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FNTM: a server for predicting functional networks of tissues in mouse

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ABSTRACT

Functional Networks of Tissues in Mouse (FNTM) provides biomedical researchers with tissue-specific predictions of functional relationships between proteins in the most widely used model organism for human disease, the laboratory mouse. Users can explore FNTM-predicted functional relationships for their tissues and genes of interest or examine gene function and interaction predictions across multiple tissues, all through an interactive, multi-tissue network browser. FNTM makes predictions based on integration of a variety of functional genomic data, including over 13 000 gene expression experiments, and prior knowledge of gene function. FNTM is an ideal starting point for clinical and translational researchers considering a mouse model for their disease of interest, researchers already working with mouse models who are interested in discovering new genes related to their pathways or phenotypes of interest, and biologists working with other organisms to explore the functional relationships of their genes of interest in specific mouse tissue contexts. FNTM predicts tissue-specific functional relationships in 200 tissues, does not require any registration or installation and is freely available for use at http://fntm.princeton.edu.

INTRODUCTION

Accounting for tissue-specificity is a prerequisite to true systems-level understanding of metazoan biology. Furthermore, tissue-specific expression and function are an important aspect of many complex diseases, including stroma-tumor interactions in cancer (1), renal dysfunction following podocyte injury in glomerular microvasculature (2–6), and tissue-specific effects of insulin signaling in diabetes (7). Furthermore, an increasing number of mammalian proteins are discovered to function in a tissue- and cell-lineage-specific manner; e.g., the three closely related mammalian *Ras* genes, *Hras*, *Nras* and *Kras*, are involved in tumorigenesis in distinct lineage-specific ways, often leading to distinct malignancies (8).

However, assaying protein function and interactions at a tissue-specific level is notoriously difficult. Different tissues express different and overlapping sets of genes, and interactions between proteins are dependent on the presence of other genes in that tissue, making ascertainment of tissue-specific pathway action challenging. Predicting tissue-specific gene interactions can help us understand not only how different pathways act in different tissues, but also elucidate molecular mechanisms underlying tissue-specific phenotypes (9). FNTM (Functional Networks of Tissues in Mouse) is a prediction server for tissue-specific protein interactions for the laboratory mouse *Mus musculus*, the most widely used model organism for human disease.

A number of existing resources collect genetic and functional genomic data, while providing search and visualization functions relevant to mouse. For example, the Mouse Genome Database (10) provides extensive curated information about function and phenotype and also enables access to many mouse data sets and experimental results. Resources such as Reactome (11), BioGRID (12) and IntAct (13) host hundreds of protein interactions which are unassociated with their relevant tissue-specific contexts. NCBI GEO (14) provides search and visualization of thousands of gene expression data sets. All these resources provide considerable amounts of information about mouse genes/proteins in terms of their (i) gene functions and mutant phenotypes, (ii) tissue/cell-type-naïve physical interactions and signaling pathways, and (iii) tissue-specific gene expression levels. However, for understanding multicellular gene function, it is critical to integrate these three pieces of information. Probabilistic models have been used by us and others to integrate these diverse data sets to predict genome-

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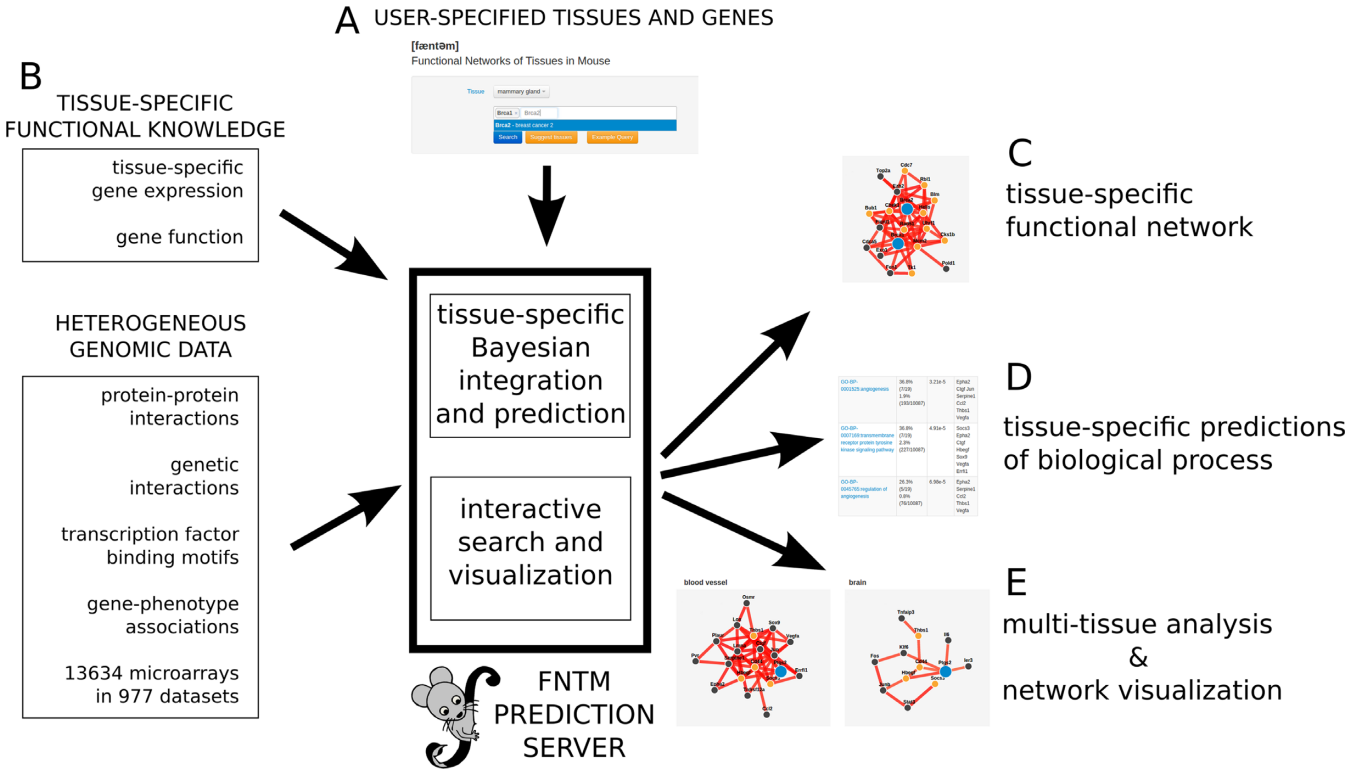

Figure 1. Overview of the FNTM prediction server. (**A**) Users initiate a prediction on FNTM with a set of genes and tissues of interest. (**B**) FNTM predicts tissue-specific functional relationships for 200 tissues by integrating heterogeneous functional genomics data with tissue-specific functional knowledge in mouse. (**C**) The server returns a network visualization of these relationships. (**D**) Using FNTM, users can then explore biological process enrichments or (**E**) add tissues to the original query to compare changes in the functional roles of their genes across tissues.

wide physical and functional interactions (15–20), and several of the resulting resources provide access to predicted networks in mouse (21–24). Nevertheless, no existing resource provides tissue-specific function and interaction prediction or ability to compare networks across tissues as provided by FNTM.

We have developed a tissue-specific data integration approach for mouse and extensively verified it in previous work (9). FNTM extends our previous tissue-specific Bayesian integration approach to generate probabilistic models for each of 200 mouse tissues, integrating functional information from over 13,000 experiments across 984 genome-scale data sets (see Supplemental Methods). FNTM enables biologists to generate hypotheses about the tissue-specific functional roles of genes by providing predicted functional interactions and making the relevant evidence easily accessible. FNTM can reveal how the role of genes changes across tissues by providing prediction and exploration capabilities that enable side-by-side exploration of multiple tissue-specific networks and biological processes represented in the networks. FNTM presents biological researchers with a flexible and user-friendly interface to search for and visualize the tissue-specific functional networks surrounding their gene/gene sets of interest, explore pathways/biological processes in which these genes participate in each tissue, view evidence underlying each relationship prediction, and directly compare networks for multiple tissues in a multi-tissue network view.

SYSTEM DESCRIPTION

FNTM analyses can provide insight on a variety of biological questions, depending on the user's specific interests, as indicated by the genes and tissues that they input into the system. For example, if users have a particular gene or gene set in a specific tissue of interest, they can investigate the functional relationships among these genes within the tissue, determine biological functions and pathways enriched in that functional context, and identify novel functional partners that can serve as candidates for further investigation. They may also be interested in comparing the functional neighborhood of this gene set across different tissues. In a situation where the user has a gene set of interest and believes them to be tissue-specific, but does not know *a priori* the relevant tissues, FNTM can also predict relevant tissues and suggest them to the user.

A FNTM prediction starts with a set of genes (or a single gene) and one or more tissues of interest specified by the user (Figure 1A). For each of the queried tissues, the server predicts the likelihood of functional relationships among these genes and to all other genes in the mouse genome by integrating 977 genome-scale expression data sets encompassing 13,634 experimental conditions (14), several sources of protein interaction data (10,25–28), tissue-specific gene expression data (29), and knowledge of shared protein function by co-annotation to GO (30) biological process terms, using the method previously described in (9) (Figure 1B, see Supplemental Table S1). The results are pre-

Figure 2. (**A**) The user has selected the tissue 'mammary gland' and entered the genes *Brca1* and *Brca2*. The resulting displayed network shows predicted functional relationships between the genes most functionally related to the query genes. The edges between genes are colored by the confidence of the predicted relationship, and the user can adjust the maximum number of genes and the minimum relationship confidence displayed with the sliders. (**B**) The top data sets contributing evidence of a functional relationship are shown when hovering the mouse over the corresponding edge in the network. A functional relationship between *Brca1* and *Exo1* is supported by several types of functional genomic data, including a variety of expression data sets. (**C**) The query gene set and its most functionally related genes are analyzed for enrichment in Gene Ontology biological process terms. Terms exceeding an FDR-corrected *P*-value of 0.05 are displayed. Adjusting the network visualization sliders also updates the gene set enrichment results to reflect the displayed genes.

sented to the user as a gene network for each queried tissue, with tissue-specific posterior probabilities of functional relationships represented as edges between the genes of interest (Figure 1C). FNTM can predict tissue-specific functional relationships for 200 tissues, covering all major mammalian organ systems.

Once FNTM has predicted the functional networks for the user-specified tissues and gene set, the user can interact with the network visualization by adjusting the coordinated layout of the networks or applying filters to the number of genes and a threshold for functional relationship confidence. The resulting network visualization can be easily exported as a text file or as a publication-quality figure. Users can further explore the network by retrieving the contribution of various data types (e.g., expression, physical interactions, etc.) and examining the top individual data sets that support any displayed functional relationship. FNTM also calculates gene set enrichment across GO biological process terms for the genes in the network neighborhood (Figure 1D). By comparing the functional relationships and GO term enrichments between tissue networks (including the tissue-naïve whole mouse network) for the same gene set (Figure 1E), biologists can find additional novel genes that are functionally related to the query genes in a specific tissue and assess how predicted gene functions change across tissues.

The method behind FNTM has been extensively evaluated by us previously (9,31). FNTM applies this tissue-specific integration approach and for the first time provides extensive tissue-specific visualization options and multi-tissue network comparison capabilities to the mouse biomedical community. In addition to the systematic evalu-

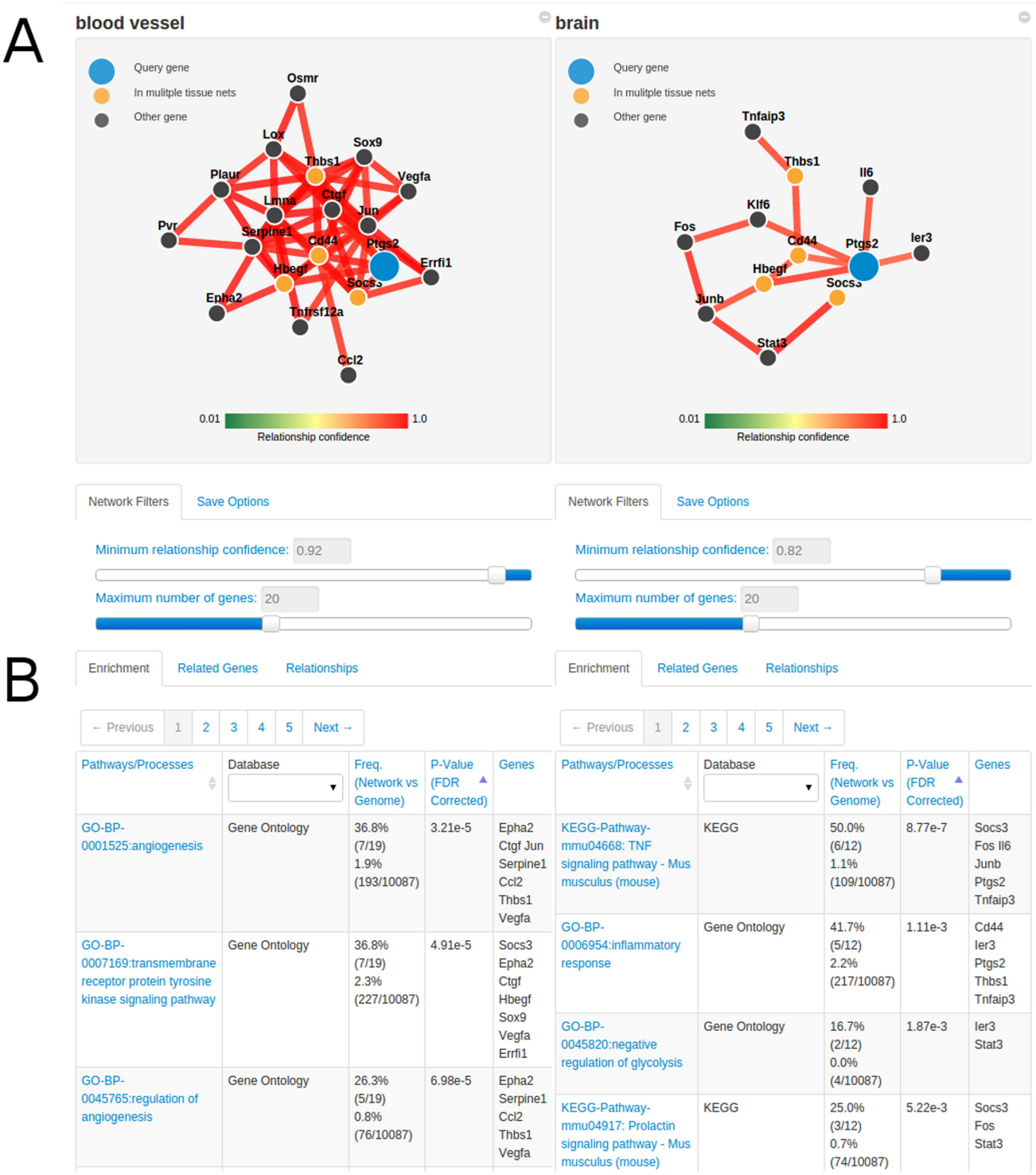

Figure 3. (**A**) The user has queried the gene *Ptgs2* (*Cox2*) for functional relationships in blood vessels and the brain. The resulting displayed networks show that *Ptgs2* has different predicted functional relationships between these two tissues. The user can adjust the maximum number of genes and the minimum relationship confidence independently for each network, and the position of the gene nodes for genes displayed in both networks is kept coordinated to ease comparison between the networks. (**B**) The tables of enrichment in Gene Ontology terms, most functionally related genes and predicted functional relationships can also be viewed side-by-side. In this case, the top functionally related genes to *Ptgs2* in blood vessels are enriched for involvement in angiogenesis, while in the brain, the top functionally related genes are enriched for inflammatory response.

ations of the approach presented in (9), we also validated the FNTM tissue-specific functional networks on an additional independent standard that assesses them in the challenging task of predicting tissue-specific gene-phenotype associations. Specifically, we held out mouse phenotype gene sets from our integration (making the integration completely independent of any phenotype information) and ranked genes based on their predicted association with each tissue-specific mouse phenotype. In our standard, we matched 575 phenotypes to 24 tissues, with a median of 60 positive and 6103 negative genes for each phenotype. FNTM demonstrated that the tissue-specific networks are informative for identifying tissue-specific gene-phenotype associations based on functional genomic data alone (mean AUC 0.613, mean precision at 5% recall 6.34-fold over background).

TISSUE-SPECIFIC FUNCTION AND NETWORK PREDICTION CASE STUDY

The simplest analysis a user can perform with FNTM is to query a gene set in a specific tissue. In Figure 2A, the user has searched for mammary gland-specific functional relationships for the genes *Brca1* and *Brca2*, two genes known to be associated with an elevated risk for breast cancer in humans through disruption of their role in DNA repair. The resulting network of functional relationship predictions (Figure 2B) shows that, in the mammary gland, these genes are functionally related to a number of other cancer-related genes such as the oncogene *Cdca5* (32) and tumor suppressors *Fen1* (33,34) and *Exo1* (35–37). In the related genes table, FNTM provides an alternative searchable view for highly connected neighbors, also identifying genes that are known to be expressed in mammary gland (*Ezh2* and *Blm*, in addition to the query genes). The gene set enrichment table (Figure 2C) indicates that *Brca1*, *Brca2* and their most functionally related genes are significantly enriched in several biological processes related to DNA replication and repair.

MULTI-TISSUE NETWORK COMPARISON CASE STUDY

A user might also be interested in comparing the functional relationships predicted among several different tissues. As shown in Figure 3, the user has queried the gene *Ptgs2* (*Cox2*) in the tissues 'blood vessel' and 'brain.' The resulting displayed networks (Figure 3A) automatically coordinate the positions of genes shared across multiple networks and retain all the functions of the single-tissue query. The user can adjust the number of displayed genes and minimum strength of functional relationships independently for each network, and the tables of gene set enrichment results, related gene lists, and functional relationships can be compared side-by-side (Figure 3B). The 20 top functionally related genes to *Cox2* in the blood vessel network are most highly enriched for angiogenesis, while for the brain network, the most highly enriched GO term is inflammatory response. Indeed, induction of *Cox2* is known to promote tumor angiogenesis (38), while it is also found to be overexpressed in the brain immediately following seizures (39), where it plays a well established role in the inflammatory response (40,41). A research physician interested in the role of *Cox2* in epilepsy could, for example, compare these networks and identify brain-specific candidate genes to knock out and study in combination with *Cox2* inhibitor treatment.

SUMMARY

FNTM provides biologists with a simple interface to explore the functional landscape of the genes and tissues relevant to their experimental questions. FNTM integrates a wide variety experimental data and curated knowledge to predict tissue-specific function for over 200 tissues. By providing tissue-specific predictions of functional relationships in a multi-tissue browser, FNTM allows users to compare the predicted functional relationships to their genes of interest across different tissues to better understand the molecular basis of tissue-specific phenotypes and to discover novel targets of clinical intervention.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

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