



Improving Interpretation of Cardiac Phenotypes and Enhancing Discovery With Expanded Knowledge in the Gene Ontology

BACKGROUND: A systems biology approach to cardiac physiology requires a comprehensive representation of how coordinated processes operate in the heart, as well as the ability to interpret relevant transcriptomic and proteomic experiments. The Gene Ontology (GO) Consortium provides structured, controlled vocabularies of biological terms that can be used to summarize and analyze functional knowledge for gene products.

METHODS AND RESULTS: In this study, we created a computational resource to facilitate genetic studies of cardiac physiology by integrating literature curation with attention to an improved and expanded ontological representation of heart processes in the Gene Ontology. As a result, the Gene Ontology now contains terms that comprehensively describe the roles of proteins in cardiac muscle cell action potential, electrical coupling, and the transmission of the electrical impulse from the sinoatrial node to the ventricles. Evaluating the effectiveness of this approach to inform data analysis demonstrated that Gene Ontology annotations, analyzed within an expanded ontological context of heart processes, can help to identify candidate genes associated with arrhythmic disease risk loci.

CONCLUSIONS: We determined that a combination of curation and ontology development for heart-specific genes and processes supports the identification and downstream analysis of genes responsible for the spread of the cardiac action potential through the heart. Annotating these genes and processes in a structured format facilitates data analysis and supports effective retrieval of gene-centric information about cardiac defects.

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Clinical Perspective

Identification of critical proteins and RNAs as potential drug targets requires computationally accessible descriptors, both in terms of their roles in biological pathways and the molecules they interact with to fulfill their actions. This information is also vital in choosing prognostic and diagnostic biomarkers, particularly for multifactorial diseases such as heart disease that might benefit from measurement of multiple biomarkers. Recent improvements in omic technologies have led to projects such as the 100 000 Genomes Project and genome-wide association studies, which are producing vast amounts of genetic data pertinent to human health. Furthermore, it is now possible to catalog which proteins or RNAs are present in normal or disease tissues, or individual cells. Understanding the molecular network or biological processes associated with a drug target can help predict off-target effects or the potential for drug repurposing because many gene products are active in multiple pathways. In addition, these networks can be used to predict the most efficacious molecules within the networks, through the identification of key positions at which the whole networks may be perturbed; these molecules are often associated with disease-causing mutations or identified as drug targets. One of the major resources used by omic researchers is the Gene Ontology. This article explains the considerable improvements made by the Gene Ontology Consortium in the bioinformatic description of cardiac physiology. These new descriptions are all based on published data and are now included in all major biological databases, thus available for use by the global scientific community to enhance the understanding of cardiovascular-relevant data.

Cardiac electrical conduction systems enable coordinated regulation of heart contraction in metazoans, ranging from fly to human. Disturbances of normal heart rhythm can occur *de novo*, but, more critically and commonly, they are an important feature of many cardiac diseases, and have substantial impacts on patient morbidity and mortality. To gain insight into the mechanisms of arrhythmia, high-throughput genome-scale methodologies (including genome-wide association studies [GWAS], transcriptomics, exon sequencing, and proteomics) are being used.^{1–3} However, interpretation of these high-throughput experiments relying on descriptions of the cellular and physiological roles of gene products, and a computational approach to interrogation of cardiac gene function, is a bottleneck in these analyses. Our work aims to fill this gap by capturing information

in the Gene Ontology (GO) resource in a structured way, thus integrating knowledge about genes, cells, tissues and organs. To support data interpretation, the GO Consortium (GOC) provides a freely available, structured, controlled vocabulary, the ontology,⁴ that enables association of defined terms, describing cellular roles and locations, with a protein or RNA. This association process, called GO annotation, provides a computer-interpretable summary of the results of many independent experiments. GO terms describe Molecular Functions (molecular activities of a gene product), Biological Processes (the broader context in which a gene product acts), and Cellular Components (the subcellular location of a gene product). Some examples of GO terms relevant to cardiac research are, respectively, *voltage-gated sodium channel activity*, *Purkinje myocyte action potential*, and *Z disc*.

GO provides users with a summary of experimentally verified or predicted functions of genes, proteins, and RNAs.^{3,5} Because of this high-impact information, GO data are incorporated into over 50 functional analysis tools and is routinely used to analyze large data sets.⁶ The coordinated action of gene products involved in cardiac conduction at the cellular level results in proper heart functioning at the organ level and in healthy conditions at the whole organism level. Therefore, detailed and interoperable knowledge about gene products' roles is essential to better analyze heart failure phenotypes and ultimately to address potentially fatal conditions. The features listed above make GO an ideal resource to aid the interpretation of large-scale cardiac physiology investigations.

Before our expansion of the cardiac function domain, there were only 3 GO terms to describe how the cardiac cycle is coordinated: *cardiac conduction*, *membrane depolarization during atrial cardiac muscle cell action potential*, and *membrane repolarization during atrial cardiac muscle cell action potential*. In this article, we detail how GO editors and biocurators worked together with experimental researchers to ensure provision of accurate structured terminology⁷ that describes features of gene products involved in cardiac physiology, and to generate GO annotations⁸ that capture those roles based on published literature, thereby improving representation of this area of biology. In particular, we focused on processes involved in and regulating the coordinated contraction of the heart. We also show that our effort improves the investigation of heart-related GWAS and transcriptomic data sets.

METHODS

The data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedure. Protein, RNA, and macromolecular complex GO annotations are available from the UniProt GO annotation and GOC sites (<https://www.ebi.ac.uk/GOA/downloads>, <http://www.geneontology.org/gene-associations/>) and searchable in the AmiGO2⁷ and QuickGO⁹ browsers; GO

terms are downloadable from the GOC site (<http://www.geneontology.org/ontology/>) and searchable in AmiGO2 and QuickGO. The annotations have also been incorporated into many biological knowledge bases, including Ensembl,¹⁰ UniProtKB,¹¹ and NCBI-Gene,¹² and exploited by numerous freely available functional analysis tools, including Database for Annotation, Visualization and Integrated Discovery,¹³ g:profiler,¹⁴ Protein Analysis Through Evolutionary Relationships (PANTHER),¹⁵ and Visual Annotation Display (VLAD).¹⁶ Full methods are available in the [Data Supplement](#).

Generation of a Prioritized List of Cardiac Physiology-Relevant Gene Products

A list of 88 human proteins known to be required for normal cardiac function was compiled based on 8 literature reviews^{17–24} (Table I in the [Data Supplement](#)). To keep the focus more specifically on ion channels, the following were not retained in the prioritized list of genes: ATPases, ATPase regulatory proteins, hormones, hormone receptors, and proteins required for normal heart development. However, angiotensinogen and 2 angiotensin I-converting enzymes were included in the prioritized protein list to ensure that the ontology was sufficiently developed to enable future projects to capture the role of gene products that regulate heart rate and contraction.²⁵ Orthologs of these 88 human proteins were identified in mouse, rat, zebrafish, and *Drosophila* using the Protein Analysis Through Evolutionary Relationships orthology prediction tool.¹⁵ In addition, a list of 7 human microRNAs (miRNAs) identified as key players in modulating cardiac excitability at the time we started our curation effort was determined from 3 reviews^{26–28}; literature available for these miRNAs was curated up to March 2016. Prioritized human gene products described above are listed in Table I in the [Data Supplement](#), and for all of them, GO annotations supported by experimental data were included in the GO database according to established procedural guidelines^{8,29,30} (details are given in Methods in the [Data Supplement](#)).

Identification of Candidate Genes Associated With Arrhythmia Risk Loci

We compiled a list of Mendelian inherited arrhythmia disorder genes associated with atrial fibrillation, long-QT syndrome, short-QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome^{1,31,32} and candidate genes associated with GWAS risk loci for these disorders^{2,31} (literature search February 2016; Table II in the [Data Supplement](#)). Nine GO terms relevant to normal cardiac physiology (such as *cardiac conduction*, *muscle contraction*, and *response to oxygen levels*) were selected to investigate whether gene annotations to these normal processes could be correlated with arrhythmia candidate genes (Table III in the [Data Supplement](#)), and the associated annotations were downloaded on March 11, 2016 using the QuickGO browser⁹ (<http://www.ebi.ac.uk/QuickGO/>; Methods in the [Data Supplement](#)).

GO Functional Analysis of Transcriptomic Data Sets

A ventricular cardiomyocyte (VCM) data set³ was analyzed using the BinGO plugin³³ within the Cytoscape v3.3.0 tool,³⁴ applying

the recommended hypergeometric test and Benjamini and Hochberg False Discovery Rate correction, and a *P* value <0.05 (full details in Methods in the [Data Supplement](#)). To determine the impact of this focused project, we used gene association files from November 2011 (ie, the start of this project) and February 2016 (ie, the end of the project; files available from <ftp://ftp.ebi.ac.uk/pub/databases/GO/goa/>). For both analyses, the ontology version March 7, 2016 was included (available from <http://geneontology.org/page/download-ontology>).

RESULTS

Representation of Cardiac-Relevant Gene Products' Features Via Ontology Development

A coordinated working group of GO editors, GO biocurators, and field experts expanded the cardiac physiology domain by adding 197 new cardiac-relevant GO terms (Methods and Table IV in the [Data Supplement](#)). Of these, 87 refer to processes that contribute to cardiac conduction and thus describe the propagation of the action potential through the conduction system and cardiac chambers. An example of an ontology branch representing cardiac-relevant GO terms is shown in Figure.

The expansion of the cardiac-related processes in GO describes events that occur at 3 key biological levels: the single cell, the tissue (multicellular), and the organ. In addition to these biological levels, the ontology was expanded to cover generic processes (such as *regulation of potassium ion export*) or developmental processes (such as *cardiac pacemaker cell differentiation*) required for the annotation of cardiac-relevant gene products. These new ontology terms enable biocurators to capture the role of gene products in specific tissues of the heart (by applying GO terms such as *adrenergic receptor signaling pathway involved in cardiac muscle relaxation*), specific cell types (eg, *atrioventricular (AV) node cell to bundle of His cell communication*), and the whole organ (eg, *regulation of the force of heart contraction by cardiac conduction*). The addition of both generic terms, and terms that reference specific anatomical structures, allowed us to overcome challenges with respect to granularity of organism specificity. For example, the term *cell communication involved in cardiac conduction* can be used for any organism with a cardiac organ, and a child term like *AV node cell to bundle of His cell communication* can be used specifically for species that have the relevant anatomical structures, in this case AV node and bundle of His. By describing processes at the various levels, curators can choose appropriate terms with respect to the experiments and organisms they are curating. Where possible, terms were defined by creating necessary and sufficient statements using relationships between GO terms and terms from cross-referenced external ontologies, such as Uberon for anatomical structures, the Cell Ontol-

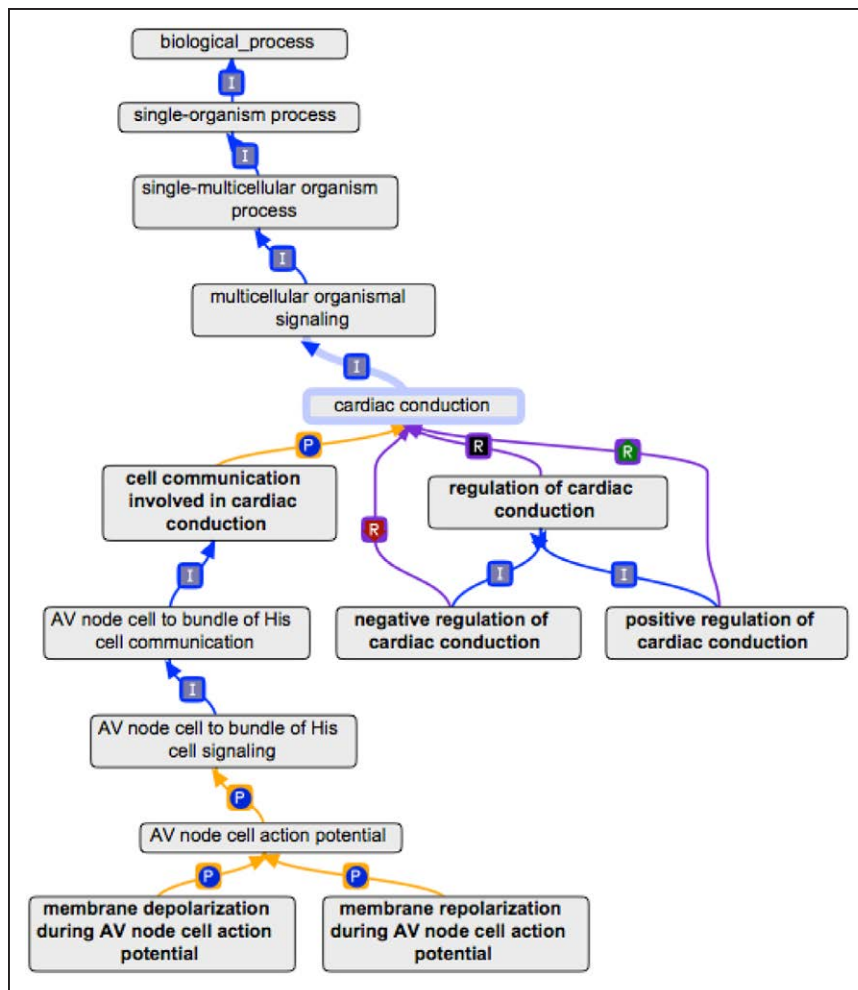


Figure. Part of the ontology describing AV node cell action potential and the regulation of ventricular cardiac muscle cell action potential.

The entire model is not shown; this portion graphically illustrates how ontology terms relate to each other. Blue lines marked with I indicate the child term is a type of its parent, and orange lines marked with P indicate that child term is always a part of its parent. Purple lines marked with R indicate regulates, positively regulates, or negatively regulates relations.

ogy for cell types, and Chemicals of Biological Interest for chemicals (ChEBI), taking advantage of their species interoperability and thus making the terms accessible to computational reasoning.³⁵

Cell-to-Cell Communication in the Heart

Cell communication is a key aspect of the coordinated activity of the heart. We created new terms, such as *cell communication involved in cardiac conduction*, to bring together all processes that mediate interactions between a cell and its surroundings and that also contribute to the process of cardiac conduction. This part of the ontology now includes terms to describe cell-to-cell impulse propagation by means of cardiac action potentials and electrical coupling (such as *AV node cell to bundle of His cell communication by electrical coupling*), as well as terms to describe the attachment of one cell to another or to the extracellular matrix (such as *bundle of His cell-Purkinje myocyte adhesion involved in cell communication*). In addition, many of the 22 new cardiac conduction-relevant Molecular Function terms describe channel or transporter activities that are necessary to propagate the electrical signals between specific cells and across the heart (eg, *gap*

junction channel activity involved in cardiac conduction electric coupling).

The cardiac action potential branch of GO includes terms referring to a variety of cell types within the heart (Figure), such as *AV node cell action potential*, *membrane depolarization during AV node cell action potential* and *membrane repolarization during AV node cell action potential*, as well as terms that describe the regulation of the action potential (not shown). Similar terms also describe action potentials in SA node cells, bundle of His cells, and Purkinje myocytes (not shown).

Ensuring Capture of Robust Information About Genetic Contributions to Cardiac Physiology via GO Annotation

There is a considerable volume of literature describing the physiological characterization of the heart. This project brought together expertise from University College London,³⁶ Queen Mary University of London, University of Oxford, Mouse Genome Informatics,³⁷ the Rat Genome Database,³⁸ the Zebrafish Information Network,³⁹ and FlyBase.⁴⁰ It was unrealistic for the information from all

cardiac physiology research papers to be captured during this project; however, over 500 papers have been reviewed and used to annotate cardiac-relevant gene products with the expanded GO structure. A key aspect of gene product GO annotation is the recognition that a single gene product may have several functions, may participate in multiple processes, and can be found in a variety of subcellular locations. Consequently, fully describing how a gene functions typically results in >1 GO term associated with a single gene product⁴ (Table 1).

The aim of creating multiple statements (annotations) about a single gene product is to comprehensively capture the knowledge about its biological role, as supported by published experimental data. For example, over 30 papers were curated to provide information about the human sodium channel SCN5A (Q14524). Individual experiments, such as immunostaining, expression of various sodium channel constructs in *Xenopus* oocytes or rat cardiomyocytes, combined with descriptions of cardiac disease associated with the protein, such as long-QT and Brugada syndromes, have provided evidence that this protein is found in the *Z disk*,⁴¹ has *voltage-gated sodium channel activity involved in cardiac muscle cell action potential*,⁴² and is involved in *membrane depolarization during Purkinje myocyte cell action potential*.⁴³ In contrast, the experimental data described in a single paper⁴⁴ supported 9 annotations

for the human protein RNF207 (Q6ZRF8). This article also resulted in 18 experimentally supported annotations to 5 other human proteins (DNAJA1, P31689; HSPA1A, P0DMV8; HSPA1B, P0DMV9; HSPA8, P11142; KCNH2, Q12809) and 1 zebrafish protein (Rnf207b, E9QHE3).

There is increasing evidence for the role of miRNAs in controlling cardiac physiology, particularly in the regulation of potassium and calcium ion channel function, where dysregulation can lead to aberrant action potential duration and cardiac conduction.^{27,28} For this project, 7 miRNAs were prioritized for annotation (Methods and Table I in the [Data Supplement](#)), resulting in 27 annotations with relevance to cardiac function. For example, Li et al⁴⁵ demonstrated that miR-1 (URS00001DC04F_9606) and miR-133a (URS00004C9052_9606) could regulate the slow delayed rectifier potassium current (I_{Ks}) in human cells during simulated hyperglycemia. Furthermore, they showed that this was because of their ability to regulate the expression of 2 potassium channel proteins, KCNE1 (P15382) and KCNQ1 (P51787), which mediate I_{Ks} . These roles of miR-1 and miR-133a have been captured by the terms *negative regulation of membrane repolarization during cardiac muscle cell action potential* and *negative regulation of delayed rectifier potassium channel activity*, as well as *gene silencing by miRNA*, with KCNE1 included as the target of miR-1 and KCNQ1 as the target of miR-133a in annotation extensions (Methods in the [Data Supplement](#)).

Table 1. Selection of GO Annotations Associated With Human ACE2

GO Identifier	GO Term Name	Code	Reference	With
Biological process				
GO:0002005	Angiotensin catabolic process in blood	IC	PMID:10924499	GO:0004180
GO:0003081	Regulation of systemic arterial blood pressure by renin-angiotensin	IMP	PMID:18258853	...
GO:0019229	Regulation of vasoconstriction	IC	PMID:15380922	GO:0004180
GO:0046813	Receptor-mediated virion attachment to host cell	IDA	PMID:18343844	...
GO:0060452	Positive regulation of cardiac muscle contraction	IEA	GO_REF:0000019	Ensembl: ENSMUSP00000107890
GO:1903598	Positive regulation of gap junction assembly	IMP	PMID:12967627	...
GO:1903779	Regulation of cardiac conduction	IMP	PMID:12967627	...
Molecular function				
GO:0004175	Endopeptidase activity	IDA	PMID:15283675	...
GO:0004180	Carboxypeptidase activity	IDA	PMID:10969042	...
GO:0005515	Protein binding	IPI	PMID:21068237	UniProtKB:O15393
Cellular component				
GO:0005576	Extracellular region	IEA	GO_REF:0000037	UniProtKB-KW:KW-0964
GO:0070062	Extracellular exosome	IDA	PMID:19056867	...
GO:0016020	Membrane	IEA	GO_REF:0000002	InterPro:IPR001548

A selection of the 61 annotations associated with human ACE2 (Q9BYF1) illustrates the range of annotations associated with a single protein. Code indicates the evidence code used to support the annotation (www.geneontology.org/GO.evidence.shtml)⁸; Reference lists the source of the data supporting the annotation, this may be the curated article or information about the electronic annotation pipeline; and the With field provides additional information to support the annotation, such as the Gene Ontology (GO) identifier which supports an IC annotation or the Ensembl identifier from which the annotation is propagated.⁸

IC indicates Inferred by Curator; IMP, Inferred from Mutant Phenotype; IDA, Inferred from Direct Assay; IEA, Inferred from Electronic Annotation; IPI, Inferred from Physical Interaction.

The Application of Information Derived From Orthologs

Experimental data to support GO annotations are not always available for human proteins and especially not for miRNAs, but may be obtainable for model organism orthologs. Inferential assertions about the roles of human gene products can be achieved by mapping annotations from their orthologous gene products. The electronic pipeline Ensembl Compara ensures that experimentally supported annotations associated with those proteins that have a 1-to-1 ortholog across human, mouse, and rat are applied to all orthologs.¹⁰ For example, the predicted 1-to-1 orthology between the mouse ACE2 (Q8R0I0) and human ACE2 (Q9BYF1) proteins as defined by Compara has enabled 3 experimentally supported mouse ACE2 annotations (including *positive regulation of cardiac muscle contraction*) to be associated with human ACE2. The GOC also provides an expert curation tool, called Phylogenetic Annotation and Inference Tool,⁴⁶ that enables biocurators to infer annotations across many species based on phylogenetic relationships and protein family membership. In addition, in some cases where knowledge from Compara and Phylogenetic Annotation and Inference Tool was not available, orthology was reviewed on a case-by-case basis and used to support transfer of annotations to the orthologous proteins⁴⁷ (see next section and Methods in the [Data Supplement](#)).

Comprehensive Capture of Information About Prioritized Gene Products Through Annotation

The manual annotation of the 88 heart-relevant human proteins that were prioritized in this effort (Table I in the [Data Supplement](#)) led to the submission of over 3100 annotations to the GO database. This represents a 4-fold increase in the number of manual annotations associated with these proteins. Furthermore, annotation of model organism experimental data has provided a further 2000 annotations to 82 of these proteins through the transfer of experimentally supported annotations to orthologous human proteins via the Ensembl Compara pipeline,¹⁰ Phylogenetic Annotation and Inference Tool,⁴⁶ and other expert curation methods.⁴⁷ To supplement the orthology-based curation, we manually transferred 50 relevant biological process annotations from mouse or rat to human, using the Inferred From Sequence or Structural Similarity evidence code.⁸ When annotations provided through other electronic pipelines⁴⁷ (such as mappings between UniProtKB Keywords and InterPro) are included, the 88 prioritized human proteins have a total of 7263 annotations (as of March 2017). The number of annotations per protein ranges from 20 associated with RNF207 (Q6ZRF8) to 272 associated with CAV1 (Q03135), with an average of 82 annotations per protein. Over 140 annotations

are associated with the 7 prioritized human miRNAs. Therefore, this curation effort allowed bioinformatic capture of knowledge of genes that were not represented before, and it enables more informative data analysis, as shown below.

Using GO to Interpret GWAS

GWAS have identified many risk loci associated with cardiac disorders.^{1,31} In some cases, the impact of a variant on a protein-coding gene is relatively easy to identify because of predicted, and often experimentally verified, deleterious nonsynonymous substitutions. However, often risk variants identified in a genomic area fall within an intronic, intergenic, or regulatory region, making it difficult to identify the true causative variant(s) associated with the risk, and which protein-coding genes or functional RNA genes should be considered as candidates contributing to a disease.^{2,31} The cost of investigating a candidate gene's role in a disease is considerable. Consequently, before experimental investigation, various *in silico* approaches are generally undertaken to try to narrow down the choice of which gene in a gene-rich region is involved in a disease. If nonsynonymous deleterious gene variants in a gene in the same region have already been associated with a similar phenotype, this is good supporting evidence for candidate gene choice. However, other approaches, such as those described by MacArthur et al,⁴⁸ may also be valuable. These include considering whether any of the potential candidate genes encode a protein that interacts with proteins previously implicated in the disease (either using *in silico* network analysis or through coimmunoprecipitation experiments), or if the gene is expressed in tissues relevant to the disease (eg, by using expression quantitative trait loci data³¹).

MacArthur et al⁴⁸ also describe selecting candidate genes based on a known function or role which is shared with other genes established as associated with the disease of interest or is consistent with their mutant phenotype. This approach can be easily undertaken using GO annotation data, and yet it is rarely included in the *in silico* investigations of GWAS results. After our focused annotation effort, the ability to use GO annotations to identify candidate genes associated with arrhythmia disorders was evaluated. Human proteins associated with 9 GO terms that are relevant to normal cardiac physiology were downloaded using QuickGO⁹ (GO terms are shown in Table IV in the [Data Supplement](#)). The corresponding genes were then compared with Mendelian genes for arrhythmia disorders (atrial fibrillation, long-QT syndrome, short-QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome^{1,31,32}) and with GWAS candidate variants associated with QT interval length and atrial fibrillation risk loci, described by Tucker et al² and Arking

et al.³¹ Of 45 Mendelian arrhythmia-associated genes (described in 3 reviews to 2015^{1,31,32}), 43 were annotated with ≥1 of the cardiac-relevant GO terms (Table II in the [Data Supplement](#)), with *SRL* and *GREM2* being the exceptions. The GO annotations associated with the 83 GWAS-identified candidate genes (associated with 48 risk loci) suggest that GO data can contribute to prioritization of candidate risk genes. Cardiac physiology-relevant GO terms suggest the prioritization of 36 of the 83 candidate genes. This selection approach compares favorably with that taken by Arking et al.³¹ In that study, authors identified 35 common variant QT interval loci and used expression quantitative trait loci, protein interaction, and coimmunoprecipitation data to identify 70 candidate genes associated with these loci (Table II in the [Data Supplement](#)). Both the GO and the expression quantitative trait loci approaches suggest 27 QT interval candidate genes, whereas coimmunoprecipitation suggests 12 genes and in silico protein interaction networks 15 genes. For example, GO annotations hint that *RNF207*, at 1p36, is a good candidate for variations in QT interval length, with annotations to 6 of the key GO terms, and that potassium transport-associated *KCNAB2* is a good alternative candidate. In contrast, in silico protein interaction data support 3 other genes at this locus (*ACOT7*, *KCNAB2*, and *RPL22*; Table 2). Similarly, GO annotation information narrows the candidates at the 3p21 locus to 3 genes (*MYL3*, *SCAP*, and *SETD2*; Table 2), with *MYL3* having the strongest anno-

tation support, because of its role in muscle contraction and heart development; the analysis provided by Arking et al.³¹ suggested 5 candidate genes at this locus. Notably, at the 1q24 risk locus, GO annotations, expression quantitative trait loci, and coimmunoprecipitation data all suggest *ATP1B1* as the candidate gene (Table 2). This illustrates that GO annotations can provide additional data to either support the choice of candidate genes or suggest alternative candidates.

Functional Analysis of Atrial and Ventricular High-Throughput Data Sets

To provide a measure of the impact of our cardiac-focused annotation project on data interpretation, we compared the functional analysis of a specific heart transcriptomic data set using GO annotations available in November 2016 to an equivalent analysis using GO annotation data available in February 2011. A VCM transcriptomic data set³ was used to investigate this, as we anticipated that a ventricular-specific transcriptome was likely to include the ion channels, and their regulators, required for cardiac repolarization and depolarization. Poon et al.³ profiled the transcriptome of human embryonic stem cells and compared this to the transcriptome of adult human VCMs, after filtering out the transcripts that were not significantly differentially expressed between the 2 cell types.³ Poon et al.³ found that GO terms describing translation elongation,

Table 2. Using GO to Support the Identification of the Likely Causative Gene Associated With 3 QT Interval Risk Loci³¹

QT Interval Risk	rs846111			rs10919070		rs17784882						
Nearest Gene	<i>RNF207</i>			<i>ATP1B1</i>		<i>ELP6</i>						
GWAS Candidate Gene		<i>ACOT7</i>	<i>KCNAB2</i>	<i>RPL22</i>		<i>NME7</i>		<i>KLHL18</i>	<i>MYL3</i>	<i>PTPN23</i>	<i>SCAP</i>	<i>SETD2</i>
GO term name												
Cardiac conduction	*				*							
Regulation of membrane potential	*				*							
Actin filament-based process	*								*			
Potassium ion transmembrane transport	*		*		*							
Sodium ion transmembrane transport					*							
Calcium ion transmembrane transport					*							
Muscle contraction	*				*				*			
Heart development	*								*			*
Response to oxygen levels					*						*	
Candidate gene predicted by												
GO annotation data	<i>RNF207</i>		<i>KCNAB2</i>		<i>ATP1B1</i>				<i>MYL3</i>		<i>SCAP</i>	<i>SETD2</i>
eQTL or protein interaction data		<i>ACOT7</i>	<i>KCNAB2</i>	<i>RPL22</i>	<i>ATP1B1</i>	<i>NME7</i>		<i>KLHL18</i>	<i>MYL3</i>	<i>PTPN23</i>	<i>SCAP</i>	<i>SETD2</i>

Gene Ontology (GO) annotation data can be used to provide additional information about candidate genes, located close to the risk loci, and add to the information provided by expression quantitative trait loci data (eQTL) or protein interaction data (full list of arrhythmia associated genes in Table II in the [Data Supplement](#)). Association of these terms with the genes in close proximity to the QT interval risk loci suggests that these are candidate causative genes. At the bottom of the table, the candidate gene predicted by either GO annotation, eQTL, or protein interaction data is listed: GO annotation data (based on the annotations listed in the table); eQTL or protein interaction data (based on eQTL, in silico QT interval loci protein network analysis or coimmunoprecipitation with 1 of 5 LQTS Mendelian proteins³¹).

*The association of 1 of the 9 selected GO terms with a listed gene.

as well as muscle system, contraction, and energy generation (their wording), were enriched within the 200 most abundant transcripts in adult human VCMs. Our analysis using the 2011 and 2016 GO annotation data sets confirms findings of Poon et al,³ with the majority of these proteins annotated to either *muscle contraction*, *mitochondrion organization*, *respiratory electron transport chain*, *gene expression*, or *developmental process* terms. Notably, our analysis also demonstrates that the terms *cardiac conduction*, *regulation of cardiac conduction*, and *regulation of the force of heart contraction* (among others) were significantly enriched in the 2016 analysis. Although VCMs are not involved in cardiac conduction, it is not unexpected that *cardiac conduction* and child terms will be enriched in a ventricular data set, because many of the same action potential-associated proteins are present in ventricular, atrial, and conduction tissues.²³ The identification of the cardiac-specific terms within this data set does, however, confirm that the GO terms and annotations created by this focused project are sufficient to enable the identification of the increased expression of genes involved in these processes. In 2011, many of the cardiac physiology GO terms did not exist, and consequently, these terms are (understandably) not enriched using the 2011 annotation data set (Table 3; Table V in the Data Supplement).

DISCUSSION

In this article, we describe work to improve the GO resource in representing relevant cardiac processes, and in capturing roles of gene products from published literature through GO annotation. The majority of publications describing heart or cardiomyocyte transcriptomic and proteomic data sets use GO annotations

to investigate the pathways associated with this important organ.^{3,5} We tested whether our recent cardiac-relevant annotations could be used to support a more informative interpretation of high-throughput studies. Our reanalysis of the top 200 differentially expressed transcripts in adult human VCMs³ (compared with the human embryonic stem cells transcriptome; Table V in the Data Supplement) confirms the original findings of Poon et al³ and, in addition, shows that the transcriptome of these cells is enriched for GO terms referring to cardiac physiology, including *cardiac conduction*, *regulation of cardiac conduction*, *regulation of cardiac muscle contraction by calcium ion signaling*, and *regulation of the force of heart contraction*. Notably, the enrichment of these terms is only possible because of the expansion of the GO resource in this area. These cardiac-relevant terms are identified despite more than half of these highly expressed proteins being associated with protein synthesis, mitochondrial respiratory systems, or having a structural cellular role. The significance of our work lies in the enhanced ability to identify cardiac-relevant genes within cardiac tissue; cardiac physiologists can now use the GO to test genomic profiles and confirm the presence of relevant genes. For example, researchers who are using in vitro cardiac cell differentiation systems can now test the profiles of gene expression in their cells to examine and confirm progression toward mature cardiomyocytes. This has potential application in the field of heart cell regeneration.

Furthermore, our analysis of QT interval length and atrial fibrillation risk loci, described by Tucker et al² and Arking et al,³¹ demonstrates that our focused GO annotation of cardiac physiological processes provides an enhanced GO resource that can be used, in combination with other experimental and in silico approaches, to suggest candidate genes associated with cardiac dis-

Table 3. Comparison of Functional Analysis of Adult Ventricular Cardiomyocyte Data³ Using Gene Ontology (Full List of Enriched Terms in Table V in the Data Supplement)

GO Identifier	GO Term Name	2011			2016		
		n	Corrected P Value	x	n	Corrected P Value	x
GO:0007005	Mitochondrion organization	#N/A	#N/A	#N/A	679	4.56E-12	24
GO:0022904	Respiratory electron transport chain	135	5.48E-34	29	157	1.67E-34	29
GO:0010467	Gene expression	2206	4.58E-11	45	5483	1.09E-13	73
GO:0032502	Developmental process	5680	4.09E-12	80	6093	1.82E-07	64
GO:0061337	Cardiac conduction	#N/A	#N/A	#N/A	126	1.71E-02	4
GO:1903779	Regulation of cardiac conduction	#N/A	#N/A	#N/A	68	1.57E-05	6
GO:0002026	Regulation of the force of heart contraction	#N/A	#N/A	#N/A	31	5.93E-06	5

A selection of Biological Process terms extracted from 2 analyses of the top 200 differentially expressed transcripts in hA-VCMs (adult human ventricular cardiomyocytes; compared with the human embryonic stem cells [hESCs] transcriptome³). Terms selected are either cardiac physiology relevant or align with terms identified by Poon et al.³ Analyses were conducted using the BinGO plugin³³ within the Cytoscape v3.3.0 tool³⁴ using either the 2011 or 2016 Gene Ontology (GO) annotation data set. n indicates the number of protein IDs associated with the GO term, and x is the number of IDs in both the submitted list and associated with the GO term. The inclusion of only the most abundant VCM transcripts probably accounts for the low number of genes in this data set associated with the cardiac terms. #N/A indicates term was not significantly enriched in the data set.

ease. In particular, our results suggest that *ATP1B1*, a Na⁺/K⁺-ATPase β-subunit, is the most likely candidate gene for further study at the 1q24 risk locus because it is associated with cardiac-relevant GO annotations. Another potential use of cardiac GO annotations is to extend protein network analysis. Overlaying proteins with relevant annotations (and hence known cardiac role) onto an existing network would highlight their interacting partners, and these could be explored as candidate genes.

With researchers turning to *Drosophila* and zebrafish as model systems for heart disease,^{49,50} there is a requirement for GO to represent cardiac physiology using terms that are species independent.⁶ The *Drosophila* pulsatile heart tube, with its anterior aorta, looks structurally very distinct from the zebrafish 2-chambered and the mammalian 4-chambered hearts. However, despite this, many of the new GO terms created during this project can be applied across all species because many orthologous genes have similar functions. The major limiting factor to the GO annotation of nonmammalian systems is the paucity of research describing the roles of individual gene products in the cardiac cycle in those species, as the majority of these data relate to mammals. Indeed, the curation effort described in this article focuses on improving analysis tools for human cardiovascular research.

Our results show that collaboration between members of relevant model organism databases and focused curation groups can improve and extend the capture of information about physiological processes in GO, in this particular study, cardiac processes. This effort was enhanced by the collaboration with experts in the cardiac research field who helped us identify key aspects of the process, key genes, and key publications on which to focus. As knowledge of the cardiac system continues to advance, there will be opportunities to capture additional cardiac information in GO. We have provided a structured framework for the addition of new knowledge to the resource, for example, to better describe information about the proteins involved in the mechanical aspect of the heart, and to fully capture roles of gene products and hormones in regulating cardiac physiology. Our work also shows that collaboration between groups developing ontologies and creating biological annotations and scientists and clinicians engaged in active research can lead to substantial improvements in the computational representation of biological knowledge. The GOC welcomes input from researchers about any aspect of our work, including changes to the ontology and suggestions of papers and gene products to annotate (goannotation@ucl.ac.uk, <http://geneontology.org/page/contributing-go>). A variety of GitHub repositories with issue trackers are in place for specific queries: for general inquiries about GO (<https://github.com/geneontology/helpdesk>), for specific questions

about annotations or annotation-related topics (<https://github.com/geneontology/go-annotation/>), and for specific questions or suggestions about the content and structure of the ontology (<https://github.com/geneontology/go-ontology/>). Such collaborations improve the value of the GO resource for the benefit of the entire cardiovascular research community and facilitate the interpretation of high-throughput data sets, toward the identification of dysregulated cardiac pathways, as well as variants and risk alleles, associated with cardiovascular diseases. This has important implications for cardiovascular physicians needing to interpret potentially pathological variants in their patients as a resource for the most up-to-date bioinformatic data to inform diagnosis and cascade screening in families.

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FOOTNOTES

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**Improving Interpretation of Cardiac Phenotypes and Enhancing Discovery With
Expanded Knowledge in the Gene Ontology**

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SUPPLEMENTAL MATERIAL

Methods

Ontology engineering

GO provides more than a simple flat list of terms. Instead, the terms have defined relations between each other, which can be represented in a graphical view (see Figure 1, which is a view of the ontology created with the OBO-Edit tool Graph Editor function using the public OBO release of GO on April 26, 2017, <http://purl.obolibrary.org/obo/go.obo>).¹ Each GO term can have multiple, more general, ‘parent’ terms and multiple, more specific, ‘child’ terms. Different relations are available to define the connection between two GO terms². Five core relations have been applied to the cardiac physiology part of the ontology: *is_a*, *part_of*, *regulates*, *positively_regulates* and *negatively_regulates*. The *is_a* relation denotes that the child term has all the characteristics of its parent but is a more specific term, with differences that distinguish it from other *is_a* children, for example ‘AV node cell to bundle of His cell communication’ is a subtype of ‘cell communication involved in cardiac conduction’ and is distinguished by the cells that are communicating. The *part_of* relation denotes that the child term is always a part of the parent term and together with additional parts make up the parent. For example, ‘AV node cell action potential’ is part of the process of ‘AV node cell to bundle of His cell signaling’ because it is required to propagate the electrical signal along the AV node cell. Another example is that GO Molecular Function terms describing channel activities required for the changes in membrane potential that are associated with an action potential have ‘*part_of*’ relationships with the relevant membrane depolarization and repolarization terms. Coupling the channel activities with the processes that regulate membrane potential in these sections of the ontology provides a good example of how the Molecular Function and Biological Process branches can be integrated. The various types of regulation relations describe when a process has a regulatory or controlling effect on another process, for example ‘regulation of cardiac conduction’ describes a type of process that has a regulatory effect on ‘cardiac conduction’. The development of the ontology to describe cardiac-related processes involved more than placing the new GO terms in the ontology. Each GO term was assigned a unique GO identifier (ID), a descriptive definition and synonyms used in the literature. Synonyms and definitions facilitate the curation of a gene product’s role by allowing easier retrieval of appropriate GO terms when searching the ontology. They also provide a clear, human-readable meaning of the term. Additionally, where applicable, GO terms are defined computationally by creating necessary and sufficient statements using relationships between GO terms and terms from cross-referenced external ontologies^{3,4}.

Expert curation using Gene Ontology

To create GO annotations supported by experimental data, expert GO curators read publications and summarised the data in annotations⁵. There is a vast number of publications describing the function of the gene products we have prioritized, therefore only a fraction of the available literature was curated. Because the curators are based at different institutes, different strategies were taken to identify the appropriate papers to annotate^{6,7}. Since the focus of this project was to capture the role of specific gene products in cardiac physiology, the papers selected usually contained experimental data describing the prioritized proteins and their role in cardiac systems.

Whenever possible, annotations also specify additional contextual information, such as the location of a function or process in a ‘regular ventricular cardiac myocyte’ or ‘heart left ventricle’, by using

annotation extensions⁴ that refer to external ontologies such as the Cell Ontology (CL)⁸⁻¹⁰ or the Uberon multi-species anatomy ontology^{11,12}. For example, human SCN5A is associated with the GO term ‘Z disc’ with the annotation extension ‘part_of’ ‘cardiac muscle cell’⁴. Thus, this annotation specifies the cell, as well as the cellular, location of this protein.

Each annotation includes the gene product identifier, a GO term, an evidence code, and a reference². The QuickGO browser (<http://www.ebi.ac.uk/QuickGO/>)¹³ or the AmiGO2 browser (<http://amigo.geneontology.org/amigo/search/ontology>)¹⁴ were used to search for the most specific GO terms to ‘capture’ the experimental data presented in each paper. Appropriate evidence codes were given to each annotation based on the type of experimental data presented in the published papers (www.geneontology.org/GO.evidence.shtml)¹⁵. The evidence code ‘Inferred by Curator’ (IC) was applied when a combination of experimental data from more than one paper supported the annotation. To ensure full annotation of the human, mouse and rat proteomes, experimentally supported annotations associated with model organism and human gene products are automatically transferred to the orthologous mammalian gene products via the Ensembl Compara pipeline¹⁶. However, 13 of the 88 prioritized proteins are members of highly conserved protein families and therefore do not have 1-to-1 orthologs in human, mouse and rat, as defined by Ensembl Compara. In these cases, GO annotations with experimental evidence codes were associated to orthologous human, mouse and rat proteins, by the expert curators, using the evidence code ISS (Inferred from Sequence Similarity), or ISO (Inferred from Orthology) based on confirmation of predicted orthology by the HUGO Gene Nomenclature Committee (<http://www.genenames.org/>) ortholog prediction tool (HCOP)¹⁷. The procedure for curation of miRNAs is detailed in Huntley et al. 2016⁵.

Identifying experimental data to annotate

The PubMed database¹⁸ was used to locate recent papers reviewing the literature for cardiac electrophysiology and channelopathies. Gene products with a known role in the cardiac cycle were identified from these reviews. PubMed searches, with each individual gene symbol, name or synonym and additional filters, were conducted to provide a comprehensive coverage of the role of these proteins with respect to the cardiac physiology. These searches included specific filters, in addition to the relevant gene-symbol and name: ‘AND cardiac’, ‘AND heart’, or ‘AND conduction’. The selection of papers to curate was then based on whether: 1) they contained experimental data; 2) new information would be added to the current GO annotation data associated with the protein; 3) it was possible to identify the species the protein or expression construct was derived from. Only papers that met all three criteria were curated. The choice of papers curated was, therefore, influenced by the information captured previously (i.e. papers already annotated with existing cardiac terms were excluded). While human gene products were the main focus of this annotation project, other species gene products were also curated where information was available.

Identification of candidate genes associated with arrhythmia risk loci

The QuickGO browser¹³, with ‘taxon’ and ‘GO term’ filters applied, was used to download all human proteins associated with nine GO terms that are relevant to normal cardiac physiology (these nine GO terms are listed in Supplemental Table IV). The Microsoft Excel VLOOKUP function was used to identify the Mendelian genes and the candidate genes (listed in Supplemental Table III) that were associated with the selected GO terms.

GO functional analysis of transcriptomic datasets

A ventricular cardiomyocyte dataset¹⁹ was analysed using the BinGO plugin²⁰ within the Cytoscape v3.3.0 tool²¹, according to the tools recommended procedure. BinGO has the facility to choose which GO annotation dataset to include in the analysis, allowing 2011 and 2016 annotation datasets to be compared. The ontology go-basic.obo (dated 7/03/2016) was downloaded from the GO Consortium website (<http://geneontology.org/page/download-ontology>), and the gene association files (containing the annotation datasets) gene_association.goa_human.104.gz (dated 14/11/2011) and gene_association.goa_human.154.gz (dated 16/02/2016), were downloaded from <ftp://ftp.ebi.ac.uk/pub/databases/GO/goa/old/HUMAN/> and <ftp://ftp.ebi.ac.uk/pub/databases/GO/goa/HUMAN/> respectively. For the analysis UniProtKB accessions were submitted with the following settings: assess overrepresentation; hypergeometric test; Benjamini & Hochberg False Discovery Rate correction; $p < 0.05$ significance level; 'whole annotation' was used as reference set, leading to a comparison of the GO terms associated with the ventricular cardiomyocyte dataset¹⁹ with the GO terms associated with the human proteome.

Supplemental Tables

Supplemental Table I. 88 Cardiac physiology gene products prioritized for annotation. Human proteins with a role in cardiac excitability were compiled based on the description of proteins listed in eleven cardiac physiology reviews²²⁻³². This list was then filtered to remove hormones and hormone receptors involved in regulating the heart rate (with the exception of AGT, ACE and ACE2) and proteins involved in regulating heart development. This enabled us to focus more specifically on ion channels and ATPases and the proteins directly regulating their activity.

Approved symbol	Approved name	UniProt ID/RNA central ID	Link to QuickGO or AmiGO annotation record
ACE	angiotensin I converting enzyme	P12821	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P12821
ACE2	angiotensin I converting enzyme 2	Q9BYF1	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9BYF1
AGT	angiotensinogen	P01019	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P01019
AKAP6	A-kinase anchoring protein 6	Q13023	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q13023
AKAP9	A-kinase anchoring protein 9	Q99966	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q99966
ANK2	ankyrin 2	Q01484	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q01484
ANK3	ankyrin 3	Q12955	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q12955
ASPH	aspartate beta-hydroxylase	Q12797	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q12797
ATP1A1	ATPase Na ⁺ /K ⁺ transporting subunit alpha 1	P05023	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P05023
ATP1A2	ATPase Na ⁺ /K ⁺ transporting subunit alpha 2	P50993	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P50993
ATP1A3	ATPase Na ⁺ /K ⁺ transporting subunit alpha 3	P13637	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P13637
ATP1B1	ATPase Na ⁺ /K ⁺ transporting subunit beta 1	P05026	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P05026
ATP2A2	ATPase sarcoplasmic/endoplasmic reticulum Ca ²⁺ transporting 2	P16815	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P16815
ATP2B4	ATPase plasma membrane Ca ²⁺ transporting 4	P23634	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P23634
CACNA1C	calcium voltage-gated channel subunit alpha1 C	Q13936	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q13936
CACNA1D	calcium voltage-gated channel subunit alpha1 D	Q01668	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q01668
CACNA1G	calcium voltage-gated channel subunit alpha1 G	O43497	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O43497
CACNAZD1	calcium voltage-gated channel auxiliary subunit alpha2delta 1	P54289	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P54289
CACNB2	calcium voltage-gated channel auxiliary subunit beta 2	O08289	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O08289
CALM1	calmodulin 1	P62158	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P62158
CAMK2D	calcium/calmodulin dependent protein kinase II delta	Q13557	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q13557
CASQ2	calsequestrin 2	O14958	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O14958
CAV1	caveolin 1	O03135	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O03135
CAV2	caveolin 2	P51636	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P51636
CAV3	caveolin 3	P56539	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P56539
CLIC2	chloride intracellular channel 2	O15247	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O15247
CNOT1	CCR4-NOT transcription complex subunit 1	AS5YK6	http://www.ebi.ac.uk/QuickGO/GProtein?ac=AS5YK6
DLG1	discs large MAGUK scaffold protein 1	Q12959	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q12959
DMD	dystrophin	P11532	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P11532
DSG2	desmoglein 2	O14126	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O14126
FGF12	fibroblast growth factor 12	P61328	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P61328
FGF13	fibroblast growth factor 13	Q92913	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q92913
FKBP1B	FK506 binding protein 1B	P68106	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P68106
FLNA	filamin A	P21333	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P21333
FXD1	FXD domain containing ion transport regulator 1	O00168	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O00168
GJA1	gap junction protein alpha 1	P17302	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P17302
GJA5	gap junction protein alpha 5	P36382	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P36382
GPDI1	glycerol-3-phosphate dehydrogenase 1 like	O8N335	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O8N335
GSTM2	glutathione S-transferase mu 2	P28161	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P28161
HCN4	hyperpolarization activated cyclic nucleotide gated potassium channel 4	Q9Y304	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9Y304
HRC	histidine rich calcium binding protein	P23327	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P23327
KCNA5	potassium voltage-gated channel subfamily A member 5	P22460	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P22460
KCNB3	potassium voltage-gated channel subfamily D member 3	O9UK17	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O9UK17
KCNE1	potassium voltage-gated channel subfamily E regulatory subunit 1	P15382	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P15382
KCNE2	potassium voltage-gated channel subfamily E regulatory subunit 2	Q9Y6J6	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9Y6J6
KCNE3	potassium voltage-gated channel subfamily E regulatory subunit 3	Q9Y6H6	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9Y6H6
KCNE5	potassium voltage-gated channel subfamily E regulatory subunit 5	Q9UJ90	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9UJ90
KCNH2	potassium voltage-gated channel subfamily H member 2	Q12809	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q12809
KCNJ2	potassium voltage-gated channel subfamily J member 2	P63252	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P63252
KCNJ5	potassium voltage-gated channel subfamily J member 5	P48544	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P48544
KCNJ8	potassium voltage-gated channel subfamily J member 8	Q15842	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q15842
KCNQ1	potassium voltage-gated channel subfamily Q member 1	P51787	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P51787
LIG3	DNA ligase 3	P49916	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P49916
LITAF	lipopolysaccharide induced TNF factor	Q99732	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q99732
NDRG4	NDRG family member 4	Q9ULP0	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9ULP0
NEDD4L	neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase	Q96PU5	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q96PU5
NOS1	nitric oxide synthase 1	P29475	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P29475
NOS1AP	nitric oxide synthase 1 adaptor protein	Q75052	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q75052
NPPA	natriuretic peptide A	P01160	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P01160
NUP155	nucleoporin 155	O75694	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O75694
PDE4B	phosphodiesterase 4B	Q07343	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q07343
PDE4D	phosphodiesterase 4D	O08499	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O08499
PKP2	plakophilin 2	Q99559	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q99559
PLN	phospholamban	P26678	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P26678
PRKACA	protein kinase cAMP-activated catalytic subunit alpha	P17612	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P17612
PTPN3	protein tyrosine phosphatase, non-receptor type 3	P26045	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P26045
RANGRF	RAN guanine nucleotide release factor	Q9HD47	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9HD47
RNF207	ring finger protein 207	Q6ZRF8	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q6ZRF8
RYR2	ryanodine receptor 2	Q92736	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q92736
SCN10A	sodium voltage-gated channel alpha subunit 10	Q9Y5Y9	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9Y5Y9
SCN1B	sodium voltage-gated channel beta subunit 1	O07699	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O07699
SCN2B	sodium voltage-gated channel beta subunit 2	O60939	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O60939
SCN3B	sodium voltage-gated channel beta subunit 3	O9NY72	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O9NY72
SCN4B	sodium voltage-gated channel beta subunit 4	O8IWT1	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O8IWT1
SCNSA	sodium voltage-gated channel alpha subunit 5	Q14524	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q14524
SLC8A1	solute carrier family 8 member A1	P32418	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P32418
SLC8B1	solute carrier family 8 member B1	O6J4K2	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O6J4K2
SLC9A1	solute carrier family 9 member A1	P19634	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P19634
SLMAP	sarcolemma associated protein	Q14BN4	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q14BN4
SNTA1	syntrophin alpha 1	Q13424	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q13424
SPTBN4	spectrin beta, non-erythrocytic 4	Q9H254	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q9H254
SRI	sorcin	P30626	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P30626
TCAP	titin-cap	O15273	http://www.ebi.ac.uk/QuickGO/GProtein?ac=O15273
TRDN	triadin	Q13061	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q13061
TRPM4	transient receptor potential cation channel subfamily M member 4	Q8TD43	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q8TD43
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon	P62258	http://www.ebi.ac.uk/QuickGO/GProtein?ac=P62258
YWHAH	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein eta	Q04917	http://www.ebi.ac.uk/QuickGO/GProtein?ac=Q04917
hsa-miR-1-3p	miR-1	URS00001DC04F_9606	http://amigo.geneontology.org/amigo/gene_product/RNACentral:URS00001DC04F_9606
hsa-miR-26a-5p	miR-26	URS000019B0F7_9606	http://amigo.geneontology.org/amigo/gene_product/RNACentral:URS000019B0F7_9606
hsa-miR-133a-3p	miR-133a	URS00004C9052_9606	http://amigo.geneontology.org/amigo/gene_product/RNACentral:URS00004C9052_9606
hsa-miR-208a-3p	miR-208a	URS00000E5433_9606	http://amigo.geneontology.org/amigo/gene_product/RNACentral:URS00000E5433_9606
hsa-miR-212-3p	miR-212	URS00001D68AE_9606	http://amigo.geneontology.org/amigo/gene_product/RNACentral:URS00001D68AE_9606
hsa-miR-328-3p	miR-328	URS00005FDE70_9606	http://amigo.geneontology.org/amigo/gene_product/RNACentral:URS00005FDE70_9606
hsa-miR-499-5p	miR-499	URS00000C7662_9606	http://amigo.geneontology.org/amigo/gene_product/RNACentral:URS00000C7662_9606

Supplemental Table II. Using Gene Ontology to support the identification of the likely causative gene associated with QT interval length and AF risk loci. 117 genes identified as either a known Mendelian gene associated with AF, LQTS, SQTS, CPVT or BrS^{33,34}, or a candidate gene associated with AF risk loci or loci associated with QT interval length, by GWAS^{33,35,36}. Nine GO terms were selected based on their potential relevance to cardiac physiology (Supplemental Table III). QuickGO¹³ was used to download all human proteins associated with these terms either directly or to a child term with one of the following relations: part_of, is_a, regulates, negatively_regulates, positively_regulates (11 March 2016). The association of these 9 GO terms with each of the AF or QT interval-associated genes was then determined, indicated by solid filled cell. Candidate genes identified by annotation to a relevant GO term were then compared with arrhythmia disorder Mendelian genes and candidate genes identified using eQTL, *in silico* QT interval loci protein network analysis (PPI-QT) or co-immunoprecipitation with one of 5 LQTS Mendelian proteins (CoIP)³³. ELP6 is the approved symbol for C3orf75.

Supplemental Table III. Cardiac physiology relevant *Biological Process* GO terms. Nine GO terms were selected based on their potential relevance to cardiac physiology.

GO identifier	GO term name
GO:0061337	cardiac conduction
GO:0042391	regulation of membrane potential
GO:0030029	actin filament-based process
GO:0071805	potassium ion transmembrane transport
GO:0035725	sodium ion transmembrane transport
GO:0070588	calcium ion transmembrane transport
GO:0006936	muscle contraction
GO:0007507	heart development
GO:0070482	response to oxygen levels

Supplemental Table IV. List of new cardiac physiology relevant GO terms.

197 new GO terms were created to support the annotation of 88 prioritized proteins and 7 miRNAs and their role in cardiac processes. These were created by the GO editors following an ontology development meeting in November 2011 and individual requests by GO curators. Table IV lists 200 GO terms as it includes 3 terms, ‘membrane depolarization during atrial cardiac muscle cell action potential’ and ‘membrane repolarization during atrial cardiac muscle cell action potential’, as well as ‘cardiac conduction’, indicated by *, that were already in the ontology). The column header ‘Aspect’ lists the ontology to which the GO term belongs, either Molecular Function or Biological Process. Information about the number of annotations associated with each GO term is provided (based on data available 18 October 2017) in two ways: as the number of direct annotations (number of times each GO term has been associated with a gene product from any species) and number of annotations to child term/s (number of times a child term for each GO term has been associated with a gene product from any species). Terms were considered as child terms if they had an is_a, part_of, occurs_in, regulates, positively_regulates or negatively_regulates relation to the parent term. The graph nature of the ontology means that some annotations will be represented more than once in this table.

Of the 197 new GO terms created, 136 have been directly associated with a gene product. Of the 63 terms without direct annotations, 22 provide a parent GO term that will facilitate gene grouping during functional analyses using GO datasets. For example, ‘atrial cardiac muscle cell membrane repolarization’ has no direct annotations, but its child terms have been used in 226 annotations. 41 terms, mostly leaf nodes, have not yet been associated with any gene product either directly or via child terms; many of these refer either to processes occurring in specific cell types, such as ‘negative regulation of AV node cell action potential’, or describe very specific functions, e.g. ‘stretch-activated, cation-selective, calcium channel activity involved in regulation of action potential’. Some of these areas of study did not fall under the focus of this project, and relevant literature was not examined in detail. Future annotation projects, for example looking at signaling pathways that regulate both the rate and strength of heart contractions, may lead to the association of proteins or RNAs with these terms.

Aspect	GO ID	GO term name	Number of annotations using term listed	Number of annotations using child term
Child terms of GO term cardiac conduction*, GO:0061337				
Biological Process	GO:0086014	atrial cardiac muscle cell action potential	215	
Biological Process	GO:0099624	atrial cardiac muscle cell membrane repolarization	0	226
Biological Process	GO:0086066	atrial cardiac muscle cell to AV node cell communication	13	
Biological Process	GO:0086044	atrial cardiac muscle cell to AV node cell communication by electrical coupling	76	
Biological Process	GO:0086026	atrial cardiac muscle cell to AV node cell signaling	0	604
Biological Process	GO:0086071	atrial cardiac muscle cell-AV node cell adhesion involved in cell communication	0	0
Biological Process	GO:0086016	AV node cell action potential	112	
Biological Process	GO:0086067	AV node cell to bundle of His cell communication	52	
Biological Process	GO:0086053	AV node cell to bundle of His cell communication by electrical coupling	121	
Biological Process	GO:0086027	AV node cell to bundle of His cell signaling	44	
Biological Process	GO:0086072	AV node cell-bundle of His cell adhesion involved in cell communication	4	
Biological Process	GO:0086043	bundle of His cell action potential	32	
Biological Process	GO:0086069	bundle of His cell to Purkinje myocyte communication	4	
Biological Process	GO:0086054	bundle of His cell to Purkinje myocyte communication by electrical coupling	35	
Biological Process	GO:0086028	bundle of His cell to Purkinje myocyte signaling	0	285
Biological Process	GO:0086073	bundle of His cell-Purkinje myocyte adhesion involved in cell communication	181	
Biological Process	GO:0086064	cell communication by electrical coupling involved in cardiac conduction	91	
Biological Process	GO:0086065	cell communication involved in cardiac conduction	39	
Biological Process	GO:0086019	cell-cell signaling involved in cardiac conduction	40	
Biological Process	GO:0098912	membrane depolarization during atrial cardiac muscle cell action potential*	71	
Biological Process	GO:0086045	membrane depolarization during AV node cell action potential	140	
Biological Process	GO:0086048	membrane depolarization during bundle of His cell action potential	62	
Biological Process	GO:0086047	membrane depolarization during Purkinje myocyte cell action potential	60	
Biological Process	GO:0086046	membrane depolarization during SA node cell action potential	138	
Biological Process	GO:0098914	membrane repolarization during atrial cardiac muscle cell action potential*	93	
Biological Process	GO:0086049	membrane repolarization during AV node cell action potential	0	0
Biological Process	GO:0086050	membrane repolarization during bundle of His cell action potential	27	
Biological Process	GO:0086051	membrane repolarization during Purkinje myocyte action potential	0	0
Biological Process	GO:0086052	membrane repolarization during SA node cell action potential	29	
Biological Process	GO:1903948	negative regulation of atrial cardiac muscle cell action potential	0	0
Biological Process	GO:1903950	negative regulation of AV node cell action potential	0	0
Biological Process	GO:1903780	negative regulation of cardiac conduction	0	0
Biological Process	GO:1901845	negative regulation of cell communication by electrical coupling involved in cardiac conduction	0	0
Biological Process	GO:1905028	negative regulation of membrane depolarization during AV node cell action potential	0	0
Biological Process	GO:1905001	negative regulation of membrane repolarization during atrial cardiac muscle cell action potential	0	0
Biological Process	GO:1903953	negative regulation of voltage-gated potassium channel activity involved in atrial cardiac muscle cell action potential repolarization	0	0
Biological Process	GO:1903949	positive regulation of atrial cardiac muscle cell action potential	3	
Biological Process	GO:1903951	positive regulation of AV node cell action potential	0	0
Biological Process	GO:1903781	positive regulation of cardiac conduction	0	8
Biological Process	GO:1901846	positive regulation of cell communication by electrical coupling involved in cardiac conduction	2	
Biological Process	GO:1905029	positive regulation of membrane depolarization during AV node cell action potential	0	0
Biological Process	GO:1905002	positive regulation of membrane repolarization during atrial cardiac muscle cell action potential	0	0
Biological Process	GO:1903954	positive regulation of voltage-gated potassium channel activity involved in atrial cardiac muscle cell action potential repolarization	3	
Biological Process	GO:0086017	Purkinje myocyte action potential	0	131
Biological Process	GO:0086068	Purkinje myocyte to ventricular cardiac muscle cell communication	0	160
Biological Process	GO:0086055	Purkinje myocyte to ventricular cardiac muscle cell communication by electrical coupling	1	
Biological Process	GO:0086029	Purkinje myocyte to ventricular cardiac muscle cell signaling	27	
Biological Process	GO:0086074	Purkinje myocyte-ventricular cardiac muscle cell adhesion involved in cell communication	0	0
Biological Process	GO:0098910	regulation of atrial cardiac muscle cell action potential	127	
Biological Process	GO:0098904	regulation of AV node cell action potential	113	
Biological Process	GO:0098905	regulation of bundle of His cell action potential	99	
Biological Process	GO:1903779	regulation of cardiac conduction	447	

<i>Biological Process</i>	GO:1901844	regulation of cell communication by electrical coupling involved in cardiac conduction	106	
<i>Biological Process</i>	GO:0086091	regulation of heart rate by cardiac conduction	1171	
<i>Biological Process</i>	GO:1905027	regulation of membrane depolarization during AV node cell action potential	0	0
<i>Biological Process</i>	GO:1905000	regulation of membrane repolarization during atrial cardiac muscle cell action potential	2	
<i>Biological Process</i>	GO:0098906	regulation of Purkinje myocyte action potential	35	
<i>Biological Process</i>	GO:0098907	regulation of SA node cell action potential	84	
<i>Biological Process</i>	GO:0086092	regulation of the force of heart contraction by cardiac conduction	68	
<i>Biological Process</i>	GO:1903952	regulation of voltage-gated potassium channel activity involved in atrial cardiac muscle cell action potential repolarization	0	3
<i>Biological Process</i>	GO:0086015	SA node cell action potential	165	
<i>Biological Process</i>	GO:0086070	SA node cell to atrial cardiac muscle cell communication	70	
<i>Biological Process</i>	GO:0086021	SA node cell to atrial cardiac muscle cell communication by electrical coupling	3	
<i>Biological Process</i>	GO:0086018	SA node cell to atrial cardiac muscle cell signalling	44	
<i>Biological Process</i>	GO:0086022	SA node cell-atrial cardiac muscle cell adhesion involved in cell communication	0	0
<i>Molecular Function</i>	GO:0086082	cell adhesive protein binding involved in AV node cell-bundle of His cell communication	2	
<i>Molecular Function</i>	GO:0086083	cell adhesive protein binding involved in bundle of His cell-Purkinje myocyte communication	17	
<i>Molecular Function</i>	GO:0086076	gap junction channel activity involved in atrial cardiac muscle cell-AV node cell electrical coupling	40	
<i>Molecular Function</i>	GO:0086077	gap junction channel activity involved in AV node cell-bundle of His cell electrical coupling	85	
<i>Molecular Function</i>	GO:0086078	gap junction channel activity involved in bundle of His cell-Purkinje myocyte electrical coupling	35	
<i>Molecular Function</i>	GO:0086075	gap junction channel activity involved in cardiac conduction electrical coupling	40	
<i>Molecular Function</i>	GO:0086079	gap junction channel activity involved in Purkinje myocyte-ventricular cardiac muscle cell electrical coupling	1	
<i>Molecular Function</i>	GO:0086020	gap junction channel activity involved in SA node cell-atrial cardiac muscle cell electrical coupling	3	
<i>Molecular Function</i>	GO:0086056	voltage-gated calcium channel activity involved in AV node cell action potential	112	
<i>Molecular Function</i>	GO:0086057	voltage-gated calcium channel activity involved in bundle of His cell action potential	34	
<i>Molecular Function</i>	GO:0086058	voltage-gated calcium channel activity involved in Purkinje myocyte cell action potential	0	0
<i>Molecular Function</i>	GO:0086059	voltage-gated calcium channel activity involved SA node cell action potential	104	
<i>Molecular Function</i>	GO:0086089	voltage-gated potassium channel activity involved in atrial cardiac muscle cell action potential repolarization	90	
<i>Molecular Function</i>	GO:0086086	voltage-gated potassium channel activity involved in AV node cell action potential repolarization	0	0
<i>Molecular Function</i>	GO:0086087	voltage-gated potassium channel activity involved in bundle of His cell action potential repolarization	27	
<i>Molecular Function</i>	GO:0086088	voltage-gated potassium channel activity involved in Purkinje myocyte action potential repolarization	0	0
<i>Molecular Function</i>	GO:0086041	voltage-gated potassium channel activity involved in SA node cell action potential depolarization	29	
<i>Molecular Function</i>	GO:0086090	voltage-gated potassium channel activity involved in SA node cell action potential repolarization	29	
<i>Molecular Function</i>	GO:0086060	voltage-gated sodium channel activity involved in AV node cell action potential	4	
<i>Molecular Function</i>	GO:0086061	voltage-gated sodium channel activity involved in bundle of His cell action potential	4	
<i>Molecular Function</i>	GO:0086062	voltage-gated sodium channel activity involved in Purkinje myocyte action potential	36	
<i>Molecular Function</i>	GO:0086063	voltage-gated sodium channel activity involved in SA node cell action potential	6	
Other cardiac-relevant GO terms				
<i>Biological Process</i>	GO:0086096	adenylate cyclase-inhibiting adrenergic receptor signaling pathway involved in heart process	0	0
<i>Biological Process</i>	GO:0086102	adenylate cyclase-inhibiting G-protein coupled acetylcholine receptor signaling pathway involved in negative regulation of heart rate	0	0
<i>Biological Process</i>	GO:0086030	adrenergic receptor signaling pathway involved in cardiac muscle relaxation	3	
<i>Biological Process</i>	GO:0086023	adrenergic receptor signaling pathway involved in heart process	62	
<i>Biological Process</i>	GO:0086024	adrenergic receptor signaling pathway involved in positive regulation of heart rate	2	
<i>Biological Process</i>	GO:0038166	angiotensin-activated signaling pathway	784	
<i>Biological Process</i>	GO:0086098	angiotensin-activated signaling pathway involved in heart process	73	
<i>Biological Process</i>	GO:0090662	ATP hydrolysis coupled transmembrane transport	2577	
<i>Biological Process</i>	GO:1903515	calcium ion transport from cytosol to endoplasmic reticulum	56	
<i>Biological Process</i>	GO:1903514	calcium ion transport from endoplasmic reticulum to cytosol	36	
<i>Biological Process</i>	GO:0086001	cardiac muscle cell action potential	65	
<i>Biological Process</i>	GO:0086002	cardiac muscle cell action potential involved in contraction	436	
<i>Biological Process</i>	GO:0086003	cardiac muscle cell contraction	12	
<i>Biological Process</i>	GO:0086042	cardiac muscle cell-cardiac muscle cell adhesion	63	
<i>Biological Process</i>	GO:0014898	cardiac muscle hypertrophy in response to stress	440	
<i>Biological Process</i>	GO:0060926	cardiac pacemaker cell development	0	100
<i>Biological Process</i>	GO:0060920	cardiac pacemaker cell differentiation	0	150
<i>Biological Process</i>	GO:0060927	cardiac pacemaker cell fate commitment	0	33
<i>Biological Process</i>	GO:1903513	endoplasmic reticulum to cytosol transport	0	1787
<i>Biological Process</i>	GO:0086100	endothelin receptor signaling pathway	561	
<i>Biological Process</i>	GO:0086101	endothelin receptor signaling pathway involved in heart process	0	0
<i>Biological Process</i>	GO:0086093	G-protein coupled acetylcholine receptor signaling pathway involved in involved in heart process	0	0
<i>Biological Process</i>	GO:0086033	G-protein coupled acetylcholine receptor signaling pathway involved in negative regulation of heart rate	0	0
<i>Biological Process</i>	GO:0086103	G-protein coupled receptor signaling pathway involved in heart process	35	
<i>Biological Process</i>	GO:0086010	membrane depolarization during action potential	757	
<i>Biological Process</i>	GO:0086012	membrane depolarization during cardiac muscle cell action potential	183	
<i>Biological Process</i>	GO:0098913	membrane depolarization during ventricular cardiac muscle cell action potential	0	0
<i>Biological Process</i>	GO:0086009	membrane repolarization	310	
<i>Biological Process</i>	GO:0086011	membrane repolarization during action potential	142	
<i>Biological Process</i>	GO:0086013	membrane repolarization during cardiac muscle cell action potential	143	

Biological Process	GO:0098915	membrane repolarization during ventricular cardiac muscle cell action potential	156	
Biological Process	GO:1901205	negative regulation of adrenergic receptor signaling pathway involved in heart process	32	
Biological Process	GO:1903246	negative regulation of adrenergic receptor signaling pathway involved in positive regulation of heart rate	0	0
Biological Process	GO:1903280	negative regulation of calcium:sodium antiporter activity	6	
Biological Process	GO:1902260	negative regulation of delayed rectifier potassium channel activity	182	
Biological Process	GO:1903597	negative regulation of gap junction assembly	36	
Biological Process	GO:1903609	negative regulation of inward rectifier potassium channel activity	36	
Biological Process	GO:1900826	negative regulation of membrane depolarization during cardiac muscle cell action potential	34	
Biological Process	GO:1905032	negative regulation of membrane repolarization during cardiac muscle cell action potential	0	36
Biological Process	GO:1905025	negative regulation of membrane repolarization during ventricular cardiac muscle cell action potential	36	
Biological Process	GO:1902309	negative regulation of peptidyl-serine dephosphorylation	102	
Biological Process	GO:1902303	negative regulation of potassium ion export	28	
Biological Process	GO:1903765	negative regulation of potassium ion export across plasma membrane	36	
Biological Process	GO:1903287	negative regulation of potassium ion import	0	0
Biological Process	GO:1903783	negative regulation of sodium ion import across plasma membrane	0	0
Biological Process	GO:1902306	negative regulation of sodium ion transmembrane transport	95	
Biological Process	GO:0098736	negative regulation of the force of heart contraction	31	
Biological Process	GO:1903946	negative regulation of ventricular cardiac muscle cell action potential	0	36
Biological Process	GO:1903761	negative regulation of voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization	0	0
Biological Process	GO:0086097	phospholipase C-activating angiotensin-activated signaling pathway	44	
Biological Process	GO:0086099	phospholipase C-activating angiotensin-activated signaling pathway involved in heart process	0	0
Biological Process	GO:0003301	physiological cardiac muscle hypertrophy	13	
Biological Process	GO:1901206	positive regulation of adrenergic receptor signaling pathway involved in heart process	29	
Biological Process	GO:1903247	positive regulation of adrenergic receptor signaling pathway involved in positive regulation of heart rate	0	0
Biological Process	GO:1903281	positive regulation of calcium:sodium antiporter activity	75	
Biological Process	GO:1903598	positive regulation of gap junction assembly	114	
Biological Process	GO:0086095	positive regulation of IKACH channel activity by G-protein coupled acetylcholine receptor signaling pathway involved in negative regulation of heart rate	0	0
Biological Process	GO:1900827	positive regulation of membrane depolarization during cardiac muscle cell action potential	3	
Biological Process	GO:1905033	positive regulation of membrane repolarization during cardiac muscle cell action potential	0	40
Biological Process	GO:1905026	positive regulation of membrane repolarization during ventricular cardiac muscle cell action potential	0	37
Biological Process	GO:1902310	positive regulation of peptidyl-serine dephosphorylation	85	
Biological Process	GO:1902304	positive regulation of potassium ion export	6	
Biological Process	GO:1903766	positive regulation of potassium ion export across plasma membrane	34	
Biological Process	GO:1903288	positive regulation of potassium ion import	138	
Biological Process	GO:0086094	positive regulation of ryanodine-sensitive calcium-release channel activity by adrenergic receptor signaling pathway involved in positive regulation of cardiac muscle contraction	0	0
Biological Process	GO:1903784	positive regulation of sodium ion import across plasma membrane	0	0
Biological Process	GO:1902307	positive regulation of sodium ion transmembrane transport	6	
Biological Process	GO:0098735	positive regulation of the force of heart contraction	161	
Biological Process	GO:1903947	positive regulation of ventricular cardiac muscle cell action potential	0	37
Biological Process	GO:1903762	positive regulation of voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization	37	
Biological Process	GO:0003165	Purkinje myocyte development	34	
Biological Process	GO:0003168	Purkinje myocyte differentiation	33	
Biological Process	GO:1901204	regulation of adrenergic receptor signaling pathway involved in heart process	0	61
Biological Process	GO:1903245	regulation of adrenergic receptor signaling pathway involved in positive regulation of heart rate	0	0
Biological Process	GO:1903279	regulation of calcium:sodium antiporter activity	0	81
Biological Process	GO:0098901	regulation of cardiac muscle cell action potential	20	
Biological Process	GO:0098909	regulation of cardiac muscle cell action potential involved in regulation of contraction	163	
Biological Process	GO:0086004	regulation of cardiac muscle cell contraction	262	
Biological Process	GO:0086036	regulation of cardiac muscle cell membrane potential	200	
Biological Process	GO:1903596	regulation of gap junction assembly	0	150
Biological Process	GO:1900825	regulation of membrane depolarization during cardiac muscle cell action potential	133	
Biological Process	GO:0060306	regulation of membrane repolarization	341	
Biological Process	GO:1905031	regulation of membrane repolarization during cardiac muscle cell action potential	3	
Biological Process	GO:1905024	regulation of membrane repolarization during ventricular cardiac muscle cell action potential	0	104
Biological Process	GO:1902308	regulation of peptidyl-serine dephosphorylation	0	187
Biological Process	GO:1902302	regulation of potassium ion export	0	135
Biological Process	GO:1903764	regulation of potassium ion export across plasma membrane	31	
Biological Process	GO:1903286	regulation of potassium ion import	31	
Biological Process	GO:0014861	regulation of skeletal muscle contraction via regulation of action potential	43	
Biological Process	GO:1903782	regulation of sodium ion import across plasma membrane	0	0
Biological Process	GO:1902305	regulation of sodium ion transmembrane transport	167	
Biological Process	GO:0098911	regulation of ventricular cardiac muscle cell action potential	337	
Biological Process	GO:0060307	regulation of ventricular cardiac muscle cell membrane repolarization	461	
Biological Process	GO:1903760	regulation of voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization	31	
Biological Process	GO:1903416	response to glycoside	78	
Biological Process	GO:0086005	ventricular cardiac muscle cell action potential	392	
Biological Process	GO:0099625	ventricular cardiac muscle cell membrane repolarization	34	
Molecular Function	GO:0086039	calcium-transporting ATPase activity involved in regulation of cardiac muscle cell membrane potential	10	
Molecular Function	GO:0086038	calcium:sodium antiporter activity involved in regulation of cardiac muscle cell membrane potential	42	

<i>Molecular Function</i>	GO:0086081	cell adhesive protein binding involved in atrial cardiac muscle cell-AV node cell communication	0	0
<i>Molecular Function</i>	GO:0086084	cell adhesive protein binding involved in Purkinje myocyte-ventricular cardiac muscle cell communication	0	0
<i>Molecular Function</i>	GO:0086085	cell adhesive protein binding involved in SA cardiac muscle cell-atrial cardiac muscle cell communication	0	0
<i>Molecular Function</i>	GO:1903763	gap junction channel activity involved in cell communication by electrical coupling	150	
<i>Molecular Function</i>	GO:0086080	protein binding involved in heterotypic cell-cell adhesion	123	
<i>Molecular Function</i>	GO:0086037	sodium:potassium-exchanging ATPase activity involved in regulation of cardiac muscle cell membrane potential	26	
<i>Molecular Function</i>	GO:0086040	sodium:proton antiporter activity involved in regulation of cardiac muscle cell membrane potential	1	
<i>Molecular Function</i>	GO:0097364	stretch-activated, cation-selective, calcium channel activity involved in regulation of action potential	0	0
<i>Molecular Function</i>	GO:0097365	stretch-activated, cation-selective, calcium channel activity involved in regulation of cardiac muscle cell action potential	0	0
<i>Molecular Function</i>	GO:0086007	voltage-gated calcium channel activity involved in cardiac muscle cell action potential	76	
<i>Molecular Function</i>	GO:0086008	voltage-gated potassium channel activity involved in cardiac muscle cell action potential repolarization	89	
<i>Molecular Function</i>	GO:1902282	voltage-gated potassium channel activity involved in ventricular cardiac muscle cell action potential repolarization	157	
<i>Molecular Function</i>	GO:0086006	voltage-gated sodium channel activity involved in cardiac muscle cell action potential	225	
Total direct annotations			16,935	

Supplemental Table Vi. hA-VCMs protein list. The 200 most abundant transcripts in hA-VCMs, as compared to hESCs transcripts, as listed by Poon et al.¹⁹

HGNC Symbol	EntrezGene ID	UniProtKB ID	comments
MYL2	4633	P10916	
MYH7	4625	P12883	
MYL3	4634	P08590	
ACTC1	70	P68032	
HS.508682			Not available
CRYAB	1410	P02511	
ACTA1	58	P68133	
CKM	1158	P06732	
ATP5B	506	P06576	
COX4I1	1327	P13073	
FARSB	10056	Q9NSD9	
TNNC1	7134	P63316	
RPS16	6217	P62249	
HSPB7	27129	Q9UBY9	
RN7SL1	6029		RNA, 7SL, cytoplasmic 1
MYOM1	8736	P52179	
HSPB1	3315	P04792	
MYBPC3	4607	Q14896	
TMSB4XP8	7117		thymosin beta 4, X-linked pseudogene 8
MYL12A	10627	P19105	
COX7C	1350	P15954	
SLC25A4	291	P12235	
RPLP2	6181	P05387	
DES	1674	P17661	
NDUFA1	4694	O15239	
EEF1A2	1917	Q05639	
ATP5A1	498	P25705	
OAZ1	4946	P54368	
COX7A1	1346	P24310	
MDH1	4190	P40925	
TPT1	7178	P13693	
NDUFA4	4697	O00483	
ATP5E	514	P56381	
RPS25	6230	P62851	
CD81	975	P60033	
MYH6	4624	P13533	
COX5B	1329	P10606	
TCAP	8557	O15273	
MYOM2	9172	P54296	
RPS27	6232	P42677	
UQCRQ	27089	O14949	
TNNI3	7137	P19429	
MDH2	4191	P40926	
CHCHD10	400916	Q8WYQ3	
COX5A	9377	P20674	
CASQ2	845	O14958	
UBC	7316	P0CG48	
LAIR1	3903	Q6GTX8	
CKMT2	1160	P17540	
MB	4151	P02144	
TPM1	7168	P09493	
RPL38	6169	P63173	
SLC7A5P2	387254		solute carrier family 7 member 5 pseudogene 2
TOMM7	54543	Q9P0U1	
FLNC	2318	Q14315	
PSAP	5660	P07602	
TNNT2	7139	P45379	
RPS10	6204	P46783	
CDH2	1000	P19022	
F2R	2149	P25116	
C19ORF31	404664		HGNC listed as a cloning artifact
RACK1	10399	P63244	
PTGDS	5730	P41222	
HRC	3270	P23327	
EEF2	1938	P13639	
RPS19	6223	P39019	
YBX3	8531	P16989	
RPL11	6135	P62913	

COX6C	1345	P09669	
RPL18A	6142	Q02543	
NDUFB8	4714	O95169	
GPX3	2878	P22352	
PAM	5066	P19021	
MFGE8	4240	Q08431	
ATP5H	10476	O75947	
EEF1A1	1915	P68104	
IL18	3606	Q14116	
NDUFAB1	4706	O14561	
ECH1	1891	Q13011	
CMYA5	202333	Q8N3K9	
GAPDH	2597	P04406	
RPS29	6235	P62273	
FTL	2512	P02792	
SRL	6345	Q86TD4	
SYNPO2L	79933	Q9H987	
APOD	347	P05090	
MYL7	58498	Q01449	
COX7A2	1347	P14406	
RPS27A	6233	P62979	
ORC6	23594	Q9Y5N6	
FHL2	2274	Q14192	
RPS20	6224	P60866	
RPLP1	6176	P05386	
UBB	7314	P0CG47	
COX8A	1351	P10176	
TUBA1B	10376	P68363	
CST3	1471	P01034	
RPL41	6171	P62945	
NAG18	57051		withdrawn by NCBI
EIF4A2	1974	Q14240	
HBB	3043	P68871	
HSPA1A	3303	P0DMV8	
ROCK2	9475	O75116	
RPL19	6143	P84098	
MSH3	4437	P20585	
NPPB	4879	P16860	
ZNF486	90649	Q96H40	
HBA1	3039	P69905	
UQCRFS1	7386	P47985	
CCNI	10983	Q14094	
RPL24	6152	P83731	
TUBA3FP	113691		tubulin alpha 3f pseudogene
RPL27	6155	P61353	
ATP2A2	488	P16615	
HSPB3	8988	Q12988	
LILRB3	11025	Q6PI73	
RPS11	6205	P62280	
NDUFS5	4725	O43920	
SOD1	6647	P00441	
CHCHD2	51142	Q9Y6H1	
JUND	3727	P17535	
ENO3	2027	P13929	
CYC1	1537	P08574	
H3F3A	3020	P84243	
RPS2	6187	P15880	
NDUFS8	4728	O00217	
PDK4	5166	Q16654	
ATP5O	539	P48047	
RPL35A	6165	P18077	
LDHB	3945	P07195	
RPS3A	6189	P61247	
NUCB1	4924	Q02818	
IDH2	3418	P48735	
EIF3E	3646	P60228	
RPS6	6194	P62753	
GOT2	2806	P00505	
NDUFA3	4696	O95167	

RHOQ	23433	P17081
VDAC3	7419	Q9Y277
VWF	7450	P04275
COX6B1	1340	P14854
MGST3	4259	O14880
RPL18	6141	Q07020
RBPMS2	348093	Q6ZRY4
HSPA1B	3304	P0DMV9
GOT1	2805	P17174
RPS12	6206	P25398
SRP14	6727	P37108
RPL6	6128	Q02878
RPL39	6170	P62891
IFITM3	10410	Q01628
NDUFB10	4716	O96000
RPS17	6218	P08708
NDUFA8	4702	P51970
TMSB10	9168	P63313
ATP5J	522	P18859
AURKAIP1	54998	Q9NWT8
ATP5C1	509	P36542
GHITM	27069	Q9H3K2
UBA52	7311	P62987
SPARCL1	8404	Q14515
RPL35	11224	P42766
RPS14	6208	P62263
DUSP3	1845	P51452
LGALS1	3956	P09382
NACA	4666	Q13765
RPL27A	6157	P46776
NMRK2	27231	Q9NPI5
FAU	2197	P35544
NPPA	4878	P01160
NCOA4	8031	Q13772
RPL3	6122	P39023
PCLAF	9768	Q15004
GABPB2	126626	Q8TAK5
MGP	4256	P08493
NDUFB5	4711	O43674
PDE4C	5143	Q08493
MT1X	4501	P80297
ALKBH5	54890	Q6P6C2
RPL10A	4736	P62906
AKR1D1	6718	P51857
RPS28	6234	P62857
HSPB6	126393	O14558
GPD1L	23171	Q8N335
PDCD7	10081	Q8N8D1
WBP2	23558	Q969T9
RPL5	6125	P46777
ACAT1	38	P24752
NDUFB2	4708	O95178
COX7B	1349	P24311
CCR6	1235	P51684
MYL6	4637	P60660
BSG	682	P35613
DECR1	1666	Q16698
TIMP1	7076	P01033
MSRB2	22921	Q9Y3D2
CALM2	805	P62158
TSPAN9	10867	O75954
RPS18	6222	P62269
SLC25A3	5250	Q00325

Supplemental Table VII. hA-VCMs BinGO 2016. BinGO analysis of the adult ventricular cardiomyocyte (hA-VCMs) data¹⁹ using the 2016 GO annotation dataset. **x** is the number of IDs in both the submitted list and associated with the GO term, **n** indicates the number of protein IDs associated with the GO term, **X** is the number of protein IDs submitted for analysis, **N** is the number of protein IDs used as the background set.

GO-ID	GO term	p-value	corr p-value	x	n	X	N	Proteins submitted in analysis that are associated with the GO term
GO:0000027	ribosomal large subunit assembly	2.49E-09	3.37E-08	6	24	190	35980	Q02878 P63173 P39023 P83731 P62913 P46777
GO:0000028	ribosomal small subunit assembly	5.13E-10	7.26E-09	6	19	190	35980	P42677 P63173 P08078 P62263 P46783 P39019
GO:0000075	cell cycle checkpoint	1.57E-02	4.33E-02	5	275	190	35980	POCCG47 P62987 P83731 P62979 POCCG48
GO:0000077	DNA damage checkpoint	1.28E-02	3.77E-02	4	170	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0000082	G1/S transition of mitotic cell cycle	2.50E-03	1.02E-02	5	176	190	35980	POCCG47 P62987 Q9Y5N6 P62979 POCCG48
GO:0000086	G2/M transition of mitotic cell cycle	6.95E-03	2.33E-02	4	142	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0001165	MAPK cascade	1.39E-03	6.35E-03	8	401	190	35980	POCCG47 P51452 Q14116 P62987 P62979 P02511 P62158 POCCG48 P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P6 1247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P629 06 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0001184	nuclear-transcribed mRNA catabolic process, nonsense-mediated decay	6.70E-55	3.32E-57	37	125	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0001186	activation of MAPKK activity	1.96E-03	8.37E-03	6	244	190	35980	POCCG47 P62987 P62979 P62158 P25116 POCCG48
GO:0001187	activation of MAPK activity	1.32E-04	8.21E-04	6	146	190	35980	POCCG47 P60033 P62987 P62979 P00441 POCCG48
GO:0000271	polysaccharide biosynthetic process	1.13E-04	7.13E-04	4	47	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0000302	response to reactive oxygen species	1.97E-07	2.07E-06	10	210	190	35980	P02144 P05090 P13639 P68871 P09493 P22352 P02511 P69905 P00441 P0 1034
GO:0000422	mitophagy	6.34E-06	5.43E-05	8	183	190	35980	POCCG47 P52179 Q9P0U1 P40925 P62987 P62979 P10176 POCCG48
GO:0000423	macromitophagy	1.68E-06	1.57E-05	8	153	190	35980	POCCG47 P52179 Q9P0U1 P40925 P62987 P62979 P10176 POCCG48
GO:0000462	maturation of SSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA)	3.45E-04	1.91E-03	3	26	190	35980	P62263 P62249 P39019
GO:0000715	nucleotide-excision repair, DNA damage recognition	5.12E-06	4.49E-05	4	22	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0000724	double-strand break repair via homologous recombination	8.20E-03	2.68E-02	4	149	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0000725	recombinational repair	8.39E-03	2.72E-02	4	150	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P6 1247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P629 06 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 Q14240 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P6 2249
GO:0000956	nuclear-transcribed mRNA catabolic process	3.50E-48	6.12E-46	38	200	190	35980	P63244 P63173 P08493 Q14192 P62280 P17535 P06576 P63244 Q14192 P62280 P17535 P06576 POCCG47 P02144 P01160 P19021 P62987 P62979 P02511 Q06P6C2 POCCG48 P01034 P07602 P01033 Q14116 P09382 P68871 P04275 P62158 P04792 P19105 P2 5116 P00441 P01034 POCCG47 Q14116 P05090 P0DMV8 P0DMV9 P62987 P62979 P04792 P25116 P00441 POCCG48 POCCG47 P05090 P62987 P62979 POCCG48 POCCG47 Q14116 P0DMV8 P0DMV9 P62987 P62979 P04792 P25116 P00441 POCCG48 P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P6 1247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P629 06 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249 P07602 POCCG47 P51452 Q14116 O75116 P19022 POCCG48 P63244 P60033 P62987 P23327 P62979 P62158 P04792 P25116 Q8N335 P00441 P07602 POCCG47 Q14116 O75116 P19022 POCCG48 P63244 P60033 P62987 P62979 P62158 P25116 P00441
GO:0001503	ossification	5.25E-04	2.73E-03	7	263	190	35980	P63244 P63173 P08493 Q14192 P62280 P17535 P06576
GO:0001649	osteoblast differentiation	6.10E-04	3.10E-03	5	128	190	35980	P63244 Q14192 P62280 P17535 P06576
GO:0001666	response to hypoxia	5.41E-06	4.72E-05	10	303	190	35980	POCCG47 P02144 P01160 P19021 P62987 P62979 P02511 Q06P6C2 POCCG48 P01034 P07602 P01033 Q14116 P09382 P68871 P04275 P62158 P04792 P19105 P2 5116 P00441 P01034 POCCG47 Q14116 P05090 P0DMV8 P0DMV9 P62987 P62979 P04792 P25116 P00441 POCCG48 POCCG47 P05090 P62987 P62979 POCCG48 POCCG47 Q14116 P0DMV8 P0DMV9 P62987 P62979 P04792 P25116 P00441 POCCG48 P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P6 1247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P629 06 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249 P07602 POCCG47 P51452 Q14116 O75116 P19022 POCCG48 P63244 P60033 P62987 P23327 P62979 P62158 P04792 P25116 Q8N335 P00441 P07602 POCCG47 Q14116 O75116 P19022 POCCG48 P63244 P60033 P62987 P62979 P62158 P25116 P00441
GO:0001817	regulation of cytokine production	4.56E-04	2.43E-03	11	614	190	35980	POCCG47 P63244 P0DMV8 P0DMV9 P62987 P62979 POCCG48
GO:0001818	negative regulation of cytokine production	7.43E-03	2.45E-02	5	228	190	35980	POCCG47 P05090 P62987 P62979 POCCG48
GO:0001819	positive regulation of cytokine production	5.02E-05	3.54E-04	10	393	190	35980	POCCG47 Q14116 P0DMV8 P0DMV9 P62987 P62979 P04792 P25116 P00441 POCCG48 P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P6 1247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P629 06 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249 P07602 POCCG47 P51452 Q14116 O75116 P19022 POCCG48 P63244 P60033 P62987 P23327 P62979 P62158 P04792 P25116 Q8N335 P00441 P07602 POCCG47 Q14116 O75116 P19022 POCCG48 P63244 P60033 P62987 P62979 P62158 P25116 P00441
GO:0001887	selenium compound metabolic process	2.79E-54	8.29E-52	36	116	190	35980	POCCG47 P63244 P0DMV8 P0DMV9 P62987 P62979 POCCG48 P10916 P08590 P16615 P13533 P12883 Q14896 Q14958 P01160 P09493 P16615 P23327 P62158 P13533 Q8N335 P 12883 POCCG47 P51452 P62987 P62979 P62158 POCCG48 POCCG47 P62987 P62979 P62158 POCCG48 POCCG47 P51452 P62987 P62979 POCCG48 POCCG47 P62987 P62979 P62158 POCCG48 P52179 P40925 P62987 Q16654 Q6P6C2 P10176 P02144 P08708 P62263 P00441 P39019
GO:0001932	regulation of protein phosphorylation	2.73E-03	1.09E-02	17	1505	190	35980	POCCG47 P63244 P0DMV8 P0DMV9 P62987 P62979 POCCG48 P10916 P08590 P16615 P13533 P12883 Q14896 Q14958 P01160 P09493 P16615 P23327 P62158 P13533 Q8N335 P 12883 POCCG47 P51452 P62987 P62979 P62158 POCCG48 POCCG47 P62987 P62979 P62158 POCCG48 POCCG47 P51452 P62987 P62979 POCCG48 P52179 P40925 P62987 Q16654 Q6P6C2 P10176 P02144 P08708 P62263 P00441 P39019
GO:0001934	positive regulation of protein phosphorylation	4.24E-03	1.61E-02	13	1057	190	35980	POCCG47 P63244 P0DMV8 P0DMV9 P62987 P62979 POCCG48 P10916 P08590 P16615 P13533 P12883 Q14896 Q14958 P01160 P09493 P16615 P23327 P62158 P13533 Q8N335 P 12883 POCCG47 P51452 P62987 P62979 P62158 POCCG48 POCCG47 P62987 P62979 P62158 POCCG48 POCCG47 P51452 P62987 P62979 POCCG48 P52179 P40925 P62987 Q16654 Q6P6C2 P10176 P02144 P08708 P62263 P00441 P39019
GO:0001959	regulation of cytokine-mediated signaling pathway	1.12E-05	9.10E-05	7	142	190	35980	POCCG47 P63244 P0DMV8 P0DMV9 P62987 P62979 POCCG48
GO:0002026	regulation of the force of heart contraction	5.92E-07	5.93E-06	5	31	190	35980	P10916 P08590 P16615 P13533 P12883 Q14896 Q14958 P01160 P09493 P16615 P23327 P62158 P13533 Q8N335 P 12883
GO:0002027	regulation of heart rate	5.27E-11	7.84E-10	10	90	190	35980	Q14896 Q14958 P01160 P09493 P16615 P23327 P62158 P13533 Q8N335 P 12883
GO:0002218	activation of innate immune response	2.58E-03	1.05E-02	6	258	190	35980	POCCG47 P51452 P62987 P62979 P62158 POCCG48
GO:0002220	innate immune response activating cell surface receptor	5.09E-04	2.65E-03	5	123	190	35980	POCCG47 P62987 P62979 P62158 POCCG48
GO:0002221	pattern recognition receptor signaling pathway	1.48E-03	6.64E-03	5	156	190	35980	POCCG47 P51452 P62987 P62979 POCCG48
GO:0002223	stimulatory C-type lectin receptor signaling pathway	4.54E-04	2.43E-03	5	120	190	35980	POCCG47 P62987 P62979 P62158 POCCG48
GO:0002224	tol-like receptor signaling pathway	8.29E-04	4.08E-03	5	137	190	35980	POCCG47 P51452 P62987 P62979 POCCG48
GO:0002230	positive regulation of defense response to virus by host	3.67E-05	2.69E-04	6	116	190	35980	P52179 P40925 P62987 Q16654 Q6P6C2 P10176 P02144 P08708 P62263 P00441 P39019
GO:0002262	myeloid cell homeostasis	2.14E-04	1.26E-03	5	102	190	35980	P02144 P08708 P62263 P00441 P39019
GO:0002479	antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent	6.95E-03	2.33E-02	4	142	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0002576	platelet degranulation	9.07E-05	5.88E-04	5	85	190	35980	P07602 P01033 P04275 P62158 P00441 POCCG47 P51452 P62987 P62979 P62158 POCCG48 P52179 P40925 P62987 Q16654 Q6P6C2 P10176 P02144 P08708 P62263 P00441 P39019
GO:0002682	regulation of immune system process	7.80E-04	3.88E-03	21	1842	190	35980	POCCG47 P51452 P62987 P62979 P62158 POCCG48 P52179 P40925 P62987 Q16654 Q6P6C2 P10176 P02144 P08708 P62263 P00441 P39019
GO:0002684	positive regulation of immune system process	5.84E-03	2.01E-02	13	1099	190	35980	POCCG47 P51452 P62987 P62979 P62158 POCCG48 P52179 P40925 P62987 Q16654 Q6P6C2 P10176 P02144 P08708 P62263 P00441 P39019
GO:0002697	regulation of immune effector process	8.55E-03	2.76E-02	7	434	190	35980	P52179 P40925 P62987 Q16654 Q6P6C2 P10176 P39019
GO:0002753	cytoplasmic pattern recognition receptor signaling	3.09E-05	2.32E-04	4	34	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0002755	MyD88-dependent toll-like receptor signaling pathway	1.46E-04	9.01E-04	5	94	190	35980	POCCG47 P51452 P62987 P62979 POCCG48
GO:0002756	MyD88-independent toll-like receptor signaling pathway	9.07E-05	5.88E-04	5	85	190	35980	POCCG47 P51452 P62987 P62979 POCCG48
GO:0002758	innate immune response-activating signal transduction	2.17E-03	9.08E-03	6	249	190	35980	POCCG47 P51452 P62987 P62979 P62158 POCCG48
GO:0002831	regulation of response to biotic stimulus	1.55E-03	6.90E-03	6	233	190	35980	P52179 P40925 P62987 Q16654 Q6P6C2 P10176 Q15273 Q14896 P10916 P19429 Q14192 P08590 P09493 P68032 P45379 P 13533 P12883 P63316 P52179 P10916 P01160 P54296 P16615 P16860 Q01449 P19429 P09493 P23327 P6 2158 P45379 P00441 P02144 Q15273 Q14896 P13639 Q075116 P68133 P176 61 P68032 P13533 P19105 P12883 P17540 P06060 P08590 P02511 Q8N335 P63316 P02144 Q15273 P19429 P13639 P12883 P63316 P52179 P10916 P01160 P54296 P16615 Q01449 P19429 P09493 P23327 P6 2158 P45379 P00441 P02144 Q15273 Q14896 P13639 Q075116 P68133 P176 61 P68032 P13533 P19105 P12883 P17540 P06060 P08590 P02511 Q8N335 P63316 Q15273 Q14896 P10916 P01160 P68032 P13533 P12883 P16860 Q14958 P 19429 P68871 P08590 P09493 P45379 P25116 Q8N335 P00441 P63316 Q15273 Q14896 P10916 P68032 P13533 P12883 Q14958 P19429 P08590 P09493 P45379 P25116 P00441 P16860 P01160 P68871 P25116 P00441 P19429 P01160 P09493 P25116 Q13765 Q14896 P10916 P19429 Q14192 P08590 P09493 P45379 P13533 P 12883 P63316 Q14896 P10916 P19429 Q14192 P08590 P09493 P45379 P13533 P12883 P6 3316 Q14896 P10916 P19429 P08590 P09493 P45379 P13533 P12883 P63316 Q14896 P10916 P19429 P08590 P09493 P45379 P13533 P12883 P63316 Q13765 Q14896 P10916 P19429 P08590 P09493 P45379 P13533 P12883 P6 3316
GO:0003008	system process	2.48E-09	3.36E-08	34	2042	190	35980	POCCG47 P13929 P40926 P04406 P40925 POCCG48 P05090 P00505 P07195 P 1714 P62987 Q16654 P62979 P62158 Q8N335 P48735 POCCG47 P62987 P62979 P62158

GO:0006103	2-oxoglutarate metabolic process	1.55E-04	9.48E-04	3	20	190	35980	P00505 P17174 P48735
GO:0006107	oxaloacetate metabolic process	2.42E-07	2.51E-06	4	11	190	35980	P00505 P40926 P40925 P17174
GO:0006112	energy reserve metabolic process	2.82E-04	1.60E-03	6	168	190	35980	POCCG47 P62987 P62979 P62158 P12235 POCCG48
GO:0006119	oxidative phosphorylation	5.13E-20	1.27E-18	16	93	190	35980	O00217 O95169 P51970 O43674 O14561 O00483 O43920 P36542 O95167 P10176 O95178 O96000 P13073 O8YVYQ3 O15239 P20674
GO:0006120	mitochondrial electron transport, NADH to ubiquinone	2.08E-15	4.14E-14	11	50	190	35980	O00217 O95169 P51970 O43674 O14561 O00483 O43920 O95167 O95178 O96000 O15239
GO:0006123	mitochondrial electron transport, cytochrome c to oxygen	1.69E-05	1.33E-04	3	10	190	35980	P13073 P10176 P20674
GO:0006139	nucleobase-containing compound metabolic process	3.68E-25	1.42E-23	98	6597	190	35980	O75947 O43674 O96000 P16860 P13073 P07195 P46783 P83731 P62913 P62753 O15239 P20674 O13765 O95169 P48047 P04406 O14561 O95167 P16989 O9Y6H1 O95167 P84098 P63173 P68104 P46777 Q13772 P60866 P46776 P60228 P62249 Q8N335 P25398 P10176 O95178 P62891 P25705 P18859 Q14192 P56381 O00217 Q08493 P08708 P18077 Q6P6C2 P17535 P12883 Q8N8D1 P42677 P15880 Q02543 P62263 Q14240 P62945 P62269 POCCG47 Q8NSD9 P0DMV8 P0DMV9 P01160 P40926 P40925 P62280 Q8TAK5 P36542 POCCG48 P39019 P39023 P62273 P24311 Q8WYQ3 Q07020 P10606 Q96H40 O43920 P61353 P05386 P17081 P05387 P13929 P09669 O00483 P14854 P42766 Q02878 P84243 Q8NP15 P61247 P62857 P62979 Q15004 P62851 P51970 P62906 P15954 P13533 P62987 P20585 P06576
GO:0006163	purine nucleotide metabolic process	1.25E-23	4.01E-22	32	561	190	35980	P13929 O75947 P0DMV8 P0DMV9 P01160 O43674 O00483 P36542 P10176 O95178 O96000 P16860 P13073 P25705 P18859 P56381 O8YVYQ3 O15239 P20674 O00217 Q08493 O95169 P51970 P48047 P04406 O14561 O43920 P13533 O95167 P12883 P17081 P06576
GO:0006164	purine nucleotide biosynthetic process	3.16E-07	3.24E-06	10	221	190	35980	O75947 P16860 P25705 P48047 P18859 P01160 P36542 P56381 Q8WYQ3 P06576
GO:0006283	transcription-coupled nucleotide-excision repair	6.17E-04	3.14E-03	4	73	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0006289	nucleotide-excision repair	7.12E-03	2.37E-02	4	143	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0006297	nucleotide-excision repair, DNA gap filling	6.17E-06	5.31E-05	4	23	190	35980	POCCG47 P62987 P62979 POCCG48
GO:0006301	postreplication repair	2.31E-05	1.79E-04	5	64	190	35980	POCCG47 P62987 P62979 Q15004 POCCG48
GO:0006352	DNA-templated transcription, initiation	8.68E-09	1.10E-07	14	359	190	35980	POCCG47 P10606 P09669 P01160 O00483 P14854 P15954 P10176 POCCG48 P13073 P62987 P62979 P24311 P20674
GO:0006364	rRNA processing	4.67E-08	5.28E-07	10	180	190	35980	P42766 P08708 P62263 P18077 P62857 P62913 P46777 P62753 P62249 P39019
GO:0006366	transcription from RNA polymerase II promoter	4.03E-05	2.90E-04	15	833	190	35980	POCCG47 P10606 P09669 P01160 O00483 P14854 P15954 P10176 P17535 POCCG48 P13073 P62987 P62979 P24311 P20674
GO:0006367	transcription initiation from RNA polymerase II promoter	3.10E-10	4.46E-09	14	277	190	35980	POCCG47 P10606 P09669 P01160 O00483 P14854 P15954 P10176 POCCG48 P13073 P62987 P62979 P24311 P20674
GO:0006396	RNA processing	1.58E-02	4.33E-02	12	1115	190	35980	P42766 P08708 P62263 P18077 P62857 P62913 P46777 Q6P6C2 P62753 P62249 P39019 Q8N8D1
GO:0006401	RNA catabolic process	2.19E-44	2.84E-42	38	248	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P62906 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 Q14240 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0006402	mRNA catabolic process	9.90E-47	1.55E-44	38	217	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P62906 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 Q14240 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0006412	translation	2.90E-31	1.63E-29	47	985	190	35980	P25398 Q8NSD9 P62280 P12235 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q13765 Q07020 P13639 P08708 P62906 P18077 P37108 P42677 P84098 P15880 Q05639 P63173 Q02543 P61353 P62263 P62987 P63173 P68104 Q02543 Q9NWT8 P61353 Q00325 P62263 P62987 Q14240 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0006413	translational initiation	2.69E-42	3.20E-40	39	306	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P62906 P18077 P42677 P84098 P15880 P63173 Q02543 Q9NWT8 P61353 P62263 P62987 Q14240 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0006414	translational elongation	1.19E-49	2.52E-47	40	223	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P13639 P08708 P62906 P18077 P42677 P84098 P15880 Q05639 P63173 P68104 Q02543 Q9NWT8 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0006415	translational termination	5.34E-48	8.83E-46	37	183	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P62906 P18077 P42677 P84098 P15880 P63173 Q02543 Q9NWT8 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P62249
GO:0006417	regulation of translation	5.45E-04	2.82E-03	9	435	190	35980	P63244 P13639 P63173 P04406 P62283 Q14240 P16899 P04792 P60228
GO:0006461	protein complex assembly	1.70E-08	2.08E-07	26	1366	190	35980	O43674 O95178 P39019 O96000 P84243 P6887 P22325 Q16689 P69905 P45379 P24752 O15239 O00217 O15273 Q14896 O95169 P51970 O14561 P19021 P19022 O43920 O95167 O14958 Q9Y3D2 P02511 P04275
GO:0006518	peptide metabolic process	8.01E-30	4.10E-28	49	1183	190	35980	Q8NSD9 P62280 P39019 P39023 P62273 P46783 P83731 P62913 P62753 Q13765 Q07020 P13639 P19021 P37108 P84098 Q05639 P63173 P68104 P61353 P46777 P05386 P60866 P46776 P62269 P05387 P12235 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0006520	cellular amino acid metabolic process	2.61E-31	1.49E-29	42	722	190	35980	P06732 P25398 Q8NSD9 P62280 P39019 P62891 P42766 Q02878 P00505 P39023 P62273 P17174 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 P24752 Q07020 P08708 P62906 P18077 P42677 P84098 P15880 P17540 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P62249
GO:0006575	cellular modified amino acid metabolic process	3.29E-39	3.50E-37	40	397	190	35980	P06732 P25398 P62280 P39019 P62891 P42766 Q02878 P00505 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 P0041 Q07020 P08708 P62906 P18077 P42677 P84098 P15880 P17540 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P62249
GO:0006595	polyamine metabolic process	1.71E-03	7.50E-03	4	96	190	35980	P54368 P06732 P17540 P17174
GO:0006605	protein targeting	2.78E-37	2.67E-35	41	479	190	35980	P25398 P62280 P35613 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 Q9P0U1 P08708 P62906 P18077 P37108 Q9Y6H1 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P25116 P62249
GO:0006612	protein targeting to membrane	1.73E-49	3.44E-47	38	186	190	35980	P25398 P62280 P35613 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P62906 P18077 P37108 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P62249
GO:0006613	cotranslational protein targeting to membrane	9.45E-55	3.51E-52	37	126	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P62906 P18077 P37108 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0006614	SRP-dependent cotranslational protein targeting to membrane	3.34E-55	1.98E-52	37	123	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 P08708 P62906 P18077 P37108 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0006732	coenzyme metabolic process	1.40E-02	4.02E-02	7	478	190	35980	O75947 O43674 O96000 P16860 P13073 P07195 P46783 P83731 P62913 P62753 O15239 P20674 O13765 O95169 P48047 P04406 O14561 O95167 P16989 O9Y6H1 O95167 P84098 P63173 P68104 P46777 Q13772 P60866 P46776 P60228 P62249 Q8N335 P25398 P10176 O95178 P62891 P25705 P18859 Q14192 P56381 O00217 Q08493 P08708 P18077 Q6P6C2 P17535 P12883 Q8N8D1 P42677 P15880 Q02543 P62263 Q14240 P62945 P62269 POCCG47 Q8NSD9 P0DMV8 P0DMV9 P01160 P40926 P40925 P62280 Q8TAK5 P36542 POCCG48 P39019 P00505 P39023 P62273 P24311 Q8WYQ3 Q07020 P10606 Q96H40 O43920 P61353 P05386 P17081 P05387 P13929 P09669 O00483 P14854 P42766 Q02878 P84243 Q8NP15 P61247 P62857 P62979 Q15004 P62851 P51970 P62906 P15954 P13533 P62987 P20585 P06576
GO:0006733	oxidoreduction coenzyme metabolic process	4.47E-04	2.39E-03	7	256	190	35980	P13929 P40926 P04406 Q8NSD9 P07195 P40925 Q8N335
GO:0006734	NADH metabolic process	1.48E-06	1.41E-05	5	37	190	35980	P13929 P40926 P04406 P40925 Q8N335

GO:0006753	nucleoside phosphate metabolic process	6.37E-24	2.06E-22	37	809	190	35980	P13929 O75947 P0DMV8 P0DMV9 P01160 O43674 P40926 P40925 O00483 P36542 P10176 O95178 O96000 P16860 P13073 P25705 P18859 Q9NP15 P07195 P56381 Q8WYQ3 O15239 P20674 O00217 O43920 O95167 P17081 Q8N335 P048047 P04406 O14561 O43920 P13533 O95167 P12883 P17081 Q8N335 P06576
GO:0006754	ATP biosynthetic process	5.96E-10	8.36E-09	8	56	190	35980	O75947 P25705 P48047 P18859 P36542 P56381 Q8WYQ3 P06576 P0CCG47 O75947 P06732 P0DMV8 P0DMV9 P01160 O43674 P40926 P40925 P36542 P0CCG48 O96000 P16860 P13073 P07195 P62158 Q8WYQ3 O15239 P20674 O95169 P48047 P04406 O14561 O43920 O95167 P02511 P17081 Q8N335 P13929 O00483 P10176 O95178 P25705 P18859 Q9NP15 Q16654 P62979 P56381 P51452 O00217 Q14116 Q08493 P51970 O75116 P13533 P12883 P17540 P62987 P25116 P06576
GO:0006793	phosphorus metabolic process	6.88E-09	8.78E-08	50	4056	190	35980	P0CCG47 O75947 P06732 P0DMV8 P0DMV9 P01160 O43674 P40926 P40925 P36542 P0CCG48 O96000 P16860 P13073 P07195 P62158 Q8WYQ3 O15239 P20674 O95169 P48047 P04406 O14561 O43920 O95167 P02511 P17081 Q8N335 P13929 O00483 P10176 O95178 P25705 P18859 Q9NP15 Q16654 P62979 P56381 P51452 O00217 Q14116 Q08493 P51970 O75116 P13533 P12883 P17540 P62987 P25116 P06576
GO:0006796	phosphate-containing compound metabolic process	3.67E-09	4.78E-08	50	3980	190	35980	P0CCG47 O75947 P06732 P0DMV8 P0DMV9 P01160 O43674 P40926 P40925 P36542 P0CCG48 O96000 P16860 P13073 P07195 P62158 Q8WYQ3 O15239 P20674 O95169 P48047 P04406 O14561 O43920 O95167 P02511 P17081 Q8N335 P13929 O00483 P10176 O95178 P25705 P18859 Q9NP15 Q16654 P62979 P56381 P51452 O00217 Q14116 Q08493 P51970 O75116 P13533 P12883 P17540 P62987 P25116 P06576
GO:0006807	nitrogen compound metabolic process	5.01E-27	2.26E-25	115	8603	190	35980	O75947 O43674 O96000 P16860 P13073 P07195 P46783 P83731 P62913 P62753 P24752 O15239 P20674 Q13765 O95169 P13639 P48047 P04406 O14561 Q8Y5N6 P16989 Q8Y6H1 O95167 P84099 P53173 P68104 P46777 Q13772 P05086 P46776 P62289 P62249 Q8N335 P07602 P22538 P10176 O95178 P12235 P62891 P25705 P18859 O14192 P56381 P00441 P54368 O00217 Q08493 P08708 P18077 Q6P6C2 P17535 P12883 Q8N8D1 P42677 P1588 O1P17540 O02543 Q9NWT8 P62263 Q12420 P62945 P62289 P0CCG47 P06732 Q8N5D9 P0DMV8 P0DMV9 P01160 P40926 P40925 P62280 Q8TAK5 P36542 P0CCG48 P39019 P00505 P39023 P62273 P62158 P24311 Q8WYQ3 Q07020 P10606 Q96H40 O14880 P19021 P37108 O43920 O05639 P61353 P05386 P17081 P05387 P13929 P09669 O00483 P14854 P42766 Q02878 P84243 Q9NP15 P17174 P61247 P62857 P62979 Q15004 P62851 P51970 P62906 P15954 P13533 Q00325 P62987 P20585 P06576
GO:0006810	transport	1.36E-18	3.12E-17	90	6916	190	35980	P0CCG47 O75947 P0DMV8 P16615 P62280 P36542 P35613 P0CCG48 P39019 P16860 P00509 P13073 P00505 O14949 P39023 P62273 P46783 P83731 P62913 P24310 P69905 P62158 P24311 P62753 P20674 Q13765 Q07020 P01033 P10606 P48047 Q9Y277 P19021 P14406 P37108 Q9Y6H1 Q08431 P84098 O14958 P63173 P61353 P47985 P46777 P05386 P60866 P46776 P05387 P62249 P07602 P22398 P09669 P68363 O00483 P14854 P10176 P12235 P13693 P62891 P42766 Q02878 P25705 P18859 P60033 P68871 P61247 P62857 P62979 P56381 P62851 P00441 P54368 P02144 Q9P0U1 P08708 P62906 P18077 P15954 Q6P6C2 P42677 P41222 P15880 Q02543 Q00325 P62263 P62987 P62945 P04275 P62289 P25116 P06576
GO:0006811	ion transport	1.47E-07	1.56E-06	34	2414	190	35980	P0CCG47 O75947 P02792 P09669 O00483 P14854 P16615 P36542 P10176 P0CCG48 P13693 P13073 P25705 P00505 P18859 O14949 P68871 P62979 P56381 P24310 P69905 P24311 P20674 P10606 P48047 Q9Y277 P14406 P15954 O14958 Q00325 P62987 P47985 P25116 P06576
GO:0006812	cation transport	1.49E-06	1.41E-05	24	1503	190	35980	O75947 P10606 P02792 P09669 P48047 P14406 O00483 P14854 P16615 P36542 P15954 P10176 P13693 P13073 P25705 P18859 O14949 P47985 P56381 P24310 P24311 P25116 P06576 P20674
GO:0006818	hydrogen transport	1.88E-16	3.89E-15	20	298	190	35980	O75947 P10606 P09669 P48047 P14406 O00483 P14854 P36542 P15954 P10176 P13073 P25705 P18859 O14949 P47985 P56381 P24310 P24311 P06576 P20674
GO:0006839	mitochondrial transport	2.45E-07	2.54E-06	10	215	190	35980	O75947 P0DMV8 P25705 Q9P0U1 P48047 P18859 P36542 Q9Y6H1 P56381 P06576
GO:0006873	cellular ion homeostasis	5.79E-04	2.96E-03	10	533	190	35980	P13693 P02792 P51684 O14958 P19429 P16615 P23327 P25116 P00441 P06576
GO:0006874	cellular calcium ion homeostasis	1.67E-03	7.33E-03	7	321	190	35980	P13693 P51684 O14958 P19429 P16615 P23327 P25116 P00441 P25398 P62280 P35613 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q07020 Q9P0U1 P08708 P62906 P18077 P37108 Q9Y6H1 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62289 P05387 P25116 P62249
GO:0006875	cellular metal ion homeostasis	9.41E-04	4.57E-03	9	470	190	35980	P0CCG47 P52179 Q9P0U1 P40925 P62987 Q16654 P62979 Q6P6C2 P10176 P0CCG48
GO:0006886	intracellular protein transport	7.28E-23	2.14E-21	41	1120	190	35980	P0CCG47 O4406 Q9H3K2 P68032 P12235 P0CCG48 Q8N8D1 P63244 P09382 P62987 P62979 P02511 P25116 P01034
GO:0006914	autophagy	1.02E-04	6.52E-04	10	428	190	35980	P0CCG47 P10816 P051684 P35613 P0CCG48 P39019 P19429 P09493 P83731 P62979 P62158 P45379 P00441 O15273 Q14896 O75116 P19022 P68133 P17661 P68032 P13533 P19105 P12883 P60660 P08590 P62987 P04792 Q8N335 P06576 P63316
GO:0006915	apoptotic process	4.33E-03	1.64E-02	14	1185	190	35980	P0CCG47 P04406 Q9H3K2 P68032 P12235 P0CCG48 Q8N8D1 P63244 P09382 P62987 P62979 P02511 P25116 P01034
GO:0006928	movement of cell or subcellular component	6.42E-08	7.07E-07	30	1882	190	35980	P0CCG47 P10816 P051684 P35613 P0CCG48 P39019 P19429 P09493 P83731 P62979 P62158 P45379 P00441 O15273 Q14896 O75116 P19022 P68133 P17661 P68032 P13533 P19105 P12883 P60660 P08590 P62987 P04792 Q8N335 P06576 P63316
GO:0006935	chemotaxis	7.38E-03	2.44E-02	11	880	190	35980	P0CCG47 P51684 P60660 O75116 P62987 P83731 P62979 P62158 P19105 P0CCG48 P39019
GO:0006936	muscle contraction	9.35E-27	4.09E-25	27	264	190	35980	P52179 P10916 P54296 Q01449 P19429 P09493 P23327 P62158 P45379 P02144 Q15273 Q14896 P13639 O75116 P68133 P17661 P68032 P13533 P19105 P12883 O14958 P17540 P60660 P08590 P02511 Q8N335 P63316 Q14896 P10916 P01160 P16615 P12883 O14958 P19429 P08590 P09493 P23327 P62158 P45379 P25116 O15273 Q14896 P10916 P13639 P68032 P13533 P12883 O14958 P19429 P08590 P09493 P45379 Q8N335 P63316
GO:0006937	regulation of muscle contraction	2.42E-15	4.80E-14	16	179	190	35980	Q14896 P10916 P01160 P08590 P16615 P23327 P62158 P12883 P0CCG47 P0DMV8 P0DMV9 Q12988 P01160 P40925 P16615 P35613 P0CCG48 P05090 P09493 P69905 P62158 P24752 P01034 Q13765 P01033 P13639 P04406 P19021 P16989 P19105 P09382 P02511 P07602 P52179 P13929 P51684 P10176 P62891 P84243 P60033 P68871 Q9Y6H1 Q16654 P22352 P62979 Q15004 Q01628 P00441 P51452 O00217 P02144 Q14116 O15273 Q9P0U1 Q6P6C2 Q9Y3D2 P62987 P04275 P04792 P25116 P20585
GO:0006940	regulation of smooth muscle contraction	6.62E-03	2.24E-02	3	72	190	35980	P0CCG47 P51452 P52179 Q14116 P51684 P04406 P40925 Q6P6C2 P10176 P0CCG48 P62891 P62987 Q16654 P62979 P62158 Q01628 P25116 P01034
GO:0006941	striated muscle contraction	7.91E-18	1.74E-16	15	101	190	35980	P0CCG47 P62987 P62979 P0CCG48
GO:0006942	regulation of striated muscle contraction	6.20E-10	8.65E-09	9	83	190	35980	O00217 P02144 P0DMV8 P13639 P0DMV9 P16615 P05090 Q9Y3D2 P68871 P09493 P22352 P02511 P69905 P00441 P01034
GO:0006950	response to stress	2.36E-08	2.77E-07	53	4615	190	35980	P0CCG47 P10916 P0DMV8 O43674 P40925 P16615 P0CCG48 P39019 O96000 P39023 P09493 P46783 P83731 P62913 P45379 Q8WYQ3 O15239 Q14896 O95169 P04406 O14561 O43920 Q9Y6H1 P68032 O95167 O14958 P63173 P46777 P02511 P17081 P52179 P68363 P68871 P17661 P68032 P13533 O14958 Q9Y3D2 P09493 P02511 Q15004 P63313 P17081 P45379 P0441
GO:0006952	defense response	1.52E-02	4.33E-02	18	1947	190	35980	O15273 Q9Y3D2 P68133 P68032 P63313 P45379 P0CCG47 P62987 P68373 P62979 P0CCG48
GO:0006977	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest	4.20E-04	2.27E-03	4	66	190	35980	P0CCG47 P51452 P52179 Q14116 P51684 P04406 P40925 Q6P6C2 P10176 P0CCG48 P62891 P62987 Q16654 P62979 P62158 Q01628 P25116 P01034
GO:0006979	response to oxidative stress	2.80E-08	3.27E-07	15	461	190	35980	O00217 P02144 P0DMV8 P13639 P0DMV9 P16615 P05090 Q9Y3D2 P68871 P09493 P22352 P02511 P69905 P00441 P01034
GO:0006996	organelle organization	3.70E-11	5.62E-10	58	4481	190	35980	P0CCG47 P10916 P0DMV8 O43674 P40925 P16615 P0CCG48 P39019 O96000 P39023 P09493 P46783 P83731 P62913 P45379 Q8WYQ3 O15239 Q14896 O95169 P04406 O14561 O43920 Q9Y6H1 P68032 O95167 O14958 P63173 P46777 P02511 P17081 P52179 P68363 P68871 P17661 P68032 P13533 O14958 Q9Y3D2 P09493 P02511 Q15004 P63313 P17081 P45379 P0441
GO:0007005	mitochondrion organization	2.58E-13	4.56E-12	24	679	190	35980	P0CCG47 P52179 O00217 O95169 P0DMV8 P51970 Q9P0U1 O43674 O14561 P40925 O43920 Q9Y6H1 O95167 P10176 O95178 P12235 P0CCG48 O96000 Q9NWT8 P62987 P62979 Q8WYQ3 P06576 O15239
GO:0007009	plasma membrane organization	1.28E-02	3.76E-02	5	261	190	35980	O75116 P19022 P16615 P35613 P00441
GO:0007010	cytoskeleton organization	3.37E-04	1.88E-03	19	1479	190	35980	O15273 Q14896 P10916 P04406 O75116 P68363 P68133 P17661 P68032 P13533 O14958 Q9Y3D2 P09493 P02511 Q15004 P63313 P17081 P45379 P0441
GO:0007015	actin filament organization	1.28E-02	3.77E-02	6	362	190	35980	O15273 Q9Y3D2 P68133 P68032 P63313 P45379 P0CCG47 P62987 P68373 P62979 P0CCG48
GO:0007093	mitotic cell cycle checkpoint	3.47E-03	1.35E-02	5	190	190	35980	P0CCG47 P51452 P52179 Q14116 P51684 P04406 P40925 P16615 P35613 P0CCG48 P16860 P06660 P62987 Q16654 P62979 P62158 P17081 P04792 P62753
GO:0007167	enzyme linked receptor protein signaling pathway	7.18E-04	3.62E-03	16	1207	190	35980	P0CCG47 P51452 P52179 Q14116 P51684 P04406 P40925 P16615 P35613 P0CCG48 P16860 P06660 P62987 Q16654 P62979 P62158 P17081 P04792 P62753
GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	1.33E-03	6.10E-03	13	923	190	35980	P62158 P17081 P04792 P62753
GO:0007179	transforming growth factor beta receptor signaling	1.31E-02	3.82E-02	4	171	190	35980	P0CCG47 P62987 P62979 P0CCG48
GO:0007219	Notch signaling pathway	3.61E-04	1.99E-03	6	176	190	35980	P0CCG47 P17174 P62887 P62979 P0CCG48 P39019
GO:0007220	Notch receptor processing	6.17E-06	5.31E-05	4	23	190	35980	P0CCG47 P62987 P62979 P0CCG48
GO:0007249	I-kappaB kinase/NF-kappaB signaling	4.37E-05	3.12E-04	5	73	190	35980	P0CCG47 O75116 P62887 P62979 P0CCG48
GO:0007254	JNK cascade	1.30E-03	6.00E-03	4	89	190	35980	P0CCG47 P62987 P62979 P0CCG48
GO:0007265	Ras protein signal transduction	1.18E-02	3.48E-02	6	355	190	35980	P0CCG47 O75116 P62887 P62979 P62158 P0CCG48

GO:0007275	multicellular organism development	1.72E-07	1.82E-06	55	5183	190	35980	P0CG47 P10916 P01160 P35613 P0CG48 P39019 P63244 P05090 O14949 P09493 P83731 P62158 P45379 P24311 P24752 P01034 Q13765 P01033 P4896 P13639 P19021 P19022 P16989 P68032 Q08431 P19105 P63173 P08493 P06606 P09382 P02511 Q13772 P07602 P14854 P19429 P25705 P84243 P18859 Q14192 P62979 P00441 P02144 Q14116 O15273 O75116 P68133 P13533 P12883 P08590 P62263 P62987 P04275 P20585 P06576 P63316
GO:0007399	nervous system development	1.81E-02	4.91E-02	22	2582	190	35980	P0CG47 P13639 O75116 P19021 P19022 P14854 P19105 P0CG48 P05090 P84243 P18859 O14949 P06606 P09382 P62987 P83731 P62979 P62158 P24311 P24752 P00441 P01034
GO:0007409	axonogenesis	1.30E-02	3.82E-02	9	705	190	35980	P0CG47 P06606 O75116 P62987 P83731 P62979 P62158 P19105 P0CG48
GO:0007411	central nervous system development	5.11E-03	1.85E-02	12	957	190	35980	P0CG47 P06606 O75116 P62987 P83731 P62979 P62158 P19105 P0CG48
GO:0007420	brain development	6.06E-03	2.07E-02	10	737	190	35980	P0CG47 P05090 P84243 P18859 O14949 P19022 P14854 P62158 P24752 P01034
GO:0007507	heart development	3.22E-08	3.74E-07	16	537	190	35980	Q13765 P02144 O15273 Q14896 P10916 P01160 P19021 P68032 P13533 P12883 P19429 Q14192 P08590 P09493 P45379 P63316
GO:0007512	adult heart development	7.72E-05	5.20E-04	3	16	190	35980	O15273 Q14896 P10916 P13639 P68133 P68032 P13533 P12883 P19429 P6060 P08590 P09493 P02511 P45379 P63316
GO:0007517	muscle organ development	8.22E-11	1.22E-09	15	300	190	35980	O15273 Q14896 P10916 P13639 P68133 P68032 P13533 P12883 P19429 P6060 P08590 P09493 P02511 P45379 P63316
GO:0007519	skeletal muscle tissue development	5.83E-03	2.01E-02	4	135	190	35980	P13639 P06606 P08590 P68133
GO:0007565	female pregnancy	4.40E-03	1.68E-02	5	201	190	35980	P01160 P19021 P35613 P00441 P01034
GO:0007566	embryo implantation	1.86E-03	8.00E-03	3	46	190	35980	P35613 P00441 P01034
GO:0007568	aging	7.91E-04	3.92E-03	7	282	190	35980	P01033 P13929 P05090 P13639 P02511 P17535 P00441
GO:0007596	blood coagulation	3.41E-05	2.54E-04	12	541	190	35980	P07602 P01033 P84243 P68871 P16615 P04275 P62158 P04792 P35613 P19105 P25116 P00441
GO:0007599	hemostasis	3.73E-05	2.73E-04	12	546	190	35980	P07602 P01033 P84243 P68871 P16615 P04275 P62158 P04792 P35613 P19105 P25116 P00441
GO:0007623	circadian rhythm	2.24E-04	1.30E-03	6	161	190	35980	P0CG47 P62987 P62979 P17535 P0CG48 P01034
GO:0008015	blood circulation	5.95E-12	9.50E-11	18	401	190	35980	O15273 Q14896 P10916 P01160 P68032 P13533 P12883 P16860 Q14958 P19429 P68871 P08590 P09493 P45379 P25116 Q8N335 P00441 P63316
GO:0008016	regulation of heart contraction	2.90E-13	5.04E-12	16	243	190	35980	Q14896 P10916 P01160 P16615 P17661 P13533 P12883 O14958 P19429 Q9UB9Y P08590 P09493 P23327 P62158 P45379 Q8N335
GO:0008104	protein localization	2.01E-14	3.83E-13	46	2432	190	35980	P25398 Q96979 P62280 P35613 P39019 P62891 P42766 Q02878 P60033 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62851 P62753 Q13765 Q07020 Q9P0U1 P08708 O75116 P62906 P19022 P18077 P37108 Q9Y6H1 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P762945 P46777 P05386 P60866 P46776 P62269 P05387 P25116 P62249
GO:0008152	metabolic process	1.65E-10	2.39E-09	148	2093	190	35980	O75947 O43674 P16615 O96000 P16860 P13073 O14949 P07195 P46783 P83731 P62913 P62753 P24752 O15239 P20674 Q13765 O95169 P13639 P48047 P04406 O14561 P08297 Q9Y5N6 P16989 Q9Y6H1 O95167 Q08431 P84098 P63173 P68104 P08574 P47985 P46777 Q13772 P60866 P46776 P6022 P62249 Q13011 Q8N335 P07602 P52179 P25398 P68363 P01176 O95178 P12235 P62891 P25705 P18859 Q14192 P68871 Q16654 P65381 P00441 P54368 Q00217 Q14116 Q08493 P08708 O75116 P18077 Q6P6C2 P17535 P12883 Q8N8D1 P42677 P41222 P15880 P17540 Q02543 Q9NWT8 Q9Y3D2 P62263 Q14240 P62945 P62269 P0CG47 P06732 Q8NSD9 P0DMV8 P0DMV9 P01160 P40926 P40925 P62280 Q8TAK5 P36542 P35613 P0CG48 P39019 P63244 P05090 P00505 P39023 P62273 P24311 P69905 P62158 P24311 Q8WYQ3 P01034 Q07020 P10606 Q96H40 O14880 P19021 P37108 Q43920 Q05639 P61353 P02511 P05386 P17081 P05387 P13929 P09669 Q00483 P14854 P42766 Q02878 P84243 P60033 Q9N51P P17174 P61247 P62857 P22352 Q16698 P62979 Q15004 P62851 P51970 Q9P0U1 P62906 P15954 P51857 P13533 Q00325 P08590 P62987 P04275 P04792 P25116 P20585 P06576 P48735
GO:0008217	regulation of blood pressure	7.43E-06	6.20E-05	8	187	190	35980	P16860 P19429 P01160 P68871 P09493 P13533 P25116 P00441
GO:0008219	cell death	7.25E-03	2.41E-02	14	1259	190	35980	P0CG47 P04406 Q09H3K2 P68032 P12235 P0CG48 Q8N8D1 P63244 P09382 P62987 P62979 P02511 P25116 P01034
GO:0008286	insulin receptor signaling pathway	2.33E-04	1.35E-03	8	305	190	35980	P0CG47 P62987 Q16654 P62979 P62158 P17081 P62753 P0CG48
GO:0008406	gonad development	7.84E-03	2.57E-02	5	231	190	35980	P0CG47 P16989 Q13772 P00441 P01034
GO:0008584	male gonad development	6.29E-03	2.14E-02	4	138	190	35980	P0CG47 P16989 Q13772 P01034
GO:0009056	catabolic process	3.68E-24	1.24E-22	58	2321	190	35980	P0CG47 P40925 P62280 P0CG48 P39019 P00505 P39023 P62273 P46783 P83731 P62913 P69905 P62158 P62753 P24752 Q07020 P04406 P64098 P63173 P61353 P46777 P05386 P60866 P46776 P05387 P62249 Q13011 Q8N335 P52179 P13929 P25398 P10176 P62891 P42766 Q02878 P68871 P17174 P61247 P62857 P22352 Q16698 P62979 P62851 Q08493 Q9P0U1 P08708 P62906 P18077 P51857 P42677 P15880 Q02543 P62263 P62987 Q14240 P62945 P62269
GO:0009057	macromolecule catabolic process	7.48E-22	2.04E-20	41	1193	190	35980	P0CG47 P25398 P62280 P0CG48 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62158 P62851 P62753 Q07020 P08708 P62906 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 Q14240 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P60228 P62249
GO:0009058	biosynthetic process	8.64E-21	2.25E-19	94	6964	190	35980	P0CG47 O75947 P06732 Q8NSD9 P01160 P40926 P40925 P62280 Q8TAK5 P36542 P0CG48 P39019 P16860 P13073 P00505 P39023 P62273 P46783 P83731 P62913 P24311 P62753 Q8WYQ3 P24752 P02674 Q13765 Q07020 P10606 Q96H40 P13639 P48047 P04406 O14561 Q14880 Q9Y5N6 P37108 P16989 Q9Y6H1 P84098 Q05639 P63173 P68104 P61353 P46777 P05386 Q13772 P60866 P46776 P6022 P62249 Q13011 Q8N335 P07602 P52179 P25398 P68363 P01176 O95178 P12235 P62891 P25705 P18859 Q14192 P68871 Q16654 P65381 P00441 P54368 Q14116 P08708 P62906 P18077 P15954 P51857 P17535 P42677 P41222 P15880 Q02543 Q9NWT8 Q00325 P62263 P62987 Q14240 P62945 P62269 P06576
GO:0009059	macromolecule biosynthetic process	5.89E-13	1.01E-11	68	5325	190	35980	P0CG47 Q9NSD9 P01160 P62280 Q8TAK5 P0CG48 P39019 P13073 P39023 P62273 P46783 P83731 P62913 P24311 P62753 P20674 Q13765 Q07020 P10606 Q96H40 P13639 P48047 P04406 O14561 Q14880 Q9Y5N6 P37108 P16989 Q9Y6H1 P84098 Q05639 P63173 P68104 P61353 P46777 P05386 Q13772 P60866 P46776 P6022 P62249 Q13011 Q8N335 P07602 P52179 P25398 P68363 P01176 O95178 P12235 P62891 P25705 P18859 Q14192 Q9NPI5 P17174 P61247 P62857 P62979 P6381 Q15004 P62851 P00441 P54368 Q14116 P08708 P62906 P18077 P15954 P51857 P17535 P42677 P41222 P15880 Q02543 Q9NWT8 Q00325 P62263 P62987 Q14240 P62945 P62269 P06576
GO:0009060	aerobic respiration	8.71E-04	4.27E-03	4	80	190	35980	P13073 P40926 P40925 P48735
GO:0009069	serine family amino acid metabolic process	3.86E-51	8.83E-49	36	138	190	35980	P25398 P62280 P39019 P62891 P42766 Q02878 P39023 P62273 P46783 P61247 P83731 P62857 P62913 P62979 P62158 P62851 P62753 Q07020 P08708 P62906 P18077 P42677 P84098 P15880 P63173 Q02543 P61353 P62263 P62987 P62945 P46777 P05386 P60866 P46776 P62269 P05387 P62249
GO:0009116	nucleoside metabolic process	1.22E-20	3.16E-19	29	545	190	35980	P13929 O75947 P0DMV8 P0DMV9 O43674 O00483 P36542 P01176 O95178 Q96000 P13073 P25705 P18859 P56381 Q8WYQ3 Q15239 P20674 Q00217 O95169 P51970 P48047 P04406 O14561 Q43920 P13533 O95167 P12883 P17081 P06576
GO:0009117	nucleotide metabolic process	3.06E-24	1.07E-22	37	792	190	35980	P13929 O75947 P0DMV8 P0DMV9 O43674 O00483 P36542 P01176 O95178 Q96000 P13073 P25705 P18859 P56381 Q8WYQ3 Q15239 P20674 Q00217 O95169 P51970 P48047 P04406 O14561 Q43920 P13533 O95167 P12883 P17081 P06576
GO:0009119	ribonucleoside metabolic process	1.50E-21	4.05E-20	29	505	190	35980	P13929 O75947 P0DMV8 P0DMV9 O43674 O00483 P36542 P01176 O95178 Q96000 P13073 P25705 P18859 P56381 Q8WYQ3 Q15239 P20674 Q00217 O95169 P51970 P48047 P04406 O14561 Q43920 P13533 O95167 P12883 P17081 P06576
GO:0009123	nucleoside monophosphate metabolic process	4.63E-23	1.38E-21	28	403	190	35980	P13929 O75947 P0DMV8 P0DMV9 O43674 O00483 P36542 P01176 O95178 Q96000 P13073 P25705 P18859 P56381 Q8WYQ3 Q15239 P20674 Q00217 O95169 P51970 P48047 P04406 O14561 Q43920 P13533 O95167 P12883 P17081 P06576
GO:0009124	nucleoside monophosphate biosynthetic process	4.61E-07	4.65E-06	8	129	190	35980	O75947 P25705 P48047 P18859 P36542 P56381 Q8WYQ3 P06576
GO:0009126	purine nucleoside monophosphate metabolic process	4.48E-24	1.48E-22	28	370	190	35980	P13929 O75947 P0DMV8 P0DMV9 O43674 O00483 P36542 P01176 O95178 Q96000 P13073 P25705 P18859 P56381 Q8WYQ3 Q15239 P20674 Q00217 O95169 P51970 P48047 P04406 O14561 Q43920 P13533 O95167 P12883 P17081 P06576
GO:0009127	purine nucleoside monophosphate biosynthetic process	6.41E-08	7.07E-07	8	100	190	35980	O75947 P25705 P48047 P18859 P36542 P56381 Q8WYQ3 P06576
GO:0009141	nucleoside triphosphate metabolic process	1.00E-24	3.68E-23	29	389	190	35980	P13929 O75947 P0DMV8 P0DMV9 O43674 O00483 P36542 P01176 O95178 Q96000 P13073 P25705 P18859 P56381 Q8WYQ3 Q15239 P20674 Q00217 O95169 P51970 P48047 P04406 O14561 Q43920 P13533 O95167 P12883 P17081 P06576

GO:0032502	developmental process	1.47E-08	1.82E-07	64	6093	35980	P0CG47 P10916 P01160 P16615 P62280 P35613 P0CG48 P39019 P63244 P05090 O14949 P09493 P83731 P62158 P45379 P24311 P24752 P01034 Q13765 P01033 Q14896 P13639 P19021 P19022 P16989 P68032 Q08431 P19105 O14958 P63173 P08493 P06606 P09382 P02511 Q13772 P07602 P13929 P14854 P19429 P25705 P08424 P18859 Q14192 P61247 P62979 P00441 P02144 Q14315 Q14116 O15273 O75116 P68133 Q6P6C2 P13533 P17535 P12883 P08590 P06263 P62987 P04275 P25116 P20585 P06576 P63316
GO:0032677	regulation of interleukin-8 production	4.17E-03	1.58E-02	3	61	190	35980
GO:0032757	positive regulation of interleukin-8 production	1.75E-03	7.63E-03	3	45	190	35980
GO:0032774	RNA biosynthetic process	3.70E-16	7.53E-15	57	3310	190	35980
GO:0032781	positive regulation of ATPase activity	7.91E-05	5.31E-04	4	43	190	35980
GO:0032787	monocarboxylic acid metabolic process	9.66E-05	6.24E-04	13	699	190	35980
GO:0032844	regulation of homeostatic process	3.97E-03	1.51E-02	8	476	190	35980
GO:0032868	response to insulin	1.10E-04	6.99E-04	10	432	190	35980
GO:0032869	cellular response to insulin stimulus	1.74E-04	1.05E-03	9	372	190	35980
GO:0032870	cellular response to hormone stimulus	1.85E-04	1.10E-03	14	850	190	35980
GO:0032879	regulation of localization	5.28E-06	4.62E-05	33	2703	190	35980
GO:0032880	regulation of protein localization	3.39E-03	1.33E-02	13	1029	190	35980
GO:0032970	regulation of actin filament-based process	3.15E-03	1.24E-02	8	458	190	35980
GO:0032971	regulation of muscle filament sliding	5.78E-07	5.80E-06	3	4	190	35980
GO:0032981	mitochondrial respiratory chain complex I assembly	1.13E-12	1.88E-11	10	62	190	35980
GO:0032984	macromolecular complex disassembly	7.76E-42	8.87E-40	37	262	190	35980
GO:0032989	cellular component morphogenesis	1.37E-04	8.49E-04	19	1377	190	35980
GO:0033036	macromolecule localization	4.88E-14	8.96E-13	50	2915	190	35980
GO:0033108	mitochondrial respiratory chain complex assembly	4.71E-11	7.10E-10	10	89	190	35980
GO:0033157	regulation of intracellular protein transport	1.63E-02	4.46E-02	6	382	190	35980
GO:0033209	tumor necrosis factor-mediated signaling pathway	1.44E-03	6.49E-03	5	155	190	35980
GO:0033275	actin-myosin filament sliding	1.08E-22	3.13E-21	14	39	190	35980
GO:0033365	protein localization to organelle	4.18E-32	2.44E-30	41	644	190	35980
GO:0033354	cellular response to stress	2.51E-03	1.02E-02	22	2165	190	35980
GO:0033674	positive regulation of kinase activity	1.00E-02	3.16E-02	9	675	190	35980
GO:0033683	nucleotide-excision repair, DNA incision	5.36E-05	3.72E-04	4	39	190	35980
GO:0033692	cellular polysaccharide biosynthetic process	8.67E-05	5.65E-04	4	44	190	35980
GO:0033993	response to lipid	5.80E-06	5.02E-05	18	989	190	35980
GO:0034097	response to cytokine	2.25E-04	1.31E-03	15	974	190	35980
GO:0034103	erythrocyte homeostasis	1.00E-03	4.79E-03	4	83	190	35980
GO:0034104	regulation of tissue remodeling	5.65E-03	1.96E-02	3	68	190	35980
GO:0034134	toll-like receptor 2 signaling pathway	5.68E-05	3.91E-04	5	77	190	35980
GO:0034138	toll-like receptor 3 signaling pathway	1.01E-04	6.52E-04	5	87	190	35980
GO:0034142	toll-like receptor 4 signaling pathway	2.35E-04	1.35E-03	5	104	190	35980
GO:0034146	toll-like receptor 5 signaling pathway	3.33E-05	2.48E-04	5	69	190	35980
GO:0034162	toll-like receptor 9 signaling pathway	5.31E-05	3.71E-04	5	76	190	35980
GO:0034166	toll-like receptor 10 signaling pathway	3.57E-05	2.63E-04	5	70	190	35980
GO:0034220	ion transmembrane transport	4.32E-08	4.90E-07	28	1636	190	35980
GO:0034248	regulation of cellular amide metabolic process	8.35E-04	4.09E-03	9	462	190	35980
GO:0034470	ncRNA processing	1.99E-04	1.18E-03	10	465	190	35980
GO:0034599	cellular response to oxidative stress	1.21E-03	5.67E-03	6	222	190	35980
GO:0034612	response to tumor necrosis factor	3.41E-03	1.33E-02	6	273	190	35980
GO:0034613	cellular protein localization	2.70E-19	6.41E-18	44	1641	190	35980
GO:0034622	cellular macromolecular complex assembly	3.44E-14	6.43E-13	28	885	190	35980
GO:0034637	cellular carbohydrate biosynthetic process	1.97E-05	1.54E-04	5	62	190	35980
GO:0034641	cellular nitrogen compound metabolic process	1.26E-27	5.87E-26	112	8039	190	35980
GO:0034645	cellular macromolecule biosynthetic process	2.51E-13	4.46E-12	68	5231	190	35980

GO ID	GO Term	Count	Ratio	Score	Log-Odds	Ratio	Count	Ratio	Score	Log-Odds	Ratio	Count	Ratio
GO:0034654	nucleobase-containing compound biosynthetic process	3.06E-20	7.71E-19	68	3838	190	35980						
GO:0034655	nucleobase-containing compound catabolic process	1.28E-37	1.27E-35	39	401	190	35980						
GO:0034660	ncRNA metabolic process	1.70E-03	7.46E-03	11	723	190	35980						
GO:0034762	regulation of transmembrane transport	9.86E-03	3.11E-02	8	557	190	35980						
GO:0034763	negative regulation of transmembrane transport	1.22E-02	3.60E-02	3	90	190	35980						
GO:0035051	cardiocyte differentiation	3.85E-05	2.81E-04	6	117	190	35980						
GO:0035150	regulation of tube size	1.99E-03	8.47E-03	5	167	190	35980						
GO:0035637	multicellular organismal signaling	2.26E-03	9.40E-03	5	172	190	35980						
GO:0035666	TRIF-dependent toll-like receptor signaling pathway	7.21E-05	4.89E-04	5	81	190	35980						
GO:0035872	nucleotide-binding domain, leucine rich repeat containing receptor signaling pathway	1.03E-04	6.61E-04	4	46	190	35980						
GO:0036293	response to decreased oxygen levels	6.99E-06	5.91E-05	10	312	190	35980						
GO:0036294	cellular response to decreased oxygen levels	6.78E-03	2.28E-02	4	141	190	35980						
GO:0036297	interstrand cross-link repair	7.21E-05	4.89E-04	4	42	190	35980						
GO:0038061	NIK/NF-kappaB signaling	1.92E-03	8.23E-03	4	99	190	35980						
GO:0038123	toll-like receptor TLR1:TLR2 signaling pathway	5.31E-05	3.71E-04	5	76	190	35980						
GO:0038124	toll-like receptor TLR6:TLR2 signaling pathway	5.31E-05	3.71E-04	5	76	190	35980						
GO:0040008	regulation of growth	3.51E-04	1.94E-03	12	695	190	35980						
GO:0040011	locomotion	4.58E-03	1.71E-02	17	1585	190	35980						
GO:0040012	regulation of locomotion	4.51E-03	1.69E-02	11	822	190	35980						
GO:0042058	regulation of epidermal growth factor receptor signaling	9.56E-04	4.63E-03	4	82	190	35980						
GO:0042059	negative regulation of epidermal growth factor receptor	7.21E-05	4.89E-04	4	42	190	35980						
GO:0042060	wound healing	1.32E-06	1.28E-05	16	709	190	35980						
GO:0042176	regulation of protein catabolic process	4.17E-04	2.26E-03	9	419	190	35980						
GO:0042221	response to chemical	1.53E-18	3.47E-17	74	4840	190	35980						
GO:0042246	tissue regeneration	3.98E-03	1.51E-02	3	60	190	35980						
GO:0042254	ribosome biogenesis	5.02E-12	8.07E-11	16	293	190	35980						
GO:0042255	ribosome assembly	3.22E-14	6.07E-13	11	63	190	35980						
GO:0042273	ribosomal large subunit biogenesis	2.32E-10	3.34E-09	8	50	190	35980						
GO:0042274	ribosomal small subunit biogenesis	6.63E-12	1.05E-10	9	51	190	35980						
GO:0042276	error-prone translesion synthesis	2.74E-06	2.52E-05	4	19	190	35980						
GO:0042278	purine nucleoside metabolic process	2.17E-22	6.15E-21	29	471	190	35980						
GO:0042325	regulation of phosphorylation	2.58E-03	1.05E-02	18	1628	190	35980						
GO:0042327	positive regulation of phosphorylation	2.24E-03	9.31E-03	14	1100	190	35980						
GO:0042330	taxis	7.38E-03	2.44E-02	11	880	190	35980						
GO:0042391	regulation of membrane potential	3.72E-03	1.43E-02	7	371	190	35980						
GO:0042451	purine nucleoside biosynthetic process	1.45E-06	1.38E-05	8	150	190	35980						
GO:0042455	ribonucleoside biosynthetic process	4.96E-06	4.38E-05	8	177	190	35980						
GO:0042493	response to drug	3.57E-05	2.63E-04	11	458	190	35980						
GO:0042542	response to hydrogen peroxide	2.78E-06	2.53E-05	7	115	190	35980						
GO:0042590	antigen processing and presentation of exogenous peptide antigen via MHC class I	7.65E-03	2.52E-02	4	146	190	35980						
GO:0042592	homeostatic process	1.25E-05	1.00E-04	23	1590	190	35980						
GO:0042692	muscle cell differentiation	5.11E-11	7.63E-10	15	290	190	35980						
GO:0042743	hydrogen peroxide metabolic process	2.41E-05	1.85E-04	4	32	190	35980						
GO:0042744	hydrogen peroxide catabolic process	1.32E-04	8.21E-04	3	19	190	35980						
GO:0042769	DNA damage response, detection of DNA damage	3.89E-05	2.81E-04	4	36	190	35980						
GO:0042770	signal transduction in response to DNA damage	2.63E-03	1.06E-02	4	108	190	35980						
GO:0042773	ATP synthesis coupled electron transport	1.55E-17	3.37E-16	14	83	190	35980						
GO:0042775	mitochondrial ATP synthesis coupled electron transport	5.07E-18	1.12E-16	14	77	190	35980						
GO:0042776	mitochondrial ATP synthesis coupled proton transport	4.89E-12	7.99E-11	7	19	190	35980						
GO:0042981	regulation of apoptotic process	3.10E-05	2.32E-04	23	1685	190	35980						
GO:0043043	peptide biosynthetic process	1.35E-30	7.32E-29	47	1020	190	35980						
GO:0043065	positive regulation of apoptotic process	2.73E-03	1.09E-02	10	657	190	35980						
GO:0043066	negative regulation of apoptotic process	2.93E-06	2.66E-05	18	941	190	35980						
GO:0043067	regulation of programmed cell death	3.72E-06	3.31E-05	25	1698	190	35980						
GO:0043068	positive regulation of programmed cell death	2.88E-03	1.14E-02	10	662	190	35980						
GO:0043069	negative regulation of programmed cell death	8.07E-07	7.97E-06	19	951	190	35980						
GO:0043086	negative regulation of catalytic activity	4.54E-05	3.23E-04	17	1048	190	35980						
GO:0043122	regulation of I-kappaB kinase/NF-kappaB signaling	5.62E-05	3.89E-04	8	248	190	35980						
GO:0043123	positive regulation of I-kappaB kinase/NF-kappaB	7.95E-05	5.33E-04	7	193	190	35980						

Table with 7 columns: ID, Description, X1, X2, X3, X4, X5. It lists biological processes such as 'biological regulation', 'regulation of biological quality', 'regulation of molecular function', etc., with associated numerical data for each entry.

GO:1903362	regulation of cellular protein catabolic process	4.80E-03	1.79E-02	6	293	190	35980	P0CG47 P63244 P60033 P62987 P62979 P0CG48
GO:1903364	positive regulation of cellular protein catabolic process	4.70E-04	2.49E-03	6	185	190	35980	P0CG47 P63244 P60033 P62987 P62979 P0CG48
GO:1903508	positive regulation of nucleic acid-templated transcription	9.65E-03	3.05E-02	16	1575	190	35980	P0CG47 Q13765 P0DMV8 P0DMV9 Q969T9 Q8TAK5 Q9Y6H1 P17535 P0CG48 P60033 Q14192 P62987 P62979 Q13772 P17081 P25116
GO:1903522	regulation of blood circulation	1.84E-13	3.31E-12	18	326	190	35980	Q14896 P10916 P01160 P16615 P17661 P13533 P12883 P16860 O14958 P19429 Q9UBY9 P08590 P09493 P23327 P62158 P45379 P25116 Q8N335
GO:1903524	positive regulation of blood circulation	1.69E-04	1.02E-03	5	97	190	35980	P01160 P09493 P16615 P23327 P25116
GO:1903649	regulation of cytoplasmic transport	3.32E-03	1.30E-02	8	462	190	35980	Q14116 P63244 P05090 O14958 Q9P0U1 P23327 P62158 P25116
GO:1903651	positive regulation of cytoplasmic transport	1.50E-02	4.29E-02	5	272	190	35980	Q14116 P63244 Q9P0U1 P62158 P25116
GO:1903779	regulation of cardiac conduction	1.67E-06	1.57E-05	6	68	190	35980	O14958 P19429 P01160 P16615 P23327 P62158
GO:1903827	regulation of cellular protein localization	3.12E-03	1.23E-02	9	561	190	35980	P54368 Q14116 P63244 P05090 Q9P0U1 Q02818 P19022 P17081 Q8N335
GO:1903844	regulation of cellular response to transforming growth factor beta stimulus	3.41E-03	1.33E-02	4	116	190	35980	P0CG47 P62987 P62979 P0CG48
GO:1903845	negative regulation of cellular response to transforming growth factor beta stimulus	9.56E-04	4.63E-03	4	82	190	35980	P0CG47 P62987 P62979 P0CG48
GO:1904062	regulation of cation transmembrane transport	1.45E-03	6.56E-03	6	230	190	35980	O14958 P01160 P23327 P62158 P25116 Q8N335
GO:1990267	response to transition metal nanoparticle	1.61E-03	7.10E-03	5	159	190	35980	P80297 P19021 Q02818 P35613 P00441
GO:1990542	mitochondrial transmembrane transport	1.79E-09	2.44E-08	8	64	190	35980	O75947 P25705 Q9P0U1 P48047 P18859 P36542 P56381 P06576
GO:1990748	cellular detoxification	1.32E-03	6.07E-03	5	152	190	35980	P68871 O14880 P22352 P69905 P00441
GO:2000021	regulation of ion homeostasis	1.38E-04	8.56E-04	7	211	190	35980	P63244 P16860 O14958 P23327 P62158 P25116 Q8N335
GO:2000045	regulation of G1/S transition of mitotic cell cycle	1.07E-02	3.23E-02	4	161	190	35980	P0CG47 P62987 P62979 P0CG48
GO:2000058	regulation of protein ubiquitination involved in ubiquitin-dependent protein catabolic process	1.78E-03	7.70E-03	4	97	190	35980	P0CG47 P62987 P62979 P0CG48
GO:2000060	positive regulation of protein ubiquitination involved in ubiquitin-dependent protein catabolic process	1.24E-03	5.79E-03	4	88	190	35980	P0CG47 P62987 P62979 P0CG48
GO:2000134	negative regulation of G1/S transition of mitotic cell cycle	3.51E-03	1.36E-02	4	117	190	35980	P0CG47 P62987 P62979 P0CG48
GO:2001233	regulation of apoptotic signaling pathway	3.09E-04	1.74E-03	9	402	190	35980	P0CG47 P13693 P63244 P0DMV8 P0DMV9 P16989 P04792 P00441 Q8N8D1
GO:2001234	negative regulation of apoptotic signaling pathway	5.83E-03	2.01E-02	5	215	190	35980	P13693 P0DMV8 P0DMV9 P16989 P04792
GO:2001242	regulation of intrinsic apoptotic signaling pathway	1.97E-05	1.54E-04	7	155	190	35980	P0CG47 P13693 P63244 P0DMV8 P16989 P04792 P00441
GO:2001243	negative regulation of intrinsic apoptotic signaling pathway	1.65E-03	7.26E-03	4	95	190	35980	P13693 P0DMV8 P16989 P04792
GO:2001244	positive regulation of intrinsic apoptotic signaling pathway	3.79E-03	1.45E-02	3	59	190	35980	P0CG47 P63244 P00441
GO:2001257	regulation of cation channel activity	2.14E-03	9.02E-03	4	102	190	35980	O14958 P01160 P23327 P62158

Supplemental Table VIII. hA-VCMs BinGO 2011. BinGO analysis of the adult ventricular cardiomyocyte (hA-VCMs) data¹⁹ using the 2011 GO annotation dataset. **x** is the number of IDs in both the submitted list and associated with the GO term, **n** indicates the number of protein IDs associated with the GO term, **X** is the number of protein IDs submitted for analysis, **N** is the number of protein IDs used as the background set.

GO:1901700	response to oxygen-containing compound	1.64E-04	1.49E-03	21	1348	178	27688	P01033 P02144 Q14116 P01160 P19021 P68032 P35613 P12883 P16860 P00505 P09382 P68871 P09493 P17174 P08574 P22352 P69905 P17081 P62753 P25116 P00441
GO:1901988	negative regulation of cell cycle phase transition	8.29E-03	3.54E-02	4	123	178	27688	POCG47 P62987 P62979 POCG48
GO:1901991	negative regulation of mitotic cell cycle phase	7.61E-03	3.29E-02	4	120	178	27688	POCG47 P62987 P62979 POCG48
GO:1902400	intracellular signal transduction involved in G1	8.72E-04	6.35E-03	4	66	178	27688	POCG47 P62987 P62979 POCG48
GO:1902402	signal transduction involved in mitotic DNA	9.23E-04	6.59E-03	4	67	178	27688	POCG47 P62987 P62979 POCG48
GO:1902403	signal transduction involved in mitotic DNA	9.23E-04	6.59E-03	4	67	178	27688	POCG47 P62987 P62979 POCG48
GO:1902578	single-organism localization	1.20E-02	4.81E-02	36	3840	178	27688	P07602 POCG47 O75947 P02792 P68363 P16615 P36542 P35613 P12235 POCG48 P39019 P13693 P16860 P05090 P25705 P00505 P18859 P68871 P62913 P62979 P56381 P69905 P62158 P00441 P01033 Q9POU1 P48047 Q9V277 P37108 Q08431 P19105 P62987 P04275 P63313 P25116 P06576
GO:1902582	single-organism intracellular transport	1.83E-05	2.05E-04	19	975	178	27688	POCG47 O75947 P02792 Q9POU1 P48047 P68363 P37108 P16615 P36542 P19105 POCG48 P25705 P18859 P62987 P62913 P62979 P56381 P25116 P06576
GO:1902600	hydrogen ion transmembrane transport	8.78E-06	1.06E-04	7	113	178	27688	O75947 P25705 P48047 P18859 P36542 P56381 P06576
GO:1902806	regulation of cell cycle G1/S phase transition	3.09E-03	1.66E-02	4	93	178	27688	POCG47 P62987 P62979 POCG48
GO:1902807	negative regulation of cell cycle G1/S phase	1.63E-03	1.02E-02	4	78	178	27688	POCG47 P62987 P62979 POCG48
GO:1903050	regulation of proteolysis involved in cellular	2.82E-03	1.56E-02	5	149	178	27688	POCG47 P63244 P62987 P62979 POCG48
GO:1903052	positive regulation of proteolysis involved in cellular protein catabolic process	7.99E-04	6.02E-03	5	112	178	27688	POCG47 P63244 P62987 P62979 POCG48
GO:1903321	negative regulation of protein modification by small protein conjugation or removal	4.30E-03	2.17E-02	4	102	178	27688	POCG47 P62987 P62979 POCG48
GO:1903322	positive regulation of protein modification by small protein conjugation or removal	9.50E-03	3.98E-02	4	128	178	27688	POCG47 P62987 P62979 POCG48
GO:1903362	regulation of cellular protein catabolic process	3.25E-03	1.74E-02	5	154	178	27688	POCG47 P63244 P62987 P62979 POCG48
GO:1903364	positive regulation of cellular protein catabolic	8.32E-04	6.23E-03	5	113	178	27688	POCG47 P63244 P62987 P62979 POCG48
GO:1903522	regulation of blood circulation	4.52E-06	5.62E-05	9	192	178	27688	P16860 Q9UBV9 P08590 P09493 P17661 P45379 P13533 P25116 P12883
GO:1990267	response to transition metal nanoparticle	9.25E-03	3.89E-02	4	127	178	27688	P80297 P19021 P35613 P00441
GO:1990542	mitochondrial transmembrane transport	6.28E-09	1.01E-07	7	40	178	27688	O75947 P25705 P48047 P18859 P36542 P56381 P06576
GO:2000045	regulation of G1/S transition of mitotic cell cycle	3.09E-03	1.66E-02	4	93	178	27688	POCG47 P62987 P62979 POCG48
GO:2000058	regulation of protein ubiquitination involved in ubiquitin-dependent protein catabolic process	1.79E-03	1.10E-02	4	80	178	27688	POCG47 P62987 P62979 POCG48
GO:2000060	positive regulation of protein ubiquitination involved in ubiquitin-dependent protein catabolic	1.48E-03	9.54E-03	4	76	178	27688	POCG47 P62987 P62979 POCG48
GO:2000134	negative regulation of G1/S transition of mitotic	1.63E-03	1.02E-02	4	78	178	27688	POCG47 P62987 P62979 POCG48

Supplemental Table Viv. 2011 v 2016 comparison. A selection of *Biological Process* GO terms extracted from two BinGO analyses, using either the 2016 or the 2011 GO annotation dataset and adult ventricular cardiomyocyte data¹⁹ (2016-hA-VCMs and 2011-hA-VCMs, respectively). GO terms selected either align with the GO terms identified by Poon et al., 2013, or a descriptive GO term associated with a large proportion of the analysed dataset, or are terms from the ‘*cardiac conduction*’ domain of the ontology. **n** indicates the number of protein IDs associated with the GO term, **corr p-value** is the p-value after Benjamini & Hochberg False Discovery Rate correction, **x** is the number of IDs in both the submitted list and associated with the GO term, #N/A indicates that this term was not significantly enriched in the dataset. The corrected p-values in the 2016 analysis are highlighted in green if the p-value is more significant in the 2016 analysis, and orange if the p-value is more significant in the 2011 analysis.

Description	n	2016-hA-VCMS		2011-hA-VCMS		
		corr p-value	x	n	corr p-value	x
GO:0006614 SRP-dependent cotranslational protein targeting to membrane	123	1.98E-52	37		#N/A	#N/A
GO:0045047 protein targeting to ER	127	4.39E-52	37		#N/A	#N/A
GO:0072599 establishment of protein localization to endoplasmic reticulum	131	1.36E-51	37		#N/A	#N/A
GO:0006414 translational elongation	223	2.52E-47	40	110	1.40E-53	38
GO:0006091 generation of precursor metabolites and energy	574	1.06E-34	43	552	1.89E-28	40
GO:0022904 respiratory electron transport chain	157	1.67E-34	29	135	5.48E-34	29
GO:0022411 cellular component disassembly	673	2.76E-34	45	221	1.73E-39	37
GO:0045333 cellular respiration	231	5.04E-34	32	206	6.99E-33	32
GO:0044419 interspecies interaction between organisms	830	1.26E-31	46	781	5.40E-27	44
GO:0061024 membrane organization	1211	1.16E-27	49	444	1.37E-02	9
GO:0003012 muscle system process	319	7.11E-27	30	233	1.38E-21	25
GO:0016071 mRNA metabolic process	743	7.53E-27	40	651	6.93E-27	41
GO:0006936 muscle contraction	264	4.09E-25	27	205	1.36E-21	24
GO:0033275 actin-myosin filament sliding	39	3.13E-21	14	38	5.24E-20	14
GO:0070252 actin-mediated cell contraction	76	2.08E-18	15	40	1.19E-19	14
GO:0051234 establishment of localization	7073	2.56E-18	93	5116	1.50E-03	53
GO:0006810 transport	6916	3.12E-17	90	5023	1.00E-03	53
GO:0042775 mitochondrial ATP synthesis coupled electron transport	77	1.12E-16	14	68	1.45E-11	11
GO:0006941 striated muscle contraction	101	1.74E-16	15	61	1.28E-10	10
GO:0060047 heart contraction	80	1.96E-16	14	39	5.64E-11	9
GO:0060048 cardiac muscle contraction	69	1.03E-15	13	30	1.31E-08	7
GO:0032774 RNA biosynthetic process	3310	7.53E-15	57	669	3.45E-22	37
GO:0006937 regulation of muscle contraction	179	4.80E-14	16	98	2.31E-07	9
GO:0010467 gene expression	5483	1.09E-13	73	2206	4.58E-11	45
GO:0090257 regulation of muscle system process	230	1.48E-13	17	122	1.45E-06	9
GO:0061061 muscle structure development	502	6.98E-13	22	449	5.91E-07	16
GO:1903522 regulation of blood circulation	326	3.31E-12	18	192	5.62E-05	9
GO:0009725 response to hormone	1187	3.76E-12	31	1086	2.69E-05	22
GO:0007005 mitochondrion organization	679	4.56E-12	24		#N/A	#N/A
GO:0008016 regulation of heart contraction	243	5.04E-12	16	116	1.22E-04	7
GO:0055001 muscle cell development	153	3.42E-11	13	98	4.34E-05	7
GO:0048738 cardiac muscle tissue development	164	8.07E-11	13	138	1.99E-09	12
GO:0008015 blood circulation	401	9.50E-11	18	319	4.44E-08	15
GO:0042692 muscle cell differentiation	290	7.63E-10	15	245	3.41E-04	9
GO:0002027 regulation of heart rate	90	7.84E-10	10	39	1.19E-02	3
GO:0051146 striated muscle cell differentiation	211	1.74E-09	13	152	6.09E-04	7
GO:0044267 cellular protein metabolic process	6461	4.75E-08	68	3447	4.00E-09	54
GO:0009888 tissue development	1677	6.35E-08	30	1526	6.26E-03	21
GO:0032502 developmental process	6093	1.82E-07	64	5680	4.09E-12	80
GO:0030029 actin filament-based process	823	2.13E-07	20	505	5.02E-07	17
GO:0072358 cardiovascular system development	915	2.40E-07	21	822	1.25E-06	21
GO:0006950 response to stress	4615	2.77E-07	53	3628	5.91E-03	39
GO:0007507 heart development	537	3.74E-07	16	489	1.78E-06	16
GO:0009653 anatomical structure morphogenesis	2626	4.21E-07	37	2300	1.82E-02	26
GO:0034220 ion transmembrane transport	1636	4.90E-07	28	336	2.90E-03	9
GO:0009611 response to wounding	798	6.28E-07	19	835	7.37E-03	14
GO:0050896 response to stimulus	11437	6.60E-07	96		#N/A	#N/A
GO:0010941 regulation of cell death	1800	9.40E-07	29	1340	3.38E-03	20
GO:0006811 ion transport	2414	1.56E-06	34		#N/A	#N/A
GO:0002026 regulation of the force of heart contraction	31	5.93E-06	5		#N/A	#N/A
GO:0043434 response to peptide hormone	591	6.71E-06	15	527	3.18E-02	9
GO:0048468 cell development	1903	9.01E-06	28		#N/A	#N/A
GO:0030154 cell differentiation	3701	1.36E-05	42		#N/A	#N/A
GO:1903779 regulation of cardiac conduction	68	1.57E-05	6		#N/A	#N/A
GO:0048869 cellular developmental process	3946	6.01E-05	42		#N/A	#N/A
GO:0010882 regulation of cardiac muscle contraction by calcium ion signaling	24	6.19E-05	4		#N/A	#N/A
GO:0007596 blood coagulation	541	2.54E-04	12	518	1.19E-02	10
GO:0006366 transcription from RNA polymerase II promoter	833	2.90E-04	15		#N/A	#N/A
GO:0010881 regulation of cardiac muscle contraction by regulation of the release of sequestered calcium ion	20	9.48E-04	3		#N/A	#N/A
GO:0007010 cytoskeleton organization	1479	1.88E-03	19		#N/A	#N/A
GO:1902533 positive regulation of intracellular signal transduction	1054	2.67E-03	15		#N/A	#N/A
GO:0033554 cellular response to stress	2165	1.02E-02	22		#N/A	#N/A
GO:0061337 cardiac conduction	126	1.71E-02	4		#N/A	#N/A
GO:0012501 programmed cell death	1204	1.83E-02	14		#N/A	#N/A
GO:0045893 positive regulation of transcription, DNA-templated	1575	3.05E-02	16		#N/A	#N/A

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