# VRG: a database of vascular dysfunctions related genes

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**Abstract**

Heart and vascular defects occur in a large number of hereditary and sporadic human diseases as result of a complex interplay of genetic factors. Since genome sequencing of many organisms disclosed similarities among genomes, animal models are crucial for the discovery of genes involved in those pathological processes. Therefore we propose *VRG* database, in which human data have been manually managed and integrated with mouse information in order to create a catalogue of genes involved in vascular diseases.

**Keywords:** genome, database, human vascular diseases, animal models.

# 1 Introduction

Heart and blood vessels dysfunctions are predominant causes of disability and death in humans [1]. In 2003, the World Health Organization [2] estimated that 16.7 million people die each year of cardiovascular (CV) diseases, covering 29% of all deaths around the globe, thus highlighting the value of devoting resources to study the pathogenesis of these settings.

Phenotypic alterations result from a complex network of genetic modifications [3] and a huge effort has to be done to better understand their mechanisms at the molecular scale. Even though experimental approaches could be relevant [4, 5, 6, 7], computer science provides an important support as well. It is essential, in fact, a comprehensive collection and integration of public available data generated by the research community [8, 9, 10] to allow an easy access and recovery of information. To date, different databases collect information of known genes involved in human vascular diseases. For instance, the Online Mendelian Inheritance in Man (OMIM) [10] catalogues phenotypes and genotypes classified by phenotypic features and mutated gene while the Cardiovascular Comparative Genomic Database (CVCGD) [11, 12] collects well known and comparatively annotated cardiovascular genes. However, it is not straightforward to recover a complete list of genes related to vascular dysfunctions. OMIM, for example, allows only a free-text search of clinical synopsis thus rendering difficult the selection of genes involved in vascular dysfunctions. Therefore, in order to generate an accurate collection of human genes, it would be useful to review all phenotypic OMIM entries, select those directly or indirectly related to vascular dysfunctions, and collect the corresponding genes into a catalogue as complete as possible.

The increasing availability of genomic sequences from many organisms [13, 14, 15] provided the opportunity of orthologous-sequences comparison [16, 17].

This analysis revealed that sequences performing important functions are frequently conserved among evolutionarily distant species [18, 19]. Moreover, animal models yield the identification of novel genes that often cause defects when mutated in humans and therefore they are used as a tool to investigate both mono and multifactorial human diseases [6, 8, 20, 21, 22]. Because they can be subject of large scale mutation screenings [23, 24], animals are a simple model to apply genomic strategies. For instance, knock-out (KO) mice proved useful in elucidating gene function and provided many insights into human biology and diseases [19, 23, 24]. Therefore, genome-wide collections of KO mice can significantly contribute to biomedical discovery [23]. A prominent example is represented by the Mouse Genome Database (MGD) [9, 25], a publicly available resource of KO mice which collects genomic, genetic, functional, and phenotypic data about mouse genes in order to identify candidate genes associated with complex phenotypes [26]. Since MGD has generated an ontology in order to catalogue the altered phenotypes of mutant mice, it results simple to select genes related to particular vascular dysfunctions.

Gene regulation is one of the major mechanisms underpinning the correct cardiovascular system morphogenesis and function [1, 24] and it has been demonstrated that similar molecular mechanisms are involved in its regulation both in physiological (i.e. during embryogenesis) and pathological conditions [27]. Therefore, an in depth analysis of the embryonic vascular development could yield useful information to understand the pathogenesis of vascular diseases in adults [28]. Also in this case animal models, i.e. zebrafish [29] or xenopus [30], will be crucial to improve our knowledge.

In order to reach a more comprehensive knowledge on vascular dysfunctions it could be useful to generate a complete list of human and animal genes involved in vascular phenotypic alterations. Due to the huge amount of information collected in different databases, computerized systems could simplify data recovery,

management and analysis. Therefore, we generated VRG [31], a publicly available database aimed at integrating mouse and human information, which were manually curated to create a wide catalogue of genes involved in vascular diseases.

# 2 DATABASE

## 2.1 Human section

We started with the information contained in the ftp section of the OMIM database [3] (March 2005 version). We selected two different sources of data:

- the morbidmap file
- the complete OMIM report flat-file

In the first one all the possible diseases presented in the OMIM catalogue are annotated with the corresponding related gene ids. Overall, the correspondence between a certain genetic disease and a certain pool of genes is a one-to-many relationship, meaning that it is possible to have one or more gene for a specific disease as well one or more diseases associated to the same gene id.

The second one is essentially constituted by the transposition in an ASCII computerized flat file version of the original catalogue provided by Victor McKusick's book, Mendelian Inheritance in Man. For our purposes it is necessary to specify that:

- each OMIM entry is given a unique six-digit number whose first digit indicates the mode of inheritance of the gene involved;
- each OMIM entry is characterized by a special field, called Clinical Synopsis (CS) which reports a description of the observed phenotype for the corresponding disease.

The OMIM database is actually not meant to be organized into a relational database, so an automated managing of the information contained is not straightforward. We choose the following algorithm:

For each entry of the morbid-map file, in which there is a clear correspondence between a certain gene and a certain disease, we selected the correspond-

ing CS from the OMIM file. All the possible CS collected in this catalogue were then manually-curated and divided into four main categories, where possible:

1. VASCULAR: alterations related to the vascular system
2. NEURO: alterations related to the nervous system
3. NEURO-VASCULAR: alterations related both to the nervous and the vascular system
4. INTERESTING: metabolic and/or mitochondrial alterations, so important to be related with neuro-vascular disturbs.

We than searched the Ensembl database (version 25) [32] to make a direct connection, where possible, between the gene ids internally used by OMIM and human gene ids provided by Ensembl. If available, we selected the corresponding mouse and zebrafish orthologous for each of the disease genes.

We finally grouped and stored into a MySQL relational database such information, namely:

- disease-name: name of the disease according to OMIM
- disease-id: disease identifier according to OMIM
- gene-name: gene name according to OMIM
- ENSG-id: human gene name according to Ensembl
- gene-mol-descr: description of the molecular activity of the gene
- gene-id: gene identifier according to OMIM
- location: location of the gene involved in the disease
- cs: the Clinical Synopses for the disease
- mouse-ortholog: mouse ortholog according to Ensembl
- zebrafish-ortholog: zebrafish ortholog according to Ensembl

## 2.2 Mouse section

The second source of data for our work was the Mouse Genome Informatics - MGI database [25], 3.44 version. The MGI database is a collection of a large amount of data related to all the aspects of the mouse biology and genomics. In particular we concentrated our attention on the manually curated list of mouse KO experiments recorded in the ftp section of the database. In this section, each mouse gene is annotated together with the outcome of the corresponding KO experiment, if available, and the complete list of phenotypes is then organized in a fixed and controlled vocabulary provided by the curators with unique identifiers. The vocabulary of phenotypes is internally organized in an ontology-based way. Unlike from the human case, in which a similar collection of information does not exist, the list of genes / KO phenotype can be hence handled by computational means in a rigorous manner. The MGI database also provides a connection with external databases, in particular with the Ensembl database and also includes annotations of human/mouse orthology.

For our purposes, we extracted from the MGI a list of genes related to three particular different phenotype annotations:

- MP:0005385 cardiovascular
- MP:0003631 nervous system
- MP:0005386 behavior/neurological phenotype

We identified the corresponding human and zebrafish orthologous for each of the genes selected as described above.

We finally grouped and stored into a MySQL relational database such information, namely:

- MGI-id: internal gene identifier of the MGI
- gene-id: gene identifier according to MGI

- ENSMUSG-id: mouse gene name according to Ensembl
- phenotype-id: knockout phenotype according to MGI
- human-ortholog: human ortholog according to Ensembl
- zebrafish-ortholog: zebrafish ortholog according to Ensembl

for each of three phenotypes previously selected.

Once equipped with those two relational databases, respectively built from the OMIM and MGI data, we developed a set of tools devoted to the automatic extraction of data (queries) from these databases themselves and to the automatic generation of a set of html web pages building up the VRG Disease Database, available at: `http://www.to.infn.it/ftbio/VRG-database/main.html`.

In Fig. 1 and 2 we reported two snapshots of the VRG database.

# 3 Perspectives

Here we propose a publicly available web based database collecting vascular related genes. Earlier studies have shown the advantage of comparative approaches to better understand human biological processes and their altered counterparts [19, 23, 24]. By using OMIM [3] and MGD [9, 25] , we integrated human and mouse information to create the Vascular Related Genes (VRG) database, which is structured to easily access and recover information about genes involved in vascular dysfunctions from multiple species. This allows determining similar pathogenetic mechanisms or selected specificities characterizing the role of a gene in different species or combining them thus having a more complete view of the molecular mechanisms regulating disease onset and maintaining. Moreover, it allows the exploitation of lower organisms to retrieve information that could give useful insights on human genes function and eventually to discover new diagnostic tools or therapeutic targets to treat vascular dysfunctions. However, to reach these goals additional work is required to include data coming from other animal models. Indeed, we are going to integrate zebrafish data for its qualities as a model for studies of vertebrate genetics including cardiovascular diseases [29].

Based on the new emerging parallels in the development of vascular and nervous systems [33, 34, 35], we decided to integrate vascular and neural phenotypes within the VRG database. To this aim, human and mouse genes determining phenotypic alterations of the nervous system were included in the VRG database. In particular, genes responsible of both nervous and vascular dysfunctions are collected into a separate list and could be considered candidates as new molecules regulating nerves and vessels behavior.

Hence, we propose the VRG database as a comprehensive and easily accessible catalogue of genes related to vascular and nervous dysfunctions.

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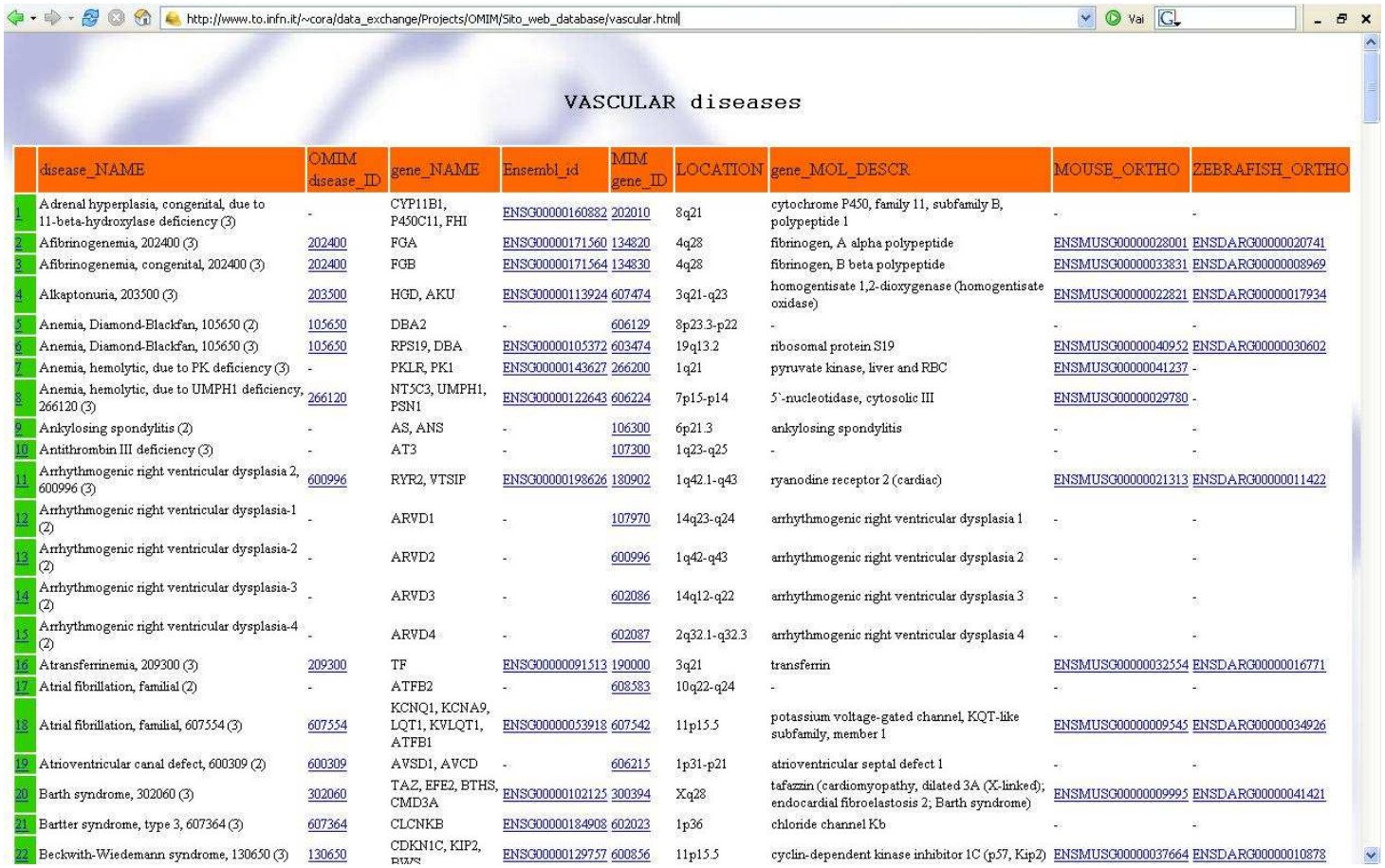
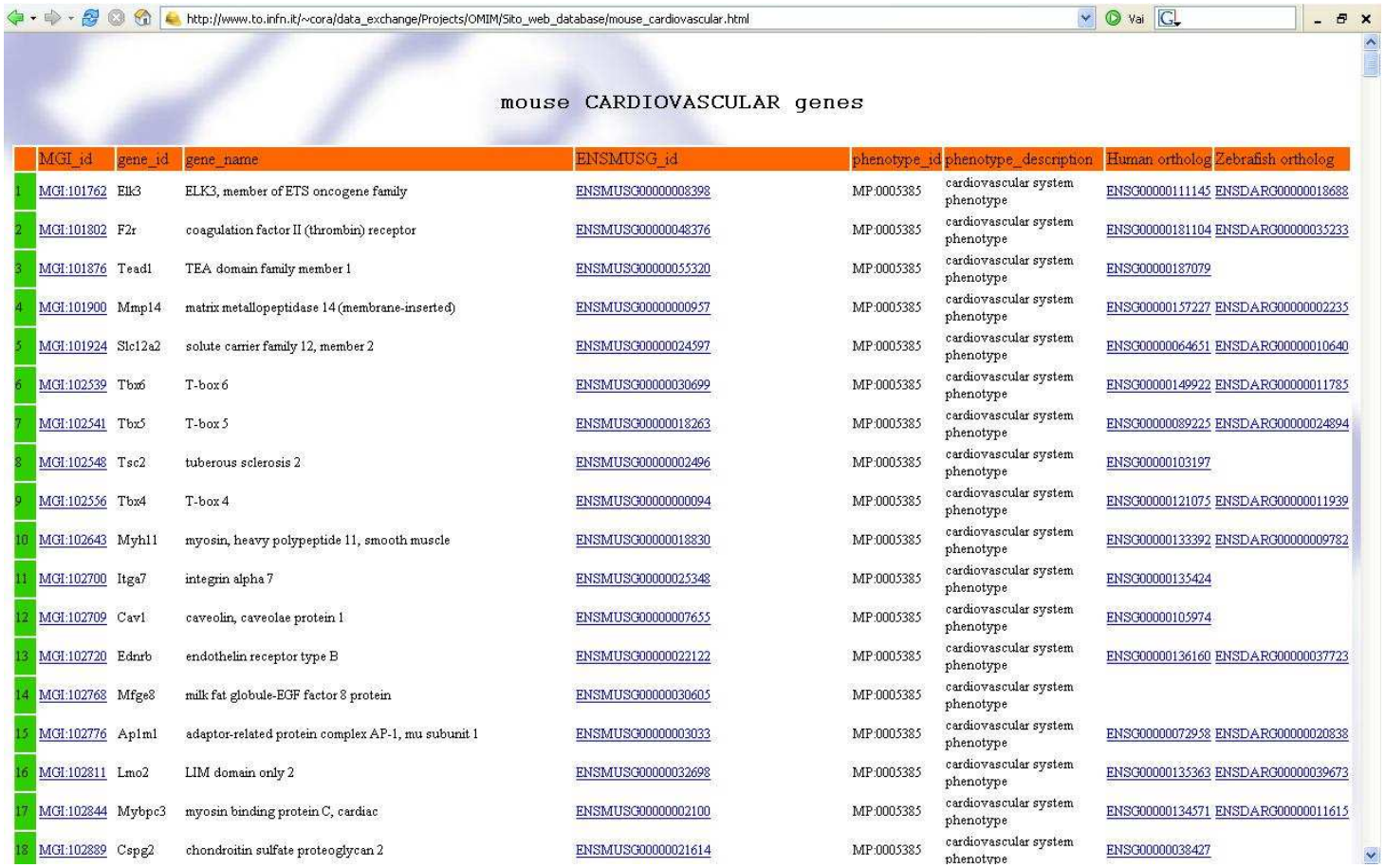



## VASCULAR diseases

| | disease_NAME | OMIM disease_ID | gene_NAME | Ensembl_id | MIM gene_ID | LOCATION | gene_MOL_DESCR | MOUSE_ORTHO | ZEBRAFISH_ORTHO |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency (3) | - | CYP11B1, P450C11, FHI | ENSG00000160882 | 202010 | 8q21 | cytochrome P450, family 11, subfamily B, polypeptide 1 | - | - |
| 2 | Afibrinogenemia, 202400 (3) | 202400 | FGA | ENSG00000171560 | 134820 | 4q28 | fibrinogen, A alpha polypeptide | ENSMUSG00000028001 | ENSDARG00000020741 |
| 3 | Afibrinogenemia, congenital, 202400 (3) | 202400 | FGB | ENSG00000171564 | 134830 | 4q28 | fibrinogen, B beta polypeptide | ENSMUSG00000033831 | ENSDARG00000008969 |
| 4 | Alkaptonuria, 203500 (3) | 203500 | HGD, AKU | ENSG00000113924 | 607474 | 3q21-q23 | homogentisate 1,2-dioxygenase (homogentisate oxidase) | ENSMUSG00000022821 | ENSDARG00000017934 |
| 5 | Anemia, Diamond-Blackfan, 105650 (2) | 105650 | DBA2 | - | 606129 | 8p23.3-p22 | - | - | - |
| 6 | Anemia, Diamond-Blackfan, 105650 (3) | 105650 | RPS19, DBA | ENSG00000105372 | 603474 | 19q13.2 | ribosomal protein S19 | ENSMUSG00000040952 | ENSDARG00000030602 |
| 7 | Anemia, hemolytic, due to PK deficiency (3) | - | PKLR, PK1 | ENSG00000143627 | 266200 | 1q21 | pyruvate kinase, liver and RBC | ENSMUSG00000041237 | - |
| 8 | Anemia, hemolytic, due to UMPH1 deficiency, 266120 (3) | 266120 | NT5C3, UMPH1, PSN1 | ENSG00000122643 | 606224 | 7p15-p14 | 5`-nucleotidase, cytosolic III | ENSMUSG00000029780 | - |
| 9 | Ankylosing spondylitis (2) | - | AS, ANS | - | 106300 | 6p21.3 | ankylosing spondylitis | - | - |
| 10 | Antithrombin III deficiency (3) | - | AT3 | - | 107300 | 1q23-q25 | - | - | - |
| 11 | Arrhythmogenic right ventricular dysplasia 2, 600996 (3) | 600996 | RYR2, VTSIP | ENSG00000198626 | 180902 | 1q42.1-q43 | ryanodine receptor 2 (cardiac) | ENSMUSG00000021313 | ENSDARG00000011422 |
| 12 | Arrhythmogenic right ventricular dysplasia-1 (2) | - | ARVD1 | - | 107970 | 14q23-q24 | arrhythmogenic right ventricular dysplasia 1 | - | - |
| 13 | Arrhythmogenic right ventricular dysplasia-2 (2) | - | ARVD2 | - | 600996 | 1q42-q43 | arrhythmogenic right ventricular dysplasia 2 | - | - |
| 14 | Arrhythmogenic right ventricular dysplasia-3 (2) | - | ARVD3 | - | 602086 | 14q12-q22 | arrhythmogenic right ventricular dysplasia 3 | - | - |
| 15 | Arrhythmogenic right ventricular dysplasia-4 (2) | - | ARVD4 | - | 602087 | 2q32.1-q32.3 | arrhythmogenic right ventricular dysplasia 4 | - | - |
| 16 | Atransferrinemia, 209300 (3) | 209300 | TF | ENSG00000091513 | 190000 | 3q21 | transferrin | ENSMUSG00000032554 | ENSDARG00000016771 |
| 17 | Atrial fibrillation, familial (2) | - | ATFB2 | - | 608583 | 10q22-q24 | - | - | - |
| 18 | Atrial fibrillation, familial, 607554 (3) | 607554 | KCNQ1, KCNA9, LQT1, KVLQT1, ATFB1 | ENSG00000053918 | 607542 | 11p15.5 | potassium voltage-gated channel, KQT-like subfamily, member 1 | ENSMUSG00000009545 | ENSDARG00000034926 |
| 19 | Atrioventricular canal defect, 600309 (2) | 600309 | AVSD1, AVCD | - | 606215 | 1p31-p21 | atrioventricular septal defect 1 | - | - |
| 20 | Barth syndrome, 302060 (3) | 302060 | TAZ, EFE2, BTHS, CMD3A | ENSG00000102125 | 300394 | Xq28 | tafazzin (cardiomyopathy, dilated 3A (X-linked); endocardial fibroelastosis 2; Barth syndrome) | ENSMUSG00000009995 | ENSDARG00000041421 |
| 21 | Bartter syndrome, type 3, 607364 (3) | 607364 | CLCNKB | ENSG00000184908 | 602023 | 1p36 | chloride channel Kb | - | - |
| 22 | Beckwith-Wiedemann syndrome, 130650 (3) | 130650 | CDKN1C, KIP2, BWS | ENSG00000129757 | 600856 | 11p15.5 | cyclin-dependent kinase inhibitor 1C (p57, Kip2) | ENSMUSG00000037664 | ENSDARG00000010878 |

Figure 1: Snapshot-1 of a page of the database.




| | MGI_id | gene_id | gene_name | ENSMUSG_id | phenotype_id | phenotype_description | Human ortholog | Zebrafish ortholog |
|---|---|---|---|---|---|---|---|---|
| 1 | MGI:101762 | Elk3 | ELK3, member of ETS oncogene family | ENSMUSG00000008398 | MP:0005385 | cardiovascular system phenotype | ENSG00000111145 | ENSDARG00000018688 |
| 2 | MGI:101802 | F2r | coagulation factor II (thrombin) receptor | ENSMUSG00000048376 | MP:0005385 | cardiovascular system phenotype | ENSG00000181104 | ENSDARG00000035233 |
| 3 | MGI:101876 | Tead1 | TEA domain family member 1 | ENSMUSG00000055320 | MP:0005385 | cardiovascular system phenotype | ENSG00000187079 | |
| 4 | MGI:101900 | Mmp14 | matrix metallopeptidase 14 (membrane-inserted) | ENSMUSG00000000957 | MP:0005385 | cardiovascular system phenotype | ENSG00000157227 | ENSDARG00000002235 |
| 5 | MGI:101924 | Slc12a2 | solute carrier family 12, member 2 | ENSMUSG00000024597 | MP:0005385 | cardiovascular system phenotype | ENSG00000064651 | ENSDARG00000010640 |
| 6 | MGI:102539 | Tbx6 | T-box 6 | ENSMUSG00000030699 | MP:0005385 | cardiovascular system phenotype | ENSG00000149922 | ENSDARG00000011785 |
| 7 | MGI:102541 | Tbx5 | T-box 5 | ENSMUSG00000018263 | MP:0005385 | cardiovascular system phenotype | ENSG00000089225 | ENSDARG00000024894 |
| 8 | MGI:102548 | Tsc2 | tuberous sclerosis 2 | ENSMUSG00000002496 | MP:0005385 | cardiovascular system phenotype | ENSG00000103197 | |
| 9 | MGI:102556 | Tbx4 | T-box 4 | ENSMUSG00000000094 | MP:0005385 | cardiovascular system phenotype | ENSG00000121075 | ENSDARG00000011939 |
| 10 | MGI:102643 | Myh11 | myosin, heavy polypeptide 11, smooth muscle | ENSMUSG00000018830 | MP:0005385 | cardiovascular system phenotype | ENSG00000133392 | ENSDARG00000009782 |
| 11 | MGI:102700 | Itga7 | integrin alpha 7 | ENSMUSG00000025348 | MP:0005385 | cardiovascular system phenotype | ENSG00000135424 | |
| 12 | MGI:102709 | Cav1 | caveolin, caveolae protein 1 | ENSMUSG00000007655 | MP:0005385 | cardiovascular system phenotype | ENSG00000105974 | |
| 13 | MGI:102720 | Ednrb | endothelin receptor type B | ENSMUSG00000022122 | MP:0005385 | cardiovascular system phenotype | ENSG00000136160 | ENSDARG00000037723 |
| 14 | MGI:102768 | Mfge8 | milk fat globule-EGF factor 8 protein | ENSMUSG00000030605 | MP:0005385 | cardiovascular system phenotype | | |
| 15 | MGI:102776 | Ap1m1 | adaptor-related protein complex AP-1, mu subunit 1 | ENSMUSG00000003033 | MP:0005385 | cardiovascular system phenotype | ENSG00000072958 | ENSDARG00000020838 |
| 16 | MGI:102811 | Lmo2 | LIM domain only 2 | ENSMUSG00000032698 | MP:0005385 | cardiovascular system phenotype | ENSG00000135363 | ENSDARG00000039673 |
| 17 | MGI:102844 | Mybpc3 | myosin binding protein C, cardiac | ENSMUSG00000002100 | MP:0005385 | cardiovascular system phenotype | ENSG00000134571 | ENSDARG00000011615 |
| 18 | MGI:102889 | Cspg2 | chondroitin sulfate proteoglycan 2 | ENSMUSG00000021614 | MP:0005385 | cardiovascular system phenotype | ENSG00000038427 | |

Figure 2: Snapshot-2 of a page of the database.