

Mouse mutants and phenotypes: Accessing information for the study of mammalian gene function

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ABSTRACT

Recent advances in high-throughput gene targeting and conditional mutagenesis are creating new and powerful resources to study the *in vivo* function of mammalian genes using the mouse as an experimental model. Mutant ES cells and mice are being generated at a rapid rate to study the molecular and phenotypic consequences of genetic mutations, and to correlate these study results with human disease conditions. Likewise, classical genetics approaches to identify mutations in the mouse genome that cause specific phenotypes have become more effective. Here, we describe methods to quickly obtain information on what mutant ES cells and mice are available, including recombinase driver lines for the generation of conditional mutants. Further, we describe means to access genetic and phenotypic data that identify mouse models for specific human diseases.

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1. Introduction

Closely related to human and readily accessible to detailed genetic, molecular, and phenotypic analysis, the mouse serves as a premier animal model in biomedical research. The classical forward genetics approach starts with a mouse phenotype that resembles a human disease and determines the mutations that cause the phenotype. Reverse genetics creates specific mutations, characterizes the resulting phenotypes and correlates them with human disease conditions. Both approaches have become much more effective in recent years because of the availability of complete genome sequences and due to the development of high-throughput targeting methods, many of which are described in this issue. Complementary in nature, both approaches deliver, at a rapid rate, mutant ES cells and/or mice as a starting point for further investigations aimed to understand the molecular mechanisms that lead from a genotype to a phenotype. This article describes methods to readily access up-to-date information on what mutant ES cells and mice are available, as well as information about mouse phenotypes and their correlation with human disease conditions. Methods are framed as use cases that start with specific questions.

2. Description of methods

2.1. Use Case 1: Are there mutant ES cells or mice available for my gene of interest? What mutations does the gene carry in these mutants? How can I obtain specific mutant ES cells or mice?

There are currently several large-scale programs underway to mutate all protein-coding genes in the mouse using gene trapping and gene targeting technologies: the Knockout Mouse Project (KOMP; USA) [1]; the European Conditional Mouse Mutagenesis Program (EUCOMM) [2]; the North American Conditional Mouse Mutagenesis Project (NorCOMM; Canada); and the high-throughput gene trapping effort by the Texas A&M Institute for Genomic Medicine (TIGM; USA) [3]. In order to pursue their work in a collaborative and coordinated manner, these groups have formed the International Knockout Mouse Consortium (IKMC) [4,5]. The IKMC web portal (www.knockoutmouse.org) is the central public web site for IKMC data, giving researchers world-wide access to up-to-date information on IKMC knockout vectors, ES cells and mice, and links to repositories from which these products can be ordered [6]. The IKMC database also provides data and tools to the IKMC for selecting and prioritizing genes. For example, it indicates to the IKMC for what genes mutant ES cells or mice have already been generated by other researchers. Because all this external information and links to pertinent resources are also readily available through the web site, the IKMC web portal is an excellent central starting point for the queries listed above. In the following, we describe a workflow for performing these queries:

Go to www.knockoutmouse.org.

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E-mail address: ringwald@informatics.jax.org (M. Ringwald).

Enter the gene symbol(s) or gene ID(s) for your gene(s) of interest into the Search box and start the search.

Search results are listed as a summary with a record (row) for each gene that matches your query (Fig. 1 top). Each record includes (i) the gene symbol; (ii) a high-level summary of IKMC

knockout attempts that states which programs are working on the gene, provides the status of the most advanced targeting effort per program with a link to more details, and indicates the availability of targeting vectors, mutant ES cells and mice, with links to the repositories that distribute the respective IKMC products; and (iii)

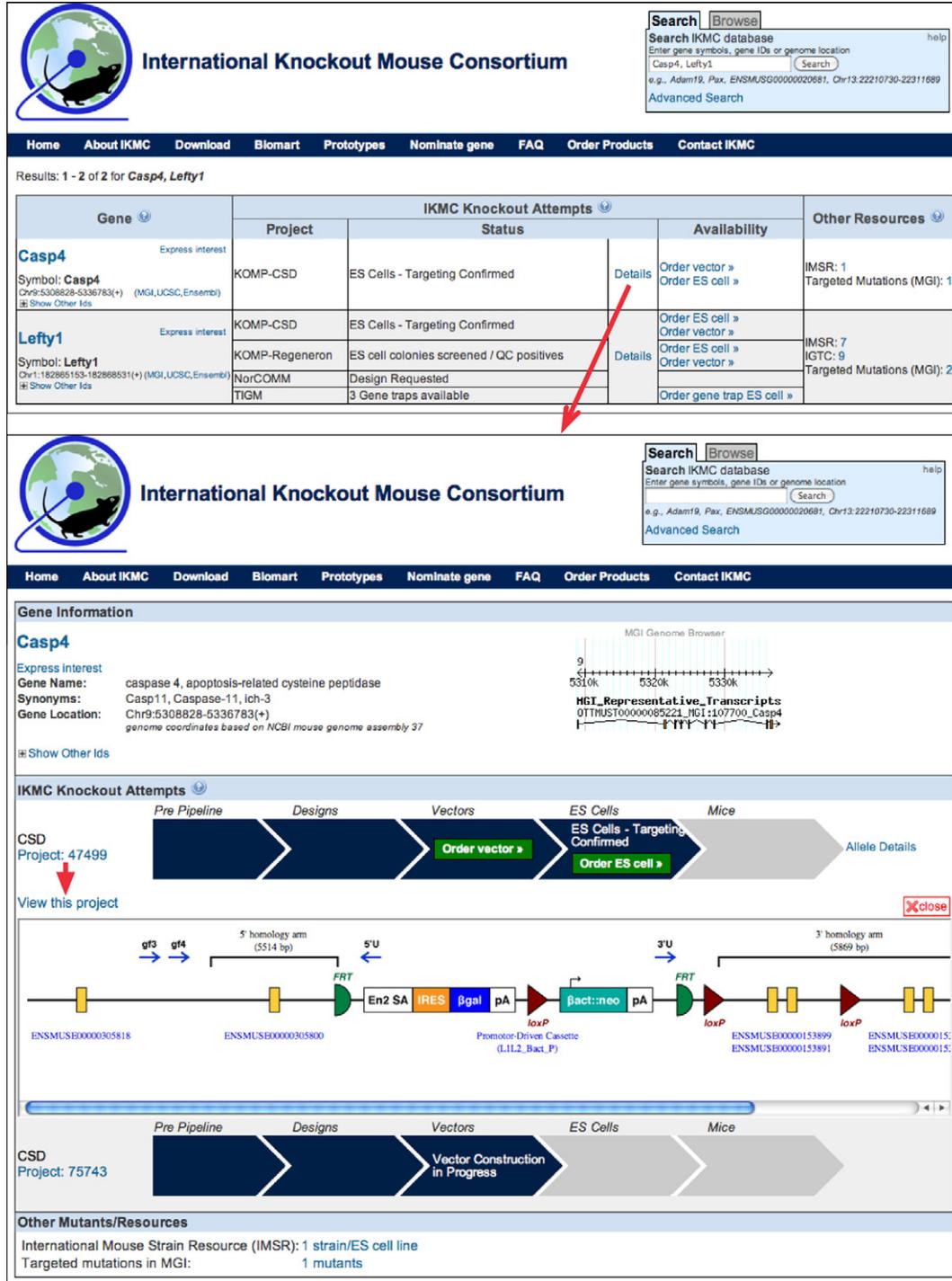


Fig. 1. Querying the IKMC web portal. Top: Query summary page. Query summaries display one record (row) for each gene matching the query. One can query by gene symbols, by various gene IDs, and by genome coordinates. A query for two genes by gene symbol (*Casp4, Lefty1*) is shown. The gene column displays the official gene symbol, linked to the corresponding gene pages at MGI. Gene specific links to genome browsers and other external sites are provided. The 'IKMC Knockout Attempts' column lists all IKMC programs working on the gene. The status of the most advanced targeting effort per program is shown, with a link to more details. The availability of IKMC products is indicated by Order links to the respective IKMC repositories. The 'Other Resources' column displays the number of mutant ES cells and mice reported by the IMSR, IGTC, and MGI with links to the corresponding entries at these sites. Bottom: Query details page. This page lists all the IKMC knockout attempts for a given gene. The most advanced projects are displayed first. Available products are indicated by Order links to the respective repositories. Clicking on the 'Allele Details' link (to the right of the project status bar) opens a graphical display illustrating the features of the mutant allele generated by the project. The 'View this project' link (red arrow) leads to more comprehensive targeting vector and mutant allele information.

other resources that report on mutant ES cells or mice for the gene of interest, with the number of, and links to, corresponding entries at the respective sites.

If you are interested in IKMC products, follow the 'Details' link in the 'IKMC Knockout Attempts' column. This brings you to a page that lists all IKMC knockout attempts for your gene of interest (Fig. 1 bottom). One program might try different targeting vectors to mutate a gene, resulting in several targeting projects. The production pipeline status for each project is displayed, and the availability of products is indicated via Order links that lead to the respective repositories. As soon as targeting vectors have been generated for a given project, an 'Allele Details' link is displayed to the right of the progress bar. Clicking on this link opens a graphical display that illustrates the salient molecular features of the targeted allele. On the top left side of this newly opened display is another link 'View this project' that leads to more comprehensive information about the mice, ES cells and targeting vector generated by a specific project. Order links guiding users to the respective repositories are provided on this page as well.

The search path just described leads to information about gene targeting products (vectors, ES cells and mice) from KOMP, EU-COMM and NorCOMM, and gene trap ES cell lines from TIGM. Information about gene trap ES cell lines from EU-COMM and NorCOMM will be fully integrated into the IKMC web portal in the near future. Then this data will be searchable and displayed in the same way as the other IKMC products described above.

Currently, if you are interested in EU-COMM and NorCOMM gene traps, or in non-IKMC products, follow the links provided in the 'Other Resources' section of the initial query summary to find the entries for your gene in these databases (Fig. 1 top). The International Mouse Strain Resource (IMSR) [7] is a searchable database of inbred and mutant mouse strains and stocks available worldwide and provides access to the respective holder sites, including all the members of FIMRE, the Federation of International Mouse Resources. The International Gene Trap Consortium (IGTC) database [8] records all gene trap lines available from the consortium and provides links to corresponding holder sites. The Mouse Genome Informatics (MGI) database [9,10] represents all mutants for a given gene that have been reported in the published literature, by the IKMC, and by the IMSR. If pertinent mutant products are recorded in MGI, the 'Other Resources' section provides two links, one to targeted mutations in MGI, one to other mutations in MGI. The latter category includes gene trap ES cell lines from EU-COMM and NorCOMM. All mutant records in MGI include a reference to the original publication. ES cells or mice that are not available through the IKMC or the IMSR might be obtained by contacting the authors.

IKMC data are also accessible through MGI and the IMSR; IKMC gene trap data are also available through the IGTC. However, the IKMC web portal provides the most up-to-date and the most detailed molecular information about its products, reports on work in progress, and maintains up-to-date links to pertinent external resources. Therefore, the search strategy presented here offers effective means to find, globally, mutant ES cells and mice together with detailed information about targeting vectors and mutant alleles.

2.2. Use Case 2: Are recombinase driver lines available under promoters of my choice? Are there recombinase driver lines that show activity in tissues of my choice?

A large number of targeted and gene trapped alleles produced by the IKMC, and an increasing number of targeted alleles generated by the biomedical research community, feature recombinase recognition sites that allow the generation of conditional mutants [2,11–13]. To take advantage of these conditional alleles, mouse lines that carry recombinases under specific promoters/enhancers

are being developed [14]. Time and tissue specificity of these recombinase lines is characterized, either by examining recombinase expression patterns, or, more accurately, by using reporter strains to determine the conditional allele pattern generated by the recombinase [15]. Pertinent data about transgenic and knock-in recombinase lines are available through the recently established Cre-Portal (www.creportal.org). The site lets you search for recombinase driver lines that display recombinase activity in specific tissues, or for mouse lines with recombinases under specific promoters/enhancers. As part of the larger MGI system, the portal provides the recombinase expression and reporter data, as well as phenotypic data obtained in conditional mutants. Further it indicates which mouse lines are available through the IMSR and provides links to corresponding entries in the IMSR database. The following query example illustrates how to find information about recombinase driver lines with specific promoters (see also Fig. 2):

Go to www.creportal.org.

In the 'Access Data' section use the 'Search for allele by promoter/driver specificity'. Select the promoter/driver of your choice from the selection list and click the 'Go' button.

The query result summary lists all the mouse lines/alleles that match your query. The 'Recombinase Data' column indicates whether recombinase activity data are available and in how many anatomic systems activity has been measured. The 'Find Mice' column indicates whether mouse lines are available and provides links to the IMSR. The 'Refs' column gives the number of publications that report on the allele/recombinase line, as one potential measure for the utility of the line, and links to the complete list of references.

To look up recombinase activity data for a specific allele, expand the corresponding information in the 'Recombinase Data' column by clicking on the triangle to the left of the phrase 'Detected in x systems'. Then follow the link for a specific anatomic system to look up pertinent data, including the specific anatomic structures in which recombinase activity was reported, pertinent image data, as well as additional assay and genetic information.

To look up all recombinase and phenotype data for a given allele, on the query results summary, in the 'Allele Symbol' column, follow the link 'phenotype data'.

The search and navigation path presented here is just one way to address this specific use case. For more information about the utility of the Cre Portal, you can consult the FAQs provided at the site and explore the database and its content in more detail.

2.3. Use Case 3: Are there mouse models available for a given human disease?

As pointed out above, mouse models are generated by forward and reverse genetic approaches. A key to both strategies is the phenotypic characterization of mouse mutants and the correlation of these data with human disease conditions. The MGI database is a primary resource for this type of information. MGI provides various means to search for genes and mouse mutants based on phenotypic and human disease information. Pertinent search forms and FAQs are available at www.informatics.jax.org/phenotypes.shtml. Here we illustrate one example: finding mouse models based on human disease terms.

In the Access Data Section, follow the link 'Human Disease (OMIM) Browser'.

OMIM [16] disease terms are listed in alphabetical order and the availability of mouse models is indicated, in parentheses, to the right of terms. Search or browse for your disease term of interest and click on the corresponding term (Fig. 3 top left).

Fig. 3 (top right) shows the entry for Angelman Syndrome; AS (OMIM ID: 105830). As indicated on this page, human disease characteristics are associated with mutations in the human gene

Access Data

FIND RECOMBINASE-CARRYING ALLELES

Search for alleles assayed for specificity/expression in a particular anatomical system.

Recombinase specificity in: (choose one) Go

Search for alleles by promoter/driver specificity.

Recombinase driven by: Nes Go

Recombinase Alleles - Tissue Specificity Summary

You can control the data displayed below. Check the boxes to show Anatomical System columns containing links to data and images. Hide or show other columns:

Adipose Tissue Head Muscle Skeletal System

Alimentary System Hemolymphoid System Nervous System Tail

Branchial Arches Integumental System Renal and Urinary System Early Embryo, All Tissues

Cardiovascular System Limbs Reproductive System Extraembryonic Component

Cavities & their Linings Liver and Biliary System Respiratory System Embryo-other (Embryonic structures not listed above)

Endocrine System Mesenchyme Sensory Organs Postnatal-other (Postnatal structures not listed above)

Allele Synonyms Allele Type IMSR Inducible References

You searched for...
Driver equals Nes

Click column headings to sort table data. Drag headings to rearrange columns.

Driver	Allele Symbol Gene; Allele Name	Recombinase Data	Allele Synonym	Find Mice (IMSR)	Refs
Nes	Tg(Nes-cre)1Atp transgene insertion 1, Andreas Trumppe (phenotype data)	No data available	Nes-Cre1, Nestin-Cre, Nestin ^{Cre} , Tg(Nes-cre)1Mtc		42
Nes	Tg(Nes-cre)1Hhan transgene insertion 1, Hua Han (phenotype data)	No data available			1
Nes	Tg(Nes-cre)1Kag transgene insertion 1, Ryoichiro Kageyama (phenotype data)	► Detected in 1 system.	Cre-Tg1, nestin-Cre		20
Nes	Tg(Nes-cre)1Kln transgene insertion 1, Rudiger Klein (phenotype data)	▼ Detected in 12 systems. alimentary system, cardiovascular system, endocrine system, head, hemolymphoid system, limbs, nervous system, postnatal- other, renal & urinary system, reproductive system, respiratory system, sensory organs	n-Cre ⁺ , Nes1Cre, NesCre, nestin-Cre, nestin/Cre, Tg(Nes- cre)	2	255

Tg(Nes-cre)1Kln - Alimentary System
Recombinase Specificity Detail

Allele Information | Tissue Information | Images | Recombinase Specificity | References

Allele Information

Allele: Tg(Nes-cre)1Kln
transgene insertion 1, Rudiger Klein

Driver: Nes
Type: Transgenic (Cre/Flp)

Synonym: n-Cre⁺, Nes1Cre, NesCre, nestin-Cre, nestin/Cre, Tg(Nes-cre)

Molecular description: This transgene expresses Cre recombinase under the control of a rat nestin (Nes) promoter. This promoter expresses Cre recombinase in neuronal and glial cell precursor. Cre recombinase activity is present in nervous tissue by embryonic day 11.

Find mice (IMSR): Mouse Strains: 2 lines available Cell Lines: 0 lines available

Additional Tissues: Tg(Nes-cre)1Kln activity also observed in:
► cardiovascular system, endocrine system, head, hemolymphoid system ... (more)

Tissue Information

Alimentary System Other recombinase alleles with activity in Alimentary System tissues:
► Aire^{tm3(cre)Mmat}, Chat^{tm1(cre)Low}, Foxa2^{tm2.1(cre)Esrl*Hoon}, Foxg1^{tm1(cre)Skm} ... (more)

Images Drag images to compare to others or to data in the table below. Drag corners to resize images for more detail. [Reset Images](#)

Recombinase Specificity Click heading to resort table.

Structure	Assayed Age	Level	Pattern	Reference Source	Assay Type	Reporter Gene	Detection Method	Assay Note
intestine	postnatal day 7	Strong	Graded	J:137887 Fig. P7-Int	Recombinase reporter	lacZ	Direct Detection	
stomach	embryonic day 15.5	Moderate	Not Specified	J:137887 Fig. E15-Stom1, Fig. E15-Stom1a, Fig. E15-Stom1b	Recombinase reporter	lacZ	Direct Detection	

References All for this allele: 255 reference(s)

Fig. 2. Querying the Cre-Portal. Top left: Part of the 'Access Data' section of the Cre-Portal home page. A query for mouse lines that carry a recombinase under the *Nes* promoter is shown. Top right: Query results summary. The bottom section lists a record for each allele/mouse line that matches the query. The 'Recombinase Data' column indicates in how many anatomic systems recombinase activity has been measured. Clicking on the triangle expands the display to show the anatomic system analyzed. An alternative way to look up data for specific anatomic systems is to add corresponding data columns to the display by checking boxes in the top half of the page and then clicking the 'Reset Page' button. Bottom: Detail Page showing the recombinase activity data for one allele, *Tg(Nes-cre)1Kln*, in one anatomic system, the alimentary system. Images can be enlarged by dragging their corners. Specific anatomic structures within the alimentary system in which activity was found are recorded, together with the assayed age, the level and patterns of activity in the specified anatomical structure, and references to figures and publications. Additional assay and genetic background information is accessible via specific tabs (bottom right section of display).

UBE3A and with mutations in the mouse orthologous gene *Ube3a*. However, mouse mutants for the *Gabrb3* and *Snrpn* genes also show disease characteristics for Angelman Syndrome although OMIM data currently do not associate the disease with the orthologous human genes. Conversely, there are three additional human genes associated with Angelman Syndrome in OMIM: *ANCR*, *CDKL5*, and *MECP2*. The mouse ortholog for *ANCR* is not yet identified, and mouse mutants in *Cdkl5* and *Mecp2* do not show the disease characteristics. This clearly illustrates that whether a mouse mutant is a good model for a human disease conditions cannot be inferred simply by orthology. The detailed curation of mouse disease model information performed by MGI is needed to enable database queries such as the one described here.

The page illustrated by the top right of Fig. 3 serves as an entry point to much more detailed information about the respective mouse models. By following the links in the 'Mouse Models'

section, you can look up the detailed annotations for each allele, including information about the nature of the mutation and the phenotypes displayed on different genetic backgrounds. If MGI has recorded expression information for the respective mutant, links to these data are provided as well. To see the full detail of the phenotype information on the 'Allele Detail' pages, use the 'show all annotated terms' or 'show all phenotypic details' functions, or expand specific sections by clicking on the triangles.

Allele Detail pages in MGI can contain a lot of information just for one specific allele. Moreover, there can be many alleles, and thus many Allele Detail pages for a given gene. All the information that MGI holds for a given gene can be accessed from the respective Gene Detail page, including information about chromosomal location, mammalian orthologs, sequences, mutant alleles and phenotypes, Gene Ontology (GO) classifications, and expression data. Many links to external resources are also provided. 'Gene

You searched for...
Human Disease Vocabulary: contains *Angelman Syndrome* searching Human Disease vocabulary, synonyms, symbols, and accession IDs.
 2 matching Human Disease terms

To see all annotations for a disease, click the disease name.

OMIM ID	Human Disease
105830	Angelman Syndrome; AS (4 mouse models)
300243	Mental Retardation, X-Linked, Syndromic, Christanson Type

Human Disease and Mouse Model Detail

Human Disease
 Term: **Angelman Syndrome; AS**
 OMIM ID: 105830

Associated Genes
 Orthologous mouse and human markers where mutations in one or both species have been associated with phenotypes characteristic of this disease.

Mouse Gene	Human Gene	Characteristics of this human disease are associated with mutations in...
Ube3a	UBE3A	...both mouse and human orthologous genes.
Gabrb3	GABRB3	...the mouse gene. OMIM data currently do not associate this disease with the orthologous human gene.
Snrpn	SNRPN	...the human gene. MGI data currently do not associate this disease with mutations in the orthologous mouse gene.
none identified	ANCR	
Cdk5	CDKL5	
Mecp2	MECP2	

Mouse Models

Allelic Composition	Note	Genetic Background	Ref(s)
Models with phenotypic similarity to human disease where etiologies involve orthologs.¹			
Ube3a^{tm1Alb}/Ube3a⁺		involves: 129S7/SvEvBrd * C57BL/6	1:50811
Ube3a^{tm1Hwf}/Ube3a⁺		B6.129S4-Ube3a ^{tm1Hwf}	1:25622
Models with phenotypic similarity to human disease where etiologies are distinct.²			
Gabrb3^{tm164y}/Gabrb3^{tm126n}		involves: 129S1/5v * 129X1/5vJ * C57BL/6J	1:39801
Snrpn^{tm1Ka}/Snrpn⁺		either: 129S1-Snrpn ^{tm1Ka} or (involves: 129S1/5v * C57BL/6J)	1:105412

Ube3a^{tm1Alb}
 Targeted Allele Detail

Nomenclature | Mutation origin | Mutation description | Find Mice (MSR) | Phenotype summary | Phenotypes by genotype | Disease models | References

Nomenclature
 Symbol: **Ube3a^{tm1Alb}**
 Name: ubiquitin protein ligase E3A; targeted mutation 1, Arthur L. Beaudet
 MGI ID: MGI:2181811
 Synonyms: E6-AP⁺, E6AP⁺
 Gene: **Ube3a** Location: Chr7:66484122-66562097 bp, + strand Genetic Position: Chr7, 33.95 cM

Mutation origin
 Germline Transmission: Earliest citation of germline transmission: J:50811
 Parent Cell Line: AB2.2 (ES Cell)
 Strain of Origin: 129S7/SvEvBrd-Hprt^{0-m2}

Mutation description
 Allele Type: Targeted (knock-out)
 Mutations: Insertion, Intragenic deletion
 A 3kb genomic region including exon 2 was replaced with a neo-loxP-hort cassette via homologous recombination, resulting in deletion of 100 N-terminal amino acids in the encoded protein and a frameshift inactivating all putative protein isoforms. Homozygous mutant animals were identified by Southern blot and PCR genotype analysis. (J:50811)

Find Mice (MSR)
 Mouse strains and cell lines available from the International Mouse Strain Resource (IMSR)
 Carrying this Mutation: Mouse Strains: 1 strain available Cell Lines: 0 lines available
 Carrying any Ube3a Mutation: 15 strains or lines available

Phenotype summary
 Phenotype Summary by Mammalian Phenotype Key: hm/homozygous ht/heterozygous
 on conditional genotype (complex: > 1 genome feature)
 tg/involves transgene (g) (either: hemizygous, indeterminate...)
 N/normal phenotype (x)expected model not found
 Genotypes are listed in the next section.

Affected Systems

Genotypes	hm1	hm2	ht3	ht4
behavior/neurological	✓	✓	✓	✓
cellular			✓	✓
endocrine/exocrine glands		✓		
growth/size	✓			✓
lethality/postnatal	✓	✓		
nervous system	✓	✓	✓	✓
reproductive system		✓		
Disease Models				✓

Phenotypic data by genotype
 Phenotypic Data by Genotype (show or hide all phenotypic details)

Genotype	Allelic Composition	Genetic Background
hm1	Ube3a ^{tm1Alb} /Ube3a ^{tm1Alb}	involves: 129S7/SvEvBrd
hm2	Ube3a ^{tm1Alb} /Ube3a ^{tm1Alb}	involves: 129S7/SvEvBrd * C57BL/6
ht3	Ube3a ^{tm1Alb} /Ube3a ⁺	involves: 129S7/SvEvBrd
ht4 Disease Model	Ube3a ^{tm1Alb} /Ube3a ⁺	involves: 129S7/SvEvBrd * C57BL/6

Disease models

Mouse Models of Human Disease	Note	Allelic Composition	Genetic Background	Ref(s)
Models with phenotypic similarity to human diseases associated with human UBE3A.				
Angelman Syndrome; AS OMIM ID: 105830		ht4 Ube3a^{tm1Alb}/Ube3a⁺	involves: 129S7/SvEvBrd * C57BL/6	1:50811

References
 J:50811 Jiang YH et al, "Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation [see comments]" Neuron 1998 Oct;21(4):799-811
 All: 11 reference(s)

Fig. 3. Finding mouse models for specific human diseases. Top left: Part of the page that shows the search results for 'Angelman Syndrome', upon using the 'Human Disease (OMIM) Browser' at MGI. Top right: 'Human Disease and Mouse Model Detail' page for Angelman Syndrome. Based on available phenotypic data, orthologous mouse and human genes are categorized according to their association with human disease characteristics. Mouse models for the respective categories are listed at the bottom part of the page. Each mouse model record specifies the exact allele composition and the genetic background under which the phenotype was observed, and points to the corresponding publication. Each mouse model record links to much more detailed allele and phenotypic data (red arrow). Bottom: 'Allele Detail' page for *Ube3a^{tm1Alb}*. This page provides detailed molecular and phenotypic information for each allele. The sections 'Phenotype summary' and 'Phenotypic data by genotype' can be expanded by using the 'show all' functions or by clicking on the triangles.

Detail' pages can be accessed by clicking on the gene symbol displayed on any of the pages described above, or via the Quick Search tool available on the top right corner of all MGI web pages.

3. Concluding remarks

There are many methods to study mammalian gene function. It is beyond the scope of this article to describe methods for

accessing all the databases that hold pertinent information. Instead we have focused on databases that deal with recent developments holding great promise for understanding the in vivo function of mammalian genes and their role in human health and disease: high-throughput gene targeting and trapping, tools to create conditional mouse mutants, and the correlation of mouse phenotype and human disease information. The methods described here access central data hubs that provide extensive, highly-curated, and

up-to-date information on these subject matters, and feature connections to many additional databases. There are other methods to query the resources described here, and the specific ways to perform the example queries illustrated in this article might change as the databases evolve. However, once one is familiar with these resources, it will be easy to exploit them more fully and to adapt to changes. All three web sites described here provide up-to-date online help and FAQ pages for further guidance.

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