The Mouse Gene Expression Database (GXD)

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Received October 11, 2000; Accepted October 17, 2000

ABSTRACT

The Gene Expression Database (GXD) is a community resource of gene expression information for the laboratory mouse. By combining the different types of expression data, GXD aims to provide increasingly complete information about the expression profiles of genes in different mouse strains and mutants, thus enabling valuable insights into the molecular networks that underlie normal development and disease. GXD is integrated with the Mouse Genome Database (MGD). Extensive interconnections with sequence databases and with databases from other species, and the development and use of shared controlled vocabularies extend GXD's utility for the analysis of gene expression information. GXD is accessible through the Mouse Genome Informatics web site at http://www.informatics.jax.org/ or directly at http://www.informatics.jax.org/menus/expression_menu.shtml.

INTRODUCTION

The laboratory mouse has become a pivotal animal model in biomedical research because it is closely related to the human and readily amenable to genetic and molecular analysis. Tissues from many different mouse strains and mutants, and from all developmental and adult stages, are easily accessible for expression analysis. The different methods used to detect gene products vary in sensitivity and spatial resolution and contribute distinct and complementary expression information. The Gene Expression Database (GXD) has been designed as an open-ended system that can integrate many different types of expression data, such as RNA *in situ* hybridization, immunohistochemistry, northern blot, western blot, RT–PCR, cDNA source and array data (1–5). Thus, as data accumulate, GXD can provide increasingly complete information about what transcripts and proteins are produced by what genes; where, when and in what amounts these gene products are expressed; and how their expression varies in different mouse strains and mutants. Expression patterns reported from assays with differing spatial resolution are described in standardized and integrated form using an extensive, hierarchically structured dictionary of anatomical terms for mouse development built in collaboration with our Edinburgh colleagues (6). Digitized images of original expression data are linked to the respective expression records. GXD is integrated with the Mouse Genome Database (MGD) (7) to enable a combined analysis of genotype, expression and phenotype information, and has comprehensive links to other resources, such as sequence databases (8–12), OMIM, MEDLINE and databases from other species. Such information places gene expression data in the larger biological and analytical context.

GXD is implemented in the Sybase relational database management system. It has been available online since July 1998 and has been updated on a daily basis. Access to data is provided primarily via Web-based query forms. Users interested in direct SQL access may arrange for an SQL account by contacting MGI User support (see below). GXD and its WWW query interface have been described in more detail previously (3,4). Here, we illustrate recent enhancements of GXD from the user's perspective, by taking the different query forms provided by GXD as an entry point.

The Gene Expression Data index

Using the GXD index, one can rapidly identify publications that contain endogenous developmental gene expression information for specific genes, for particular days of mouse development, from specific assay types or for any combination of these parameters. Additional query fields are provided for bibliographic information (authors, journals, year) and for words (text strings) that occur in the abstract of the respective articles. We continue to keep the GXD index up-to-date. All pertinent journal articles from 1993 to the present and articles from major developmental journals from 1990 to the present are indexed. As of September 28, 2000, the index includes 17 401 entries covering 5635 references and expression information for 3837 genes.

The Gene Expression Data query form

The Gene Expression Data query form provides access to data from RNA *in situ* hybridization, immunohistochemistry, northern blot, western blot, RT–PCR and RNase protection experiments. Using combinations of search parameters, one can ask increasingly complex expression queries, such as: 'In what anatomical structures and/or at what developmental stages has a specified gene or a specified set of genes been detected/not detected?' or 'What genes have been detected/not detected in a given tissue and/or at a particular time of development using a specified set of expression assays?' Due to the hierarchical structure of the anatomical dictionary, spatial queries can include anatomical substructures or superstructures. Further, it is possible to correlate gene expression with chromosomal location, a query particularly relevant for hunting candidate genes. The query capabilities for chromosomal location have been refined. It is now possible to search for

*To whom correspondence should be addressed. Tel: +1 207 288 6436; Fax: +1 207 288 6132; Email: ringwald@informatics.jax.org genes located on a particular chromosome, between specified loci or within a specified distance from a genetic locus. The most significant enhancement of the Gene Expression Data query form is that one can now also search for genes whose products perform a particular 'molecular function' (e.g. 'transcription factor' or 'DNA helicase'); are involved in a specified 'biological process' (e.g. 'apoptosis' or 'purine metabolism'); or belong to a defined 'cellular component' (e.g. 'nucleus' or 'origin recognition complex'). As a member of the Gene Ontology Project (13), we participate in building shared controlled vocabularies for these three categories and in assigning pertinent terms to genes in our database. The addition of these search parameters enables important new queries such as 'What transcription factors are expressed in the diencephalon from day 11.5–15 of mouse development?' or 'What genes involved in apoptosis have been detected in the limb?' and enhances the utility of the expression data stored in GXD.

The Mouse Anatomical Dictionary Browser

The Mouse Anatomical Dictionary Browser has been added as a new tool to navigate through the extensive dictionary hierarchies for the different developmental stages, to locate specific anatomical structures in the hierarchies and to look up expression results associated with those structures (Fig. 1). Thus, while the Gene Expression Data query form described above enables powerful combinatorial queries (including anatomical structures), the anatomy browser lets users view gene expression data directly from the developmental anatomy perspective. It must be noted that Theiler stages 23–26 have been added only recently and are still under development. So far, only limited expression data have been entered for these stages of mouse development.

The cDNA clone query form

This query form is designed for investigating expression information derived from cDNA source data. It allows one to ask questions such as 'From which tissues or cell lines have cDNAs for a given gene been isolated?' or 'What genes located in a particular chromosomal region are, according to cDNA source information, expressed in a specified tissue?' The cDNA clone query form now offers the same query capabilities for Gene Ontology classifications and chromosomal location as the Gene Expression Data query form. To make these new query parameters meaningful for the analysis of cDNA source data, we improved our means to assign cDNA clones and ESTs putatively to genes in our database. On a daily basis, GXD and MGD are establishing and curating links between genes in MGI and sequence entries in DDBJ/EMBL/Genbank (8–10). In an ongoing collaborative effort with SWISS-PROT (12), we further curate links between genes and protein entries from which additional cross-references to nucleotide sequences can be derived. Based on our curated gene/nucleotide sequence links we, in collaboration with the NCBI UniGene project (14), generate putative links between cDNA clones/ESTs and genes dynamically. By transitivity, these links provide (putative) information about chromosomal location, molecular function, biological process and cellular components for the respective cDNAs.

Electronic data submission: the Gene Expression Notebook

GXD curators continue to annotate expression data from the literature. However, extracting data from the literature and bringing them into a standardized format is a time-intensive process. Further, standard publications normally include only a small portion of the data generated by the authors. Therefore, GXD has been conceptualized from the beginning as an electronic framework for the community to store and analyze expression data. To facilitate electronic submission, we have developed the Gene Expression Notebook (GEN). It can be used as a laboratory notebook for storing expression results, images, molecular probes, specimens, experimental conditions, etc. and data can easily be exported in standardized format for electronic submission to GXD. Implemented in Microsoft Excel™, it is easy to use and to customize on both the Macintosh and the PC platform. The GEN has been described in more detail previously (4). During the last year, we have refined it based on feedback from a number of test laboratories and developed it into a tool that can now be used by the broader community. Users interested in obtaining the GEN may contact gen@informatics.jax.org. We welcome feedback and data submissions. Data submissions will receive accession numbers that can be cited in publications, and they will be subject to several levels of review as described previously (3). The GEN is primarily designed for conventional laboratories that study expression on a gene-by-gene basis. We are also working with groups that generate mouse expression data in a high-throughput fashion. Those laboratories normally maintain their own laboratory databases from which we can download data in bulk.

FUTURE DIRECTIONS

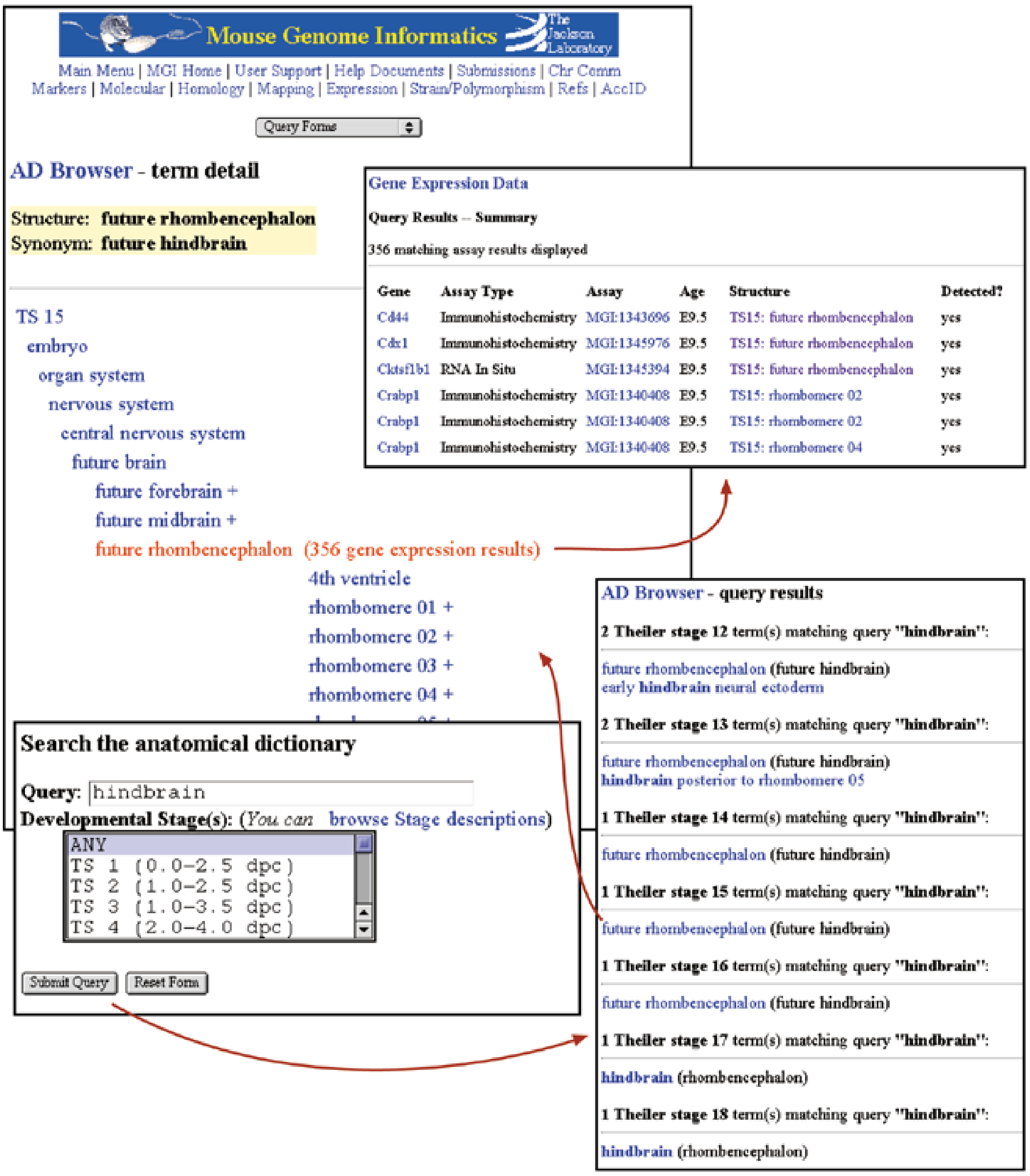
GXD will continue to acquire expression data from the literature and work with laboratories and publishers to obtain more data via electronic submission. The database will be expanded to include array expression data for the laboratory mouse. Obviously, GXD can add significant value to these data by integrating them with other types of expression data, and, via its interconnection with MGD, with genetic and phenotype data for mouse strains and mutants. We will continue to collaborate with others in establishing shared controlled vocabularies and links with external resources in order to provide an adequate and ever-improving framework for the analysis of gene expression information. Eventually, GXD will be coupled with the 3-D atlas/graphical gene expression database for mouse development, being developed by our Edinburgh colleagues, that enables a 3-D graphical storage and analysis of anatomy and *in situ* expression data (1,15,16).

USER SUPPORT

GXD provides user support through online documentation and dedicated User Support Staff. User Support can be contacted by telephone (+1 207 288 6445), fax (+1 207 288 6132) or email (mgi-help@informatics.jax.org).

CITING GXD

To reference the database itself, please cite this article. For referring to specific GXD data, we suggest the following format: These data were retrieved from the Gene Expression Database (GXD), Mouse Genome Informatics, The Jackson Laboratory, Bar Harbor, Maine, USA, World Wide Web (http://www.informatics.jax.org). [Type in date (month, year) when you retrieved the data cited.]



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Query Forms

AD Browser - term detail

Structure: future rhombencephalon
Synonym: future hindbrain

TS 15
embryo
organ system
nervous system
central nervous system
future brain
future forebrain +
future midbrain +
future rhombencephalon (356 gene expression results)
4th ventricle
rhombomere 01 +
rhombomere 02 +
rhombomere 03 +
rhombomere 04 +

Gene Expression Data

Query Results -- Summary

356 matching assay results displayed

Gene	Assay Type	Assay	Age	Structure	Detected?
Cd44	Immunohistochemistry	MGI:1343696	E9.5	TS15: future rhombencephalon	yes
Cdx1	Immunohistochemistry	MGI:1345976	E9.5	TS15: future rhombencephalon	yes
Cktsf1b1	RNA In Situ	MGI:1345394	E9.5	TS15: future rhombencephalon	yes
Crabp1	Immunohistochemistry	MGI:1340408	E9.5	TS15: rhombomere 02	yes
Crabp1	Immunohistochemistry	MGI:1340408	E9.5	TS15: rhombomere 02	yes
Crabp1	Immunohistochemistry	MGI:1340408	E9.5	TS15: rhombomere 04	yes

Search the anatomical dictionary

Query: hindbrain
Developmental Stage(s): (*You can* browse Stage descriptions)

```
ANY
TS 1 (0.0-2.5 dpc)
TS 2 (1.0-2.5 dpc)
TS 3 (1.0-3.5 dpc)
TS 4 (2.0-4.0 dpc)
```

AD Browser - query results

2 Theiler stage 12 term(s) matching query "hindbrain":

future rhombencephalon (future hindbrain)
early hindbrain neural ectoderm

2 Theiler stage 13 term(s) matching query "hindbrain":

future rhombencephalon (future hindbrain)
hindbrain posterior to rhombomere 05

1 Theiler stage 14 term(s) matching query "hindbrain":

future rhombencephalon (future hindbrain)

1 Theiler stage 15 term(s) matching query "hindbrain":

future rhombencephalon (future hindbrain)

1 Theiler stage 16 term(s) matching query "hindbrain":

future rhombencephalon (future hindbrain)

1 Theiler stage 17 term(s) matching query "hindbrain":

hindbrain (rhombencephalon)

1 Theiler stage 18 term(s) matching query "hindbrain":

hindbrain (rhombencephalon)

Figure 1. The Mouse Anatomical Dictionary Browser. The hierarchy of anatomical structures may be entered by either browsing from the top level or by searching for specific terms. Searching for a term in the Anatomical Dictionary requires a text string and optional specification of Theiler stages to search (lower left panel). Results of the query (lower right panel) are sorted by stage and each structure is linked to a detail page. The detail page for an anatomical structure displays the structure's name, synonyms and a view of the structure within the stage hierarchy (upper left panel). All superstructures, structures found at the same level as the selected structure and substructures are displayed. Each structure is linked to its own detail page. A plus sign next to a structure indicates that substructures exist. The number of expression results currently annotated to the selected structure is displayed next to the structure name. Clicking on this link retrieves expression assay result summaries (upper right panel) that lead to detailed expression data.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at NAR Online.

ACKNOWLEDGEMENTS

We would like to thank Jon Beal for his work on the Gene Expression Notebook, Lori Corbani and Prita Mani for help in software development and database maintenance, David Shaw, Paul Szauter and David Garippa for help in user support, John Boddy for artwork and Janice Ormsby for secretarial assistance. It is a pleasure to thank our colleagues Drs Jonathan Bard and Matthew Kaufman at the University of Edinburgh and Drs Duncan Davidson and Richard Baldock at the MRC Human Genetics Unit in Edinburgh for making the Dictionary of Mouse Developmental Anatomy available to us. We also would like to thank the journal *Development* for making electronic image files available to us on a regular basis. The Gene Expression Database is supported by NIH grant HD33745.

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