure 6 Searching for the Nbeal2 gene.

Try it for yourself....

Enter the term 'Nbeal2' into the search box on the homepage (arrowed in Figure 6). As you start typing the first three letters, the search engine will make a list of relevant suggestions. This is the case for any type of search on the IMPC portal.

Gene summary and ordering knockout mouse strains

At the top of the results page you will find a summary box for your gene of interest, in this case Nbeal2 (Figure 7).
Here you can learn more about this gene via International Mouse Informatics (IMI), Ensembl [8] and Gene Browser links. You will also be able to quickly establish:

- Whether there any embryonic stem (ES) cells and / or knockout mouse lines available for your gene. If knockout mice or ES cells are available, you will see a link to the repository where you can buy them directly (Figure 7A);
- If there is any phenotypic data associated with this gene (Figure 7B).

Figure 7 A summary of the information available for Nbeal2.

**Registering for updates**

If you want to follow a particular gene, you can register your interest (Figure 7C). The IMPC will then send you an email when new data is published or a knockout line becomes available for this gene. The portal is constantly being updated as the project evolves.

In the next few carousel pages, we will explore what phenotype data is available.

**Phenotype associations**

Just beneath the gene summary you will find a phenotype summary, which provides a snapshot of the phenotypes associated with your chosen gene (Figure 8).

You will notice a selection of symbols representing the major phenotype categories - hovering over these symbols gives you a short explanation of the phenotype (Figure 8A). Symbols are highlighted in blue when a specific phenotype has been identified. On the left hand side is a text summary which contains links to the phenotype pages as well as information on which sex(es) and zygosity the phenotype was identified in (Figure 8B).
Figure 8 Phenotype associations for Nbeal2.

Below the summary box is a more detailed table containing phenotype associations for your gene of interest (Figure 8C). Clicking on the graph icon (arrowed) takes you to an interactive graph that can be tailored to your needs. For example, you can visualise the data by date and also remove unwanted noise, allowing you to focus on the control or experimental data.

Where data is available but not yet complete, a pre-QC phenotype heatmap will appear beneath the table. This analysis is likely to change as more data becomes available, so should be treated with caution.

Find out more

You can learn more about the phenotype association data by exploring the documentation section [9].

Phenotype-associated images

Where available, the IMPC portal will also show you phenotype-associated images of these knockout mouse lines (Figure 9). These images have been annotated [10] using Mouse Anatomy (MA) and Mammalian Phenotype (MP) terms.
Figure 9 Phenotype-associated images for Nbeal2 knockout mice.

Beneath this section is a list of potential disease models and direct links to repositories where you can order ES cells and the same mice strains that were phenotyped in this project.

**Searching for a phenotype**

As well as searching for a gene of interest, you can also search for a phenotype (Figure 10). In this example we will look for mice with abnormal glucose homeostasis.
Figure 10 Searching for a specific phenotype.

Try it for yourself....

[1] Click on the search navigation link at the top of the homepage and then enter the term ‘glucose’ into the search box (Figure 10).

[2] You will notice that the list returns all types of results containing the word ‘glucose’ including genes, phenotypes, diseases and procedures. Use the left navigation menu and apply the phenotype filter. This will update the results to only show results related to phenotype.

[3] Each phenotype has a definition on the results page so that you can quickly identify the correct phenotype you are looking for. Select the 2nd on the list - labelled abnormal glucose homeostasis.

Phenotype summary and association stats

The phenotype page contains three main parts: the phenotype summary, gene association stats and a table of gene variants exhibiting your selected phenotype.

Phenotype summary

The phenotype summary provides synonyms and a definition from the Mammalian Phenotype (MP) Ontology, as well as information on the procedure used to test the phenotype (Figure 11).
Phenotype summary and association stats for abnormal glucose homeostasis.

Phenotype association stats

The mouse strains undergo a wide range of phenotype assays. This allows us to make estimates on the percentage of genes that (when knocked out) contribute to a specific phenotype, as shown in Figure 11.

In this example, you can see that the percentage of tested genes associated with abnormal glucose homestasis is currently 7.15% (57 out of 797 knockout mouse strains tested, Figure 11). However, these numbers will be updated as more knockout strains are created and phenotyped.

Find out more about how the phenotype association stats [11] are calculated.

Phenotype to gene associations

Beneath the phenotype variations stats is a table showing the phenotype to gene associations (Figure 11). Here you will find information on fields of interest, including the gene name, allele, zygosity, sex, procedure and a link to the graph (Figure 12).
A table of phenotype to gene associations for decreased circulating glucose level.

A gene phenotyping heatmap is also available below this table.

**Figure 12** A table of phenotype to gene associations for decreased circulating glucose level.

**Searching for a disease**

The IMPC has also put together a catalogue of diseases and potential mouse models.

When you search for a disease (e.g. rheumatoid arthritis), the portal will take you to the disease details page, containing information about the disease including synonyms, associated human genes and mouse orthologues (Figure 13). Underneath this summary, you will find a list of candidate mouse models based on phenotypic similarity of the disease clinical symptoms and the mouse phenotype annotations.
Figure 13 The disease details page and potential mouse models for rheumatoid arthritis.

If you are interested in a particular mouse model, you can click on the gene symbol to find out more and also order (where available) this particular line.

Find out more about the disease details page [12].

Summary

- The International Mouse Phenotyping Consortium (IMPC) is aiming to create and characterise 20,000 knockout mice strains, equating to one for each protein coding gene in the mouse genome.
- You can search the IMPC portal for phenotypes and diseases associated with your gene of interest and find out about the phenotype procedures used in this project.
- As well as providing data, the IMPC portal provides direct links to repositories where you can order the knockout mouse lines that were created and tested in this project.
- You can register your interest in a particular gene to be kept up-to-date when new data or knockout mouse strains become available.
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Recommended courses

You can learn more about the IMPC by watching this [webinar][18].

Get help and support on the IMPC portal

Support

You can get in touch with the IMPC by visiting our [contact us][19] page. Here you will be directed to different contact forms, depending on the nature of your enquiry.

Further help can be found on our [documentation page][20].

Funding

The IMPC is currently (as of November 2014) composed of 18 research institutions and five national funders. A full up-to-date list of these can be found on our [website][21].

Contributors