Variation in protein coding genes identifies information flow as a contributor to animal complexity

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Abstract

Across the metazoans there is a trend towards greater organismal complexity. How complexity is generated, however, is uncertain. Since *C.elegans* and humans have approximately the same number of genes, the explanation will depend on how genes are used, rather than their absolute number. Functional diversity is a measure that quantifies the isoforms, domains and paralogues of a gene. In this paper we determine functional diversity for each protein-coding gene in the human genome and its orthologues across eight commonly used model organisms. From this we derive the CompX list of genes that correlate positively with their increase in cell-type number. We then select genes common to the CompX list and the ExAC list, whose genes show minimal variation across many human genomes, and identify genes with common functions, notably in chromatin structure, RNA splicing, vesicular transport and ubiquitin-mediated protein degradation. Together these functions reveal that information flow within the cell relates to cell-type number, used as a measure of organismal complexity.

Key words: Organismal complexity; information flow; chromatin; splicing; vesicular transport; ubiquitin-mediated protein degradation

Introduction

Some animals are more complex than others. For example, the nematode worm, *C. elegans*, widely used as a model organism, has many fewer cell types than vertebrate models, such as the mouse. Consequently, cell-type number has been widely applied as a quantitative measure of complexity^{1 2}. Since the number of genes in the genome does not correlate with complexity³, it is more likely that patterns of gene expression and the nature of the encoded proteins are important determinants.

Patterns of gene expression are determined by cis-acting regulatory elements^{4 5}. Since these frequently act independently, the loss or gain of an element will have little effect on the expression pattern of the gene mediated by other elements. Cis-acting regulatory elements can therefore confer the capacity for adaptive evolution as documented by the different spatial patterns of the *Pitx1* expression in sticklebacks that cause a variation in body armour, dependent on the environment⁶ and their role in the loss of powered flight in some birds⁷. Although the Encode project⁸ has mapped many cis-acting regulatory elements within the human genome, comprehensive data is lacking for most other species. Instead, in this paper we focus on a set of factors that influence protein function, to analyse how changes to these factors in orthologues relate to the complexity of multicellular animals.

Several of these factors have been shown to correlate positively with the increase in cell-type number (CTN) across the metazoan phylogeny. For example, *C. elegans* produces on average just over 1 transcript type per gene (protein coding and non-coding), whilst in humans this rises to around 5 (based on Ensembl⁹ assembly statistics) through the wider application of alternative splicing and the use of multiple transcript start sites. The resulting transcript diversity has been positively correlated with animal complexity². In addition, the complement of protein domains and motifs within a protein across a range of species has been shown to correlate with complexity, again as measured by CTN^{1 10}. Although the overall number of genes is unlikely to contribute, variation in the number of related genes, the paralogues within a species, could also be important¹¹. When a gene is duplicated the resulting daughter genes have the opportunity either to take on new activities (neofunctionalization)¹² or to divide the activities between the two new genes (subfunctionalisation)¹³.

Combining data on the number of paralogs, transcript isoforms and protein domains associated with a gene defines a value termed the functional diversity (D_F) of the gene¹⁴. Correlating D_F with cell-type number across a range of metazoans for over 2000 genes

associated with transcription identified genes involved in chromatin dynamics as candidate contributors to animal complexity¹⁴.

This paper determines the functional diversity for each annotated gene in the human genome and then across an additional eight species commonly used as model organisms for biomedical research ([Supplementary Data 1](#)). This approach extends previous analysis to the complete human gene list and its orthologues generating data for more than 120 000 genes to identify a list of genes, the CompX list, whose function may underpin complexity. We then identify a prominent overlap between the CompX list and the ExAC list of human genes that show reduced levels of variation within the human population¹⁵. It is thought that the ExAC genes are under purifying selection because they encode proteins that play important roles within the cell. Analysis of the overlapping genes found in both lists indicates that many encode proteins that determine information flow within the organism, relating increases in cell-type number to the ability to process information. This defines a wide, systems-based context in which to evaluate the contribution of specific genes and cellular processes to animal complexity.

Methods

Data-mining and calculation of functional diversity

For each human gene, information on the number of paralogues was obtained from the Ensembl database⁹. Similarly, the number of protein coding transcripts and the number of protein domains encoded by each gene, as defined by the Ensembl Prosite Profiles¹⁶, was extracted from the Ensembl database using Biomart and adapted protocols (<https://github.com/JackDean1/OrganismComplexity>). The pipeline was then used to extract the same information for orthologues of the human genes across eight additional species from the nematode worm, *C. elegans* to the Macaque, *Macaca mulatta*. Since not all human genes have orthologues across all the species, the dataset covers 19 908 identifiable human genes (97.5% of the Ensembl human gene list, unmapped genes were excluded) and 127 355 genes in total. Details of the genomes analysed are provided in [Supplementary Data 1](#).

A value for the functional diversity (D_F) of each gene was then calculated. The protocol is essentially as described¹⁴ and is calculated from:

$$D_F = \log_2 P + \log_2 I + \sum_{I=1}^{I=n} \log_2 M$$

Where P is the number of paralogues, I the number of isoforms and M the number of protein motifs and domains associated with the gene. The complete dataset and calculation of D_F is in [Supplementary Data 2](#).

Correlation analysis

Ortho-sets, which are named after the human gene, were selected that contained the human gene and either eight, seven or six orthologues allowing for the absence, or lack of annotation, of some genes in some species. The D_F values for each gene within the ortho-set were correlated with cell type number (CTN)^{1 2 17}, taken as a measure of the complexity of an organism, using a Pearson's correlation (r) that takes account of the degrees of freedom defined by the number of orthologues in each ortho-set. A similar approach was taken to identify ortho-sets that showed only minimal change in the value of D_F for each gene of the ortho-set. Lists of ortho-sets from the 'complexity' analysis and the 'minimal change' analysis were compiled with increasing statistical probability in a two-tailed t-test for the Pearson's correlation and the overlap between the lists determined. At $p < 0.05$ there was a 10% overlap in the ortho-sets between the two lists, but this reduced to a 0.2% overlap at $p < 0.01$. Consequently, the complexity ortho-set list at $p < 0.01$, called the CompX list, was used in all analyses.

GO-term and STRING analysis of the gene lists

The CompX list of 571 genes ([Supplementary Data 3](#)) was subject to a Gene Ontology (GO) -term over-representation analysis using Amigo2 v2.5.12¹⁸ and the Panther Classification system v14^{19 20} to identify terms enriched by more than 2.5 fold and with an adjusted probability of less than 0.05 (Fisher's Exact test with Bonferroni correction for multiple testing). Redundancy between terms within and across the three major GO-terms was identified on a Circos plot (gene lists in [Supplementary Data 4](#)). Interactions between the 571 CompX genes were identified using the STRING application²¹.

Validation of the CompX – ExAC list overlap

A bootstrap approach was taken to determine whether the overlap between the CompX and ExAC gene lists was greater than might be expected at random. Using simply the numbers of genes in each list (571 for CompX, 3230 for ExAC and 19 908 for the human genome) the overlap between 571 random numbers between 1 and 19 908 and 3 230 random numbers between 1 and 19 908 was determined across 1000 iterations and the mean and standard deviation calculated. The process was then repeated replacing 571 with 362, the number of

genes in the 'no change' analysis. These calculated, expected values were then related to the actual overlaps between the gene lists.

Keywords associated with the function of each of the 159 CompX-ExAC overlap genes were extracted from GeneCards²² and validated by reference to published information. The gene list was then compiled by major function ([Supplementary Data 7](#)).

Results

Creating a database of functional diversity for human protein coding genes and their orthologues in eight metazoan species.

This analysis is based on the premise that changes to the biological activity of proteins will be one of a number of factors that contributes to organismal complexity^{1 11 14 23}. When comparing orthologous genes, the range of biological activity will depend on three factors; the number of different protein-coding transcripts that can be generated from each gene, the types and numbers of each domain that are encoded in the protein and the number of paralogues present in the genome¹⁴. Values for each of these factors were extracted from Ensembl, using Biomart, to produce a database for 19 908 human protein coding genes and 127 355 protein coding genes across the nine species considered ([Supplementary Data 2](#)) representing a comprehensive coverage of genes from many of the model organisms used in biomedical research. The values were then used to calculate the functional diversity (D_F) of each gene in each species, providing a metric for the capacity of that gene to provide the diverse biological activities that determine complexity. As described in the Methods section, correlating the change in value of D_F with the change in value of the cell type number, taken as a measure of organismal complexity, identified a list of 571 ortho-sets that forms the CompX list

GO-term over-representation analysis identifies a limited number of activities

Whilst it is possible that any one of the 571 ortho-sets may contribute to animal complexity, to identify CompX those with common features, we compared the CompX and human gene lists to identify GO-terms over-represented in the CompX list. The Panther Classification system^{19 20} was used to identify GO-terms that are over-represented more than 2.5 fold and with an adjusted p-value of less than 0.05. After the resolution of redundant, nested terms, seven GO-terms met these criteria (Fig. 1 and [Supplementary Data 4](#)). These included two associated with the processing of alcohol, two involving mRNA

Animal complexity and information flow

7

Figure 1. Over-representation assay for the 571 CompX list.

A. Combined graph for the three primary GO-term fields. 2-fold and 2.5-fold over-representation levels are shown and terms that meet the required criteria are coloured according to the primary GO-term. Terms with >2<2.5-fold over-representation are shown as open circles and are listed in [Supplementary Data 4](#). B. Circos plot showing redundant ortho-sets between the GO terms. Complete lists of ortho-sets are in [Supplementary Data 4](#). C. Identification of the major GO-terms. D. Identification of the major terms within the Panther Reactome for over-represented genes within the CompX list.

processing, including the spliceosome complex, and one each for transcription-coupled nucleotide excision repair, Golgi vesicle transport and the actin cytoskeleton. To further analyse the over-represented genes, the degeneracy between the ortho-sets both within and

across the three primary GO-terms was determined (Fig. 1B, C) to identify a definitive list of 109 ortho-sets (Supplementary Data 4). Combined with a Panther over-representation test for the reactome (Fig. 1D) this identified four main activities: ethanol oxidation, the regulation of splicing, DNA repair and membrane trafficking, specifically of ER-Golgi vesicles.

Identifying interacting subsets using STRING analysis

Identifying interactions between proteins encoded by the CompX list will point to additional functions to which these genes contribute. The bioinformatic STRING program²¹, set to identify high confidence, experimentally determined interactions identified 7 activities across 4 networks. (Fig. 2).

Figure 2: Interaction analysis of the CompX ortho-set

Only experimentally verified (confidence level 0.7) interactions and those networks containing at least one node with three connections are shown. Networks have been coloured by function. The distance between genes and the orientation is random. The analysis identified 7 major functions across 4 networks.

Conserved activities between the two approaches include RNA splicing (the regulation of splicing and snRNP complex) and protein-vesicle transport (associated mainly with the ER-Golgi). In addition, the interactions analysis identified members of the SWI/SNF chromatin

remodelling complex, proteins that impose repressive chromatin conformations, the Mediator complex and proteins that contribute to the cell cycle.

Filtering the CompX list to identify genes with a critical function

The ExAC genes are identified as the human genes that, following sequencing of over 60 000 genomes, show less than expected variation¹⁵. The suggestion is that the function of genes on the ExAC list cannot be maintained if the gene is subject to the standard rate of mutational change, indicating that their products may play critical roles in the cell¹⁵. We then hypothesise that genes from the ExAC list may be over-represented in the CompX list. This would then provide a filter to identify genes that are both vital to the cell and contribute to animal complexity.

A direct comparison shows that 159 of the ExAC list of 3230 genes are represented in the 571 gene CompX list ([Supplementary Data 5](#)). A bootstrap method of 1000 sampling events shows that the expected overlap between two groups the size of the CompX and ExAC lists, selected at random from a pool the size of the human gene list, is 92. The observed figure of 159 genes is almost 8 standard deviations greater than the expected mean for the random selection (Fig. 3A).

Figure 3: Demonstration of a prominent overlap between the 571 complexity genes set and ExAC list

A. The distribution of 1000 predicted overlap values between samples of size 571 corresponding to the complexity ortho-set list and 3230 corresponding to the ExAC gene list taken from a stock of 19908, corresponding to the number of human genes in the analysis. The actual overlap value 159 is marked by the red dot.

- 1 B. The same analysis, repeated using a sample size of 362 corresponding to the
- 2 minimal-change ortho-set. In each, the mean is marked by a red line, one standard
- 3 deviation from the mean by the amber line (*) and two standard deviations by the
- 4 green line (**).
- 5 C. GO-term over-representation analysis for the complexity and ExAC overlapping
- 6 gene list. For the analysis of the general GO-term, Biological Process, the red circles
- 7 identify terms over-represented by >3x and with adjusted $P < 0.05$.
- 8 D. Combined analysis for the general GO-terms Cellular Component (blue circles)
- 9 and Molecular Function (orange circles) (over-represented by >3x and adjusted
- 10 $P < 0.05$). The identity of the terms over-represented by >2<3x are listed in
- 11 [Supplementary Data 6](#).
- 12 E. A Circos plot of the individual genes identifies a high degree of redundancy
- 13 between the over-represented GO-terms and a unique list of 90 genes
- 14 ([Supplementary Data 6](#)).
- 15 F. Table of the over-represented GO-terms, the colours refer to the major GO-terms
- 16 as shown in C and D where red denotes Biological Process, orange is Molecular
- 17 Function and blue is Cellular Component.

18
19 In contrast, the same approach, replacing the CompX list with the 362 minimal-change ortho-
20 set, described above, predicts an overlap with the ExAC list of 58 genes, which is identical to
21 the observed figure of 58 (Fig. 3B). This approach validates the hypothesis of a relationship
22 between genes of the CompX and ExAC lists and produces an overlap-list of 159 genes.
23 Many of the genes resulting from this filter are likely to have both a crucial function in the cell
24 and critically influence animal complexity.

Analysis of the 159 genes that are common to the CompX and ExAC gene lists.

26 The 159 overlapping genes were subject to GO-term over-representation analysis to
27 highlight commonalities and the hierarchical terms rationalised using Revigo²⁴. GO-terms
28 were selected that met the criteria of a greater than 3-fold enrichment, when compared to
29 the standard human genome gene list, and with a probability of less than 0.05 (Fig. 3C and
30 D). This identified terms across the three major GO-term categories, notably associated
31 with chromatin dynamics, transcription coregulation, RNA splicing and the cell cycle. In
32 addition are the terms 'protein modification by small protein conjugation or removal' and
33 'macromolecule catabolic process' that refer extensively to protein ubiquitination and related
34 processes including the breakdown of proteins in the proteasome²⁵ and the elimination of
35 misfolded proteins in the ER-Golgi system by ERAD^{26 27} (Fig. 4).

Figure 4. The overlap list contains ortho-sets associated with protein ubiquitination. Isolating the overlap between GO:0070647 protein modification by small protein conjugation or removal and GO:0009057 macromolecule catabolic process, identifies genes involved in the tagging of proteins with ubiquitin and their recognition for breakdown in the proteasome and for the removal of misfolded proteins from the ER-Golgi by the ERAD process.

The extensive redundancy of genes within the GO-terms was plotted using Circos and identifies that 90 of the 159 ortho-sets (61%) are registered in the over-representation GO-term analysis (Supplementary Data 6).

The products of the 159 overlapping genes were analysed for protein interactions using STRING (Fig. 5).

Fig 5. Interaction analysis of the CompX versus ExAC overlap gene list.

Only networks with nodes that contained at least three connections are included. Nodes have been coloured to indicate function. The connectivity of the interacting nodes is more than expected for a random selection of genes with a $p=8.0E-06$.

STRING analysis identified a range of interacting groups that could be described in terms of the function of the genes, as described in GeneCards and identified eight major and two minor groupings (Fig. 5). Although there may seem to be little in common between the groupings, a closer consideration suggests these are all components that contribute to information flow in the cell, from access to the chromatin to the final removal of the protein. Information flow in the cell can be described as a sequence of seven events (Fig. 6 and see Discussion). In addition, the integrity of the information needs to be maintained by DNA repair mechanisms and information flow integrated with the cell cycle.

To address further the possibility that complexity relates to information flow, the functions of the genes identified in the GO-term analysis that did not appear in the STRING analysis were similarly categorized by reference to GeneCards²² and published data. In total 81 of the 97 genes could be allocated to events relating to information flow. Of the remaining 61 genes, 25 could be similarly allocated, giving a total of 106 out of 159 genes (67%) that are held in common between the CompX and ExAC gene lists that may play a role in information flow in the cell ([Supplementary data 7](#)). These genes were mapped to the seven events (Fig. 6) and those genes that contribute to more than one event indicated. In addition to DNA repair, the integrity of information flow is maintained by the removal of mis-folded proteins in the ER-Golgi system through endoplasmic reticulum-associated degradation (ERAD)^{26 27}.

These results indicate an important relationship between information flow and a cell-type number, a measure of complexity for multicellular organisms.

Figure 6 Mapping the CompX-ExAC overlap genes to the elements of information flow in the cell.

Individual genes (coloured circles) are mapped to the seven elements of gene flow and to the two maintenance factors, integrity and integration. Justification for the allocation is given in [Supplementary Data 7](#). The contribution of one gene product to more than one element is marked by a connecting arc.

Discussion

In this paper, we use a simple approach to data-mine three variables that define and quantify the functional diversity (D_F) of proteins derived from each human gene and its orthologues from up to eight other species (termed an ortho-set). The change in D_F for each gene is correlated with the change in number of different cell types in the species, a proxy for organismal complexity, to identify 571 ortho-sets with a positive correlation.

This approach subscribes to a specific model in which incremental changes in functional diversity across an ortho-set relate to an incremental change in complexity. Alternative models, in which, for example, major changes in functional diversity occur at a specific point in the phylogeny, are also likely and can be extracted from our data set ([Supplementary Data 2](#)). Whilst individual genes, acting in isolation, are likely to relate complexity in either model, GO-term over-representation and interaction analysis point towards processes and systems and it is these that will contribute to a broader understanding of the basis of organismal complexity.

This paper considers functional diversity, but this will be only one of several factors associated with animal complexity. Amongst others, an increasing diversity in cis-acting regulatory elements (CAREs) across a phylogeny will play a role^{4 5 28} and there may also be a contribution to complexity from changes to the complement of regulatory non-coding RNAs, including the miRNAs^{29 30} and lncRNAs that have been shown to modulate gene expression³¹.

We have not been able to include all the factors that affect protein functional diversity in this analysis. For example, short linear motifs (SLiMs)²³ impact on the function of proteins such as NCoR2¹¹, but these are not currently widely annotated. The functional capabilities of a protein may also be honed by a small number of changes within the sequence that affect neither protein domain number, nor the range of isoforms³². Lack of this data may mean that some ortho-sets that contribute to complexity have not been identified.

Other studies have successfully identified the contribution of individual components to complexity, such as protein domains and alternative splicing^{1 2}. A previous paper used the approach taken here to assess genes broadly associated with transcription, as listed in the AnimalTFDB 2.0 database of 2087 human genes¹⁴. The identified ortho-sets that are primarily involved in the dynamic structure and function of chromatin, including nucleosome remodeling, the modulation of chromatin activity and the Mediator function. By extending the analysis to the whole genome we aimed to expand this selection to include events outside the nucleus. GO-term over-representation analysis (Fig. 1A) indicated that the oxidation of alcohol, mRNA processing, notably splicing, aspects of DNA repair and protein transport via vesicles should also be considered. For the oxidation of alcohol, the main component of functional diversity is the reiterative gene duplication followed by sub- and neo-functionalization that have produced a range of enzymes that metabolize ethanol and related alcohols^{33 34}. Analysis of interactions amongst the CompX ortho-sets via STRING identified components of the spliceosome and of vesicular transport and in addition highlights

chromatin remodeling and the Mediator complex, consistent with the results from the previous, more limited, survey¹⁴.

In this paper we apply an additional filter by identifying the overlap between the CompX and ExAC genes lists. The ExAC genes have less than expected variation within the human population, suggesting they play important functions that are sensitive to mutation¹⁵. This might seem to contradict the essence of the CompX list, which selects for increases in functional diversity, but the CompX list reflects changes between orthologues across a wide phylogeny, rather than variation within a single species. There is a greater than expected overlap between the CompX list and the ExAC list that is not seen when the ExAC list is compared to the 'minimal-change' list of genes selected for minimally changing values of functional diversity (Fig. 4). The hypothesis is that the filter will highlight those ortho-sets that both relate to complexity and are important to the function of the cell, allowing the identification of cellular processes that are critical for organismal complexity.

Within the overlap list, GO-term analysis identified sub-terms associated with chromatin dynamics, the spliceosome, protein modification by ubiquitination and the cell cycle. Interaction analysis similarly identified ortho-sets associated with mRNA splicing and chromatin dynamics, notably nucleosome remodeling, ubiquitin-mediated protein turnover and, in addition, ortho-sets that encode proteins involved in the distribution of proteins via vesicles within the ER-Golgi apparatus.

Is there a common theme? Each of these groupings can be directly related to the concept of information flow in the cell. We hypothesise that the contribution of protein functional diversity to complexity is primarily, though not exclusively, at the level of information flow in the cell. Information flow can be explained in terms of seven sequential elements (Fig. 6). First, nucleosome re-modelling and epigenetic marks regulate access to chromatin, flipping chromatin between states that either promote or repress gene expression^{35 36 37 38 39}. The Mediator complex then promotes interactions between distant enhancer elements and the genes to be expressed^{40 41} which in combination with transcription factors and RNA polymerases will *convert* the primary information to the intermediate, RNA. The division of eukaryotic genes into exons and introns requires subsequent *processing* of the primary transcript by the spliceosome^{42 43} before *export* of the RNA to the cytosol where it is *translated* to protein. The next step in cellular information flow is one of logistics, *deploying* the product to the right location and in the correct format. Vesicular transport in the cell, associated with the ER-Golgi apparatus, transports proteins to the cell surface and for secretion¹⁵, destinations that will be important as multicellular organisms gain in complexity

and require signaling between cell types. Finally, the specific and regulated addition and removal of ubiquitin⁴⁴, coupled with the proteasome, ensures that specific proteins are turned over, to provide a *limitation* to the pathway of information flow^{45 46}.

We have also identified a number of genes whose function can be ascribed to maintaining the integrity of the information flow. These include DNA repair functions that are important for the stored information and processes such as ERAD that take place in the endoplasmic reticulum to remove defective proteins²⁷. Unsurprisingly, information flow needs to be coordinated to the cell cycle and a number of genes that function in both have been identified (Fig. 6 and [Supplementary data 7](#)).

We can speculate that the increased range of functions of key proteins at each stage increases the efficiency of information flow through processes of neo- and sub-functionalization of paralogues and isoforms⁴⁷. Whilst this paper identifies a general trend, further analysis of specific genes will be required to determine precisely how these efficiencies are achieved. It is clear, though, that the genes identified in this analysis do not greatly affect the cell-type specific activities of different differentiated cell types, rather they relate to the processing of information to generate those specific activities. Applying the concept of information flow within the cell is important because it will provide the context for a more detailed analysis and understanding of animal complexity.

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Contributions

JD collected and analysed the data, DLC analysed the data and CS analysed the data and wrote the manuscript.

Competing interests

The authors declare no competing interests.

Data availability

The authors declare that all other data supporting the findings of this study are available in the paper, in its supplementary information files (S1 and S3-7 are attached at the end of this document) and S2 is available in the University of Portsmouth repository, PURE, at DOI:

10.17029/3d3b91c7-3ae2-4ef8-9703-852709d04a8f and (S2-7) at
<https://github.com/colin17/complexity.git> .

Code availability

The code used, in R, to extract data from the Ensembl database is freely available at
<https://github.com/JackDean1/OrganismComplexity>.

Supplementary information

- S1** Table of the genome data used in this research.
- S2** Table of calculations of functional diversity for all genes across the eight species (CSV format).
- S3** The CompX list of genes (CSV format)
- S4** GO-term details for the CompX gene list (CSV format)
- S5** The CompX-ExAC overlap list of genes (CSV format)
- S6** GO-term details for the CompX-ExAC overlap gene list (CSV format)
- S7** CompX-ExAC overlap gene list, functional details (CSV format)

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Supplementary data

Supplementary Data S1, S3-7

S1

Supplementary Table 1

Organism	Classification	Genome version	Gene number ¹	Cell type Number ²
Homo sapiens	Mammal	GRCh38.p12	20,418	171
Macacca mulata	Mammal	Mmul_8.0.1	21,099	171
Mus musculus	Mammal	GRCm38.p6	22,600	157
Gallus gallus	Bird	GRCg6a	16,878	150
Xenopus tropicalis	Amphibian	JGI 4.2	18,442	121
Takifugu rubripes	Bony fish	FUGU5	20,545	114
Ciona intestinalis	Urochordate	KH	16,671	71
Drosophila melanogaster	Insect	BDGP6	13,931	60
Caenorhabditis elegans	Nematode worm	WBcel235	20,222	29

1. As given on the Ensembl database
2. Cell type number taken from :
Vogel C, Chothia C (2006) Protein family expansions and biological complexity. PLoS Comput Biol 2: e48. pmid:16733546
Hedges SB, Blair JE, Venturi ML, Shoe JL (2004) A molecular timescale of eukaryote evolution and the rise of complex multicellular life. BMC Evol Biol 4: 2. pmid:15005799

Animal complexity and information flow

24

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1  S3
2  Compx gene list,,"""Flat"" list",,
3  ABI2,,ABHD2,,
4  AC235565.2,,ADORA2A,,
5  ACOT11,,AGPAT5,,
6  ACOT7,,AK6,,
7  ACSS2,,ALAD,,
8  ADAM15,,ALG1,,
9  ADAM8,,ALG10,,
10 ADAMTS3,,ALG10B,,
11 ADH1A,,ALG8,,
12 ADH1B,,AMT,,
13 ADH1C,,ANAPC10,,
14 ADH4,,ANKZF1,,
15 ADH5,,ANXA6,,
16 ADH6,,ARHGDIA,,
17 ADH7,,ARL5A,,
18 ADORA3,,ARPC1B,,
19 ADSS,,ASAH1,,
20 AGBL4,,ASMT,,
21 AHCYL1,,ASRGL1,,
22 AKR1A1,,ATG12,,
23 ALAS2,,ATG13,,
24 ALDH1L1,,ATG9B,,
25 ANKRD50,,ATP13A1,,
26 AP1B1,,ATP6V0D1,,
27 AP1S1,,ATP6V1G3,,
28 AP1S2,,BBS1,,
29 AP2A1,,BBS2,,
30 AP2S1,,BCKDHA,,
31 AP3S2,,BCL6,,
32 APP,,BTBD3,,
33 ARAP2,,BYSL,,
34 ARFGAP1,,C15orf41,,
35 ARG2,,C1QTNF1,,
36 ARHGDIB,,C9orf64,,
37 ARID2,,CACYPB,,
38 ARIH2,,CAPSL,,
39 ARL14EP,,CARHSP1,,
40 ARL15,,CAV2,,
41 ARMC8,,CCDC124,,
42 ARNT,,CCDC181,,
43 ARPC5,,CCDC25,,
44 ASCL3,,CCNG1,,
45 ASF1B,,CCS,,
46 ASNA1,,CCZ1B,,
47 ATG2A,,CDC16,,
48 ATP5F1A,,CENPV,,
49 ATP6V1E1,,CEP78,,
50 ATXN7L3,,CFAP157,,
51 BACE1,,CFAP57,,
52 BANF2,,CHMP7,,
53 BBS9,,CHRM2,,
54 BCAP29,,CHSY1,,
55 BCL7B,,CHSY3,,
56 BCL7C,,CIRBP,,
57 BET1,,CLNS1A,,
58 BET1L,,CLPTM1L,,

```

Animal complexity and information flow

25

1 BLM,,CMC1,,
2 BNC2,,CMC2,,
3 BPNT1,,CMTR2,,
4 BSDC1,,CNDP2,,
5 BUB3,,CNKSR2,,
6 C1D,,COASY,,
7 C1QTNF3,,COL4A3BP,,
8 CA2,,COPB1,,
9 CA5A,,COX11,,
10 CALHM3,,CPA1,,
11 CALHM4,,CPA4,,
12 CALHM6,,CPLX2,,
13 CAPN3,,CPSF2,,
14 CAPZA1,,CPSF7,,
15 CAPZA2,,CRAMP1,,
16 CASP2,,CRBN,,
17 CBLN2,,CSTF1,,
18 CBX6,,CTCF,,
19 CBX8,,CTNNB1,,
20 CCDC151,,CTNNBIP1,,
21 CCNC,,CTSB,,
22 CCND1,,DAD1,,
23 CCNH,,DCAF13,,
24 CCZ1,,DDB1,,
25 CCZ1B,,DDX6,,
26 CD63,,DECR1,,
27 CDC20,,DGCR8,,
28 CDC40,,DHRS2,,
29 CDCA7,,DHX36,,
30 CDK1,,DHX38,,
31 CDK11A,,DLX4,,
32 CDK11B,,DMGDH,,
33 CDK19,,DMRT2,,
34 CDK20,,DNAAF3,,
35 CDK5,,DNAAF5,,
36 CDK7,,DNAJC18,,
37 CERS5,,DPH1,,
38 CHD5,,DPH2,,
39 CHMP2B,,DPP9,,
40 CIB2,,DTWD1,,
41 CIB3,,DUOX1,,
42 CLASRP,,DUS4L,,
43 CLIC4,,DYM,,
44 CLIC5,,DYNC2LI1,,
45 CLIC6,,EARS2,,
46 CMTM6,,EDC3,,
47 CNIH1,,EEF1AKMT2,,
48 CNIH4,,EEPD1,,
49 CNOT7,,EFCAB2,,
50 COBL,,EFHC1,,
51 COL12A1,,EFHD1,,
52 COL14A1,,EIF1AD,,
53 COL6A1,,EIF3B,,
54 COL6A2,,EIF3C,,
55 COLQ,,EIF3F,,
56 COMMD7,,EIF3H,,
57 COPA,,ELP2,,
58 COPS7A,,ELP4,,

Animal complexity and information flow

26

- 1 COPZ1,, EMC4,,
- 2 COQ8B,, EMC7,,
- 3 COQ9,, ENKUR,,
- 4 CPSF4,, ENO1,,
- 5 CRYZL1,, ERCC3,,
- 6 CTTNBP2,, EXTL3,,
- 7 CUL4B,, FAM185A,,
- 8 CWC27,, FAM72A,,
- 9 DAP3,, FAM72B,,
- 10 DBT,, FAXDC2,,
- 11 DEPD5,, FBXL16,,
- 12 DERL2,, FEM1B,,
- 13 DHX8,, FGL1,,
- 14 DHX9,, FICD,,
- 15 DIS3L2,, FMC1,,
- 16 DLST,, FNIP1,,
- 17 DNTTIP2,, FNTA,,
- 18 DOK1,, FRMD6,,
- 19 DOK6,, FRS2,,
- 20 DOPEY1,, FTCD,,
- 21 DPH5,, GAS8,,
- 22 DTL,, GATB,,
- 23 DTX3,, GATC,,
- 24 EEF1B2,, GATM,,
- 25 EEF1D,, GCNT3,,
- 26 EIF1,, GDF9,,
- 27 EIF1B,, GLDC,,
- 28 EIF3E,, GOSR1,,
- 29 ELFN1,, GOSR2,,
- 30 EMC9,, GPALPP1,,
- 31 EML4,, GPR89A,,
- 32 EMSY,, HAAO,,
- 33 ENTPD5,, HADH,,
- 34 ERCC2,, HAO2,,
- 35 ERGIC1,, HEXB,,
- 36 ERLIN1,, HSD17B4,,
- 37 ETHE1,, HSPA9,,
- 38 EXOC6,, HYDIN,,
- 39 EXOC7,, IFT74,,
- 40 EXOSC6,, IMP1L,,
- 41 EXT2,, IMP3,,
- 42 EYA3,, INTS12,,
- 43 FAM120B,, INTS14,,
- 44 FAM160A1,, INTS9,,
- 45 FAM172A,, IQUB,,
- 46 FAM206A,, IRAK4,,
- 47 FAM49B,, JOSD1,,
- 48 FAM92A,, KATNB1,,
- 49 FAM98C,, KCNC4,,
- 50 FANCD2,, KDELR2,,
- 51 FBLL1,, KDELR3,,
- 52 FBXO8,, LACTB,,
- 53 FCF1,, LARP7,,
- 54 FN1,, LARS,,
- 55 FO393400.1,, LCMT1,,
- 56 FOXP1,, LGMN,,
- 57 FREM1,, LIG4,,
- 58 GABARAP,, LONP1,,

Animal complexity and information flow

27

1 GCAT,,LRRC6,,
2 GDPD5,,LTN1,,
3 GFOD1,,MAATS1,,
4 GFOD2,,MAGEA2,,
5 GGA3,,MAGEA2B,,
6 GNA13,,MAGEA4,,
7 GNG2,,MAPK10,,
8 GNG3,,MCM4,,
9 GNL1,,MCTS1,,
10 GPATCH1,,MED17,,
11 GPC1,,MED22,,
12 GPC2,,MED9,,
13 GPS1,,MFSD8,,
14 GRIA1,,MIOS,,
15 GRIA4,,MLEC,,
16 GRIK1,,MLST8,,
17 GRIK2,,MOGS,,
18 GRTP1,,MORN5,,
19 GSX2,,MPPE1,,
20 GTF3A,,MRPL11,,
21 GUCY1B1,,MRPL16,,
22 H2AFV,,MRPL22,,
23 HACD2,,MRPL28,,
24 HADHB,,MRPL43,,
25 HAND2,,MRPL55,,
26 HDAC2,,MRPS2,,
27 HDAC8,,MRPS22,,
28 HERC2,,MSH6,,
29 HHIPL1,,MTFP1,,
30 HM13,,MTRF1,,
31 HMBS,,MTTP,,
32 HMGCL,,MVD,,
33 HNRNPH1,,MYL6B,,
34 HOOK2,,NAF1,,
35 HOOK3,,NAT9,,
36 HOXC4,,NDUFA2,,
37 HS3ST2,,NDUFAF5,,
38 HSD17B2,,NDUFAF7,,
39 ID2,,NDUFB9,,
40 ID3,,NECAP1,,
41 IDS,,NELFA,,
42 IFRD2,,NFS1,,
43 IFT140,,NHP2,,
44 IFT20,,NOP16,,
45 IGSF9,,NOP2,,
46 IL18RAP,,NOP53,,
47 ILK,,NUDT2,,
48 ILKAP,,NUDT4,,
49 IP6K2,,OSBPL2,,
50 IPO11,,OTUD4,,
51 IPP,,PAX6,,
52 IQGAP1,,PCNX4,,
53 IRAK1,,PDCD10,,
54 IRF1,,PDP2,,
55 IRX4,,PDZD3,,
56 IRX6,,PES1,,
57 ITGB4,,PGS1,,
58 JMJD7,,PHOSPHO1,,

Animal complexity and information flow

28

1 KCNC2,,PIGL,,
2 KCND3,,PIGS,,
3 KCNIP1,,PIN1,,
4 KCNIP4,,PIP4K2C,,
5 KCNK15,,PISD,,
6 KCTD1,,PKMYT1,,
7 KCTD15,,PLA2G15,,
8 KCTD3,,PNPO,,
9 KCTD8,,POLA2,,
10 KCTD9,,POLH,,
11 KIF5A,,POLR2D,,
12 KIF5C,,POLR2G,,
13 KIFAP3,,PPP2CB,,
14 KLF6,,PPWD1,,
15 KLHL10,,PRELID3A,,
16 KLHL2,,PREPL,,
17 KMT2E,,PRICKLE1,,
18 KPNA1,,PRPF8,,
19 KPNA2,,PSEN1,,
20 KPNA6,,PSMC2,,
21 KRI1,,PSMC5,,
22 KTI12,,PSMD7,,
23 LANCL1,,PSMG2,,
24 LIG3,,PTRHD1,,
25 LLGL2,,RAB10,,
26 LMAN2L,,RAB27A,,
27 LMBR1,,RAD51C,,
28 LMNA,,RAD9A,,
29 LOXHD1,,RANBP3,,
30 MAEA,,RASSF8,,
31 MAFK,,RBM15,,
32 MAGOH,,RBP5,,
33 MAGT1,,RCL1,,
34 MAP3K5,,REEP2,,
35 MAR7,,REGL,,
36 MCCC2,,RFWD3,,
37 MCRS1,,RHAG,,
38 MDH1,,RHOH,,
39 MEAF6,,RNAHEH2B,,
40 MED12L,,RNPS1,,
41 MED16,,RPL10,,
42 MED4,,RPLP0,,
43 METTL15,,RUVBL1,,
44 METTL2A,,SARAF,,
45 MIER1,,SARS2,,
46 MKS1,,SCPEP1,,
47 MRO,,SCYL1,,
48 MROH1,,SDF2,,
49 MROH2A,,SDHD,,
50 MROH7,,SERP1,,
51 MROH7-TTC4,,SETD4,,
52 MROH8,,SFXN2,,
53 MROH9,,SH3BP4,,
54 MRPL39,,SH3GL1,,
55 MRPS18A,,SIK1,,
56 MSX2,,SLC19A3,,
57 MTERF3,,SLC25A46,,
58 MTMR2,,SLC25A48,,

Animal complexity and information flow

29

- 1 MTREX,, SLC30A8,,
- 2 MXI1,, SLC35F5,,
- 3 MYBPC1,, SLC46A1,,
- 4 MYBPC3,, SLC52A2,,
- 5 MYCBP2,, SLC6A1,,
- 6 MYLK,, SLX1A,,
- 7 MYOM2,, SLX1B,,
- 8 MYOM3,, SMARCB1,,
- 9 N6AMT1,, SMARCE1,,
- 10 NAPB,, SMN2,,
- 11 NAT10,, SNF8,,
- 12 NEB,, SNRNP25,,
- 13 NEK2,, SNRPF,,
- 14 NEK7,, SNUPN,,
- 15 NEK8,, SPATA20,,
- 16 NETO2,, SPEF2,,
- 17 NEUROG2,, SPG7,,
- 18 NFIA,, SPRYD7,,
- 19 NIP7,, SSR3,,
- 20 NIPAL1,, SSU72,,
- 21 NIPAL3,, STUB1,,
- 22 NIT2,, STX16,,
- 23 NKX3-1,, SUOX,,
- 24 NME2,, SUPT4H1,,
- 25 NME7,, SUPT6H,,
- 26 NODAL,, SYS1,,
- 27 NR4A1,, TACO1,,
- 28 NR4A2,, TARBP1,,
- 29 NR4A3,, TATDN1,,
- 30 NT5C1B,, TBC1D2,,
- 31 NUP43,, TBC1D32,,
- 32 OLFM1,, TBCE,,
- 33 OLFM3,, TBCE,,
- 34 OSBPL1A,, TBCE,,
- 35 OSCP1,, TBCE,,
- 36 PANK2,, TBL1X,,
- 37 PAQR9,, TCTN1,,
- 38 PARVA,, TFIP11,,
- 39 PARVB,, TLR2,,
- 40 PBRM1,, TMEM138,,
- 41 PCBD1,, TMEM14B,,
- 42 PCBD2,, TMEM169,,
- 43 PCMT1,, TMEM41A,,
- 44 PDC,, TMEM67,,
- 45 PDCL,, TMLHE,,
- 46 PDCL3,, TPO,,
- 47 PDK3,, TPT1,,
- 48 PDS5A,, TRAPPC5,,
- 49 PDS5B,, TRAPPC8,,
- 50 PDZD11,, TROVE2,,
- 51 PDZRN4,, TRPT1,,
- 52 PELI3,, TSNAX-DISC1,,
- 53 PEPD,, TUBB6,,
- 54 PGAP1,, TVP23C,,
- 55 PGM1,, TWNK,,
- 56 PGM5,, TXNDC15,,
- 57 PHF12,, UBA5,,
- 58 PHGDH,, UBE3B,,

Animal complexity and information flow

30

1 PIGO,,UBXN1,,
2 PIP4K2A,,ULK3,,
3 PIP4K2B,,UPRT,,
4 PITPNA,,UTP15,,
5 PITPNB,,UTP4,,
6 PKD2,,VPS36,,
7 PLPPR1,,VSNL1,,
8 PLXNB2,,WARS,,
9 PLXNC1,,WASHC4,,
10 PMS1,,WDR55,,
11 PNKP,,WDR74,,
12 POLD1,,WEE1,,
13 POLR1C,,WRB,,
14 PORCN,,WWC2,,
15 PPA2,,YIPF5,,
16 PPAN,,YPEL5,,
17 PPAN-P2RY11,,ZC2HC1C,,
18 PPFIA1,,ZCCHC10,,
19 PPP1R21,,ZNF830,,
20 PPP1R8,,,,
21 PPP2R2B,,,,
22 PPP2R2C,,,,
23 PPP2R2D,,,,
24 PRMT1,,,,
25 PRPF19,,,,
26 PSME1,,,,
27 PSME3,,,,
28 QTRT2,,,,
29 RAB1A,,,,
30 RAB6A,,,,
31 RAB9B,,,,
32 RABGGTB,,,,
33 RAD1,,,,
34 RAD54L2,,,,
35 RAE1,,,,
36 RAP1GDS1,,,,
37 RASGRP1,,,,
38 RB1,,,,
39 RBL2,,,,
40 RBM12,,,,
41 RBM28,,,,
42 RBM34,,,,
43 RCAN1,,,,
44 RCAN3,,,,
45 RETSAT,,,,
46 REV3L,,,,
47 RFC5,,,,
48 RHD,,,,
49 RMND5A,,,,
50 RNF115,,,,
51 RNF126,,,,
52 RNF157,,,,
53 RNF220,,,,
54 RPL22L1,,,,
55 RPL4,,,,
56 RPS25,,,,
57 RPS6KB2,,,,
58 RRAGC,,,,

Animal complexity and information flow

31

- 1 RRM2,,,,
- 2 RTRAF,,,,
- 3 SALL2,,,,
- 4 SAT1,,,,
- 5 SATL1,,,,
- 6 SBF2,,,,
- 7 SCAF4,,,,
- 8 SCMH1,,,,
- 9 SCR2,,,,
- 10 SCR3,,,,
- 11 SDR42E2,,,,
- 12 SEC11A,,,,
- 13 SEC11C,,,,
- 14 SECISBP2,,,,
- 15 SENP3,,,,
- 16 SENP5,,,,
- 17 SEPT6,,,,
- 18 SEPT7,,,,
- 19 SESN1,,,,
- 20 SESN3,,,,
- 21 SETD3,,,,
- 22 SF3A1,,,,
- 23 SF3A2,,,,
- 24 SF3B5,,,,
- 25 SFT2D1,,,,
- 26 SFT2D2,,,,
- 27 SIGIRR,,,,
- 28 SIRT6,,,,
- 29 SIX1,,,,
- 30 SLBP,,,,
- 31 SLC10A3,,,,
- 32 SLC10A6,,,,
- 33 SLC19A1,,,,
- 34 SLC25A28,,,,
- 35 SLC35A1,,,,
- 36 SLC38A7,,,,
- 37 SLC7A6,,,,
- 38 SLC40A1,,,,
- 39 SMAD3,,,,
- 40 SMARCD2,,,,
- 41 SMARCE1,,,,
- 42 SNRNP200,,,,
- 43 SNRNP40,,,,
- 44 SNRPA,,,,
- 45 SNRPB,,,,
- 46 SNRPC,,,,
- 47 SNRPE,,,,
- 48 SNX1,,,,
- 49 SNX10,,,,
- 50 SNX12,,,,
- 51 SNX3,,,,
- 52 SORL1,,,,
- 53 SOS2,,,,
- 54 SP5,,,,
- 55 SPOUT1,,,,
- 56 SRP72,,,,
- 57 ST3GAL2,,,,
- 58 ST7,,,,

Animal complexity and information flow

32

1 STAG1,,,,,
2 STK3,,,,,
3 STK4,,,,,
4 STMN2,,,,,
5 STMN4,,,,,
6 STXBP1,,,,,
7 STXBP2,,,,,
8 SUFU,,,,,
9 SUMF1,,,,,
10 SUMF2,,,,,
11 TBC1D23,,,,,
12 TBL1XR1,,,,,
13 TBL1Y,,,,,
14 TBP,,,,,
15 TCEA1,,,,,
16 TCF3,,,,,
17 TCP1,,,,,
18 TCP11X2,,,,,
19 TECR,,,,,
20 TEK,,,,,
21 TERT,,,,,
22 TEX10,,,,,
23 TFAP2B,,,,,
24 THOC3,,,,,
25 THSD7A,,,,,
26 TMC7,,,,,
27 TMCC2,,,,,
28 TMED10,,,,,
29 TMEM106B,,,,,
30 TMEM120B,,,,,
31 TMEM131,,,,,
32 TMEM161A,,,,,
33 TMEM161B,,,,,
34 TMEM167B,,,,,
35 TMEM231,,,,,
36 TMEM63B,,,,,
37 TOPBP1,,,,,
38 TPD52,,,,,
39 TPD52L2,,,,,
40 TRAF4,,,,,
41 TRAPPC12,,,,,
42 TRAPPC3L,,,,,
43 TRAPPC6A,,,,,
44 TRIM23,,,,,
45 TRMT112,,,,,
46 TRPC6,,,,,
47 TRPM1,,,,,
48 TRPM2,,,,,
49 TRPM3,,,,,
50 TRPM8,,,,,
51 TSC2,,,,,
52 TSEN2,,,,,
53 TSFM,,,,,
54 TSN,,,,,
55 TSPAN17,,,,,
56 TSPAN3,,,,,
57 TSR1,,,,,
58 TTC1,,,,,

Animal complexity and information flow

33

1 TTC17,,,,,
2 TTC39A,,,,,
3 TTC39C,,,,,
4 TTC7A,,,,,
5 TTC7B,,,,,
6 TTLL5,,,,,
7 TTLL7,,,,,
8 TTLL9,,,,,
9 TUSC3,,,,,
10 TUT7,,,,,
11 TXLNB,,,,,
12 U2SURP,,,,,
13 UBE2A,,,,,
14 UBE2B,,,,,
15 UBE2F,,,,,
16 UBE2L3,,,,,
17 UBE2L5,,,,,
18 UBE3A,,,,,
19 UBE3C,,,,,
20 UBN1,,,,,
21 UGGT2,,,,,
22 UHRF1BP1L,,,,,
23 UNC45A,,,,,
24 UNC5C,,,,,
25 USP15,,,,,
26 USP19,,,,,
27 USP46,,,,,
28 VPS11,,,,,
29 VPS33B,,,,,
30 VPS35L,,,,,
31 VTI1A,,,,,
32 WASHC3,,,,,
33 WDR3,,,,,
34 WDR61,,,,,
35 WDR91,,,,,
36 XAB2,,,,,
37 XRCC6,,,,,
38 ZC2HC1A,,,,,
39 ZC3H14,,,,,
40 ZCCHC24,,,,,
41 ZCCHC4,,,,,
42 ZDHHC17,,,,,
43 ZEB1,,,,,
44 ZFAND2A,,,,,
45 ZFAT,,,,,
46 ZMYND11,,,,,
47 ZNF687,,,,,
48 ZSWIM8,,,,,
49 ZXDA,,,,,
50 ZXDB,,,,,
51

1 **S4**
2 ,,,,,,Gene summary,,
3 GO-term Biological Process,N, Enrich,P-value,,,,,
4 ethanol oxidation (GO:0006069),8,24.3,2.03E-04,,,GO-terms,total,genes
5 transcription-coupled nucleotide-excision repair
6 (GO:0006283),12,6.0,2.27E-02,,,5681 6283 6397,2,PRPF19
7 endoplasmic reticulum to Golgi vesicle-mediated transport
8 (GO:0006888),21,3.7,8.55E-03,,,,,XAB2
9 Golgi vesicle transport (GO:0048193),32,3.2,2.86E-04,,,4022 6069,7,ADH5
10 mRNA processing (GO:0006397),32,2.5,4.66E-02,,,,,ADH4
11 heart development (GO:0007507),34,2.4,4.53E-02,,,,,ADH1A
12 mRNA metabolic process (GO:0016071),42,2.3,2.04E-02,,,,,ADH7
13 cellular component morphogenesis (GO:0032989),49,2.3,2.71E-03,,,,,ADH1C
14 RNA processing (GO:0006396),51,2.2,3.81E-03,,,,,ADH1B
15 protein-containing complex subunit organization
16 (GO:0043933),100,2.0,8.95E-07,,,,,ADH6
17 chromosome organization (GO:0051276),56,2.0,2.14E-02,,,5681
18 6397,17,SNRNP200
19 protein transport (GO:0015031),81,2.0,1.26E-04,,,,,MAGOH
20 protein-containing complex assembly (GO:0065003),83,2.0,1.31E-
21 04,,,,,RBM28
22 ,,,,,,SNRPE
23 ,,,,,,SNRNP40
24 GO-term Molecular Function,N,Enrich ,P-value,,,,,PPP1R8
25 alcohol dehydrogenase (NAD) activity (GO:0004022),7,28.4,2.40E-
26 04,,,,,HNRNPH1
27 transcription factor binding (GO:0008134),40,2.2,2.27E-02,,,,,CWC27
28 ,,,,,,DHX8
29 ,,,,,,SF3A1
30 GO-term Cellular Compartment,N,Enrich,P-value,,,,,CDC40
31 catalytic step 2 spliceosome (GO:0071013),14,5.9,6.88E-04,,,,,SNRPB
32 spliceosomal complex (GO:0005681),19,3.8,2.69E-03,,,,,SF3B5
33 actin cytoskeleton (GO:0015629),34,2.5,4.35E-03,,,,,GPATCH1
34 catalytic complex (GO:1902494),86,2.3,9.45E-09,,,,,SF3A2
35 transferase complex (GO:1990234),46,2.1,6.94E-03,,,,,SNRPA
36 chromosomal part (GO:0044427),51,2.1,3.93E-03,,,,,SNRPC
37 chromosome (GO:0005694),57,2.0,2.13E-03,,,15629 48193,2,CAPZA2
38 ribonucleoprotein complex (GO:1990904),48,2.0,1.22E-02,,,,,CAPZA1
39 ,,,,,,15629 6397,1,DHX9
40 ,,,,,,6283 6397,3,CDK7
41 ,,,,,,ERCC2
42 ,,,,,,CCNH
43 ,,,,,,15629,31,IQGAP1
44 ,,,,,,ARPC5
45 ,,,,,,PKD2
46 ,,,,,,LLGL2
47 ,,,,,,CIB2
48 ,,,,,,KLHL2
49 ,,,,,,ILK
50 ,,,,,,TEK
51 ,,,,,,PARVA
52 ,,,,,,CLIC5
53 ,,,,,,CLIC4
54 ,,,,,,MYBPC3
55 ,,,,,,ADAM8
56 ,,,,,,NEB
57 ,,,,,,PGM5
58 ,,,,,,PARVB

Animal complexity and information flow

35

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1  , , , , , , , VPS11
2  , , , , , , , MYBPC1
3  , , , , , , , TTC17
4  , , , , , , , IPP
5  , , , , , , , TOPBP1
6  , , , , , , , COBL
7  , , , , , , , CTTNBP2
8  , , , , , , , GABARAP
9  , , , , , , , MAEA
10 , , , , , , , MYLK
11 , , , , , , , MYOM3
12 , , , , , , , PGM1
13 , , , , , , , TMEM63B
14 , , , , , , , SEPT7
15 , , , , , , , MYOM2
16 , , , , , 6069,1, ACSS2
17 , , , , , 6283,7, RFC5
18 , , , , , , , CUL4B
19 , , , , , , , GPS1
20 , , , , , , , TCEA1
21 , , , , , , , LIG3
22 , , , , , , , COPS7A
23 , , , , , , , POLD1
24 , , , , , 48193,29, ERGIC1
25 , , , , , , , LMAN2L
26 , , , , , , , DOPEY1
27 , , , , , , , COPA
28 , , , , , , , GRIA1
29 , , , , , , , PITPNB
30 , , , , , , , AP2A1
31 , , , , , , , RAB1A
32 , , , , , , , KIF5A
33 , , , , , , , TRAPPC3L
34 , , , , , , , ARFGAP1
35 , , , , , , , CNIH1
36 , , , , , , , VTI1A
37 , , , , , , , CNIH4
38 , , , , , , , COPZ1
39 , , , , , , , TRIM23
40 , , , , , , , GGA3
41 , , , , , , , BET1
42 , , , , , , , RAB6A
43 , , , , , , , PGAP1
44 , , , , , , , TMED10
45 , , , , , , , BCAP29
46 , , , , , , , SNX1
47 , , , , , , , TRAPPC12
48 , , , , , , , SORL1
49 , , , , , , , BET1L
50 , , , , , , , EXOC6
51 , , , , , , , KIFAP3
52 , , , , , , , TRAPPC6A
53 , , , , , 6397,9, FAM172A
54 , , , , , , , SLBP
55 , , , , , , , CLASRP
56 , , , , , , , THOC3
57 , , , , , , , U2SURP
58 , , , , , , , APP

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Animal complexity and information flow

36

1 , , , , , , , CPSF4
2 , , , , , , , AHCYL1
3 , , , , , , , TSEN2
4

1	S5
2	CompX ExAC overlap list
3	159 genes
4	ABI2
5	AHCYL1
6	ALAS2
7	ANKRD50
8	AP1B1
9	AP2A1
10	AP2S1
11	ARID2
12	ARIH2
13	ARMC8
14	ARNT
15	ATG2A
16	ATXN7L3
17	BACE1
18	BNC2
19	CAPZA1
20	CAPZA2
21	CBX8
22	CCNC
23	CCZ1
24	CDC40
25	CDK1
26	CDK19
27	CDK5
28	CHD5
29	CLASRP
30	CNOT7
31	COBL
32	COL12A1
33	COL6A1
34	COPA
35	COPS7A
36	CUL4B
37	DEPDC5
38	DERL2
39	DHX8
40	DHX9
41	DLST
42	DOPEY1
43	DTX3
44	ERLIN1
45	EYA3
46	FAM49B
47	FCF1
48	FOXP1
49	GNL1
50	GPS1
51	GRIA1
52	GRIA4
53	GRIK2
54	HDAC2
55	HDAC8
56	HERC2
57	HMBS
58	HNRNP1

Animal complexity and information flow

38

1	HOOK3
2	IDS
3	ILKAP
4	IP6K2
5	IPO11
6	IQGAP1
7	IRAK1
8	KCNIP4
9	KCTD1
10	KCTD3
11	KIF5A
12	KIF5C
13	KLF6
14	KLHL10
15	KLHL2
16	KMT2E
17	KPNA1
18	KPNA6
19	LMNA
20	MAP3K5
21	MDH1
22	MED12L
23	MIER1
24	MYCBP2
25	NAPB
26	NFIA
27	NODAL
28	NR4A1
29	NR4A2
30	OLFM1
31	PBRM1
32	PDS5A
33	PDS5B
34	PGM5
35	PHF12
36	PIP4K2B
37	PITPNA
38	PITPNB
39	PKD2
40	PLXNB2
41	PLXNC1
42	PORCN
43	PPFIA1
44	PPP1R8
45	PPP2R2B
46	PRMT1
47	PRPF19
48	PSME3
49	RAD54L2
50	RAE1
51	RB1
52	RBL2
53	REV3L
54	RMND5A
55	RNF220
56	RPL4
57	RRM2
58	SCAF4

Animal complexity and information flow

39

1 SENP3
2 SENP5
3 SESN3
4 SF3A1
5 SIX1
6 SMARCD2
7 SMARCE1
8 SNRNP200
9 SNX1
10 SOS2
11 ST3GAL2
12 ST7
13 STAG1
14 STMN2
15 STXBP1
16 SUFU
17 TBL1XR1
18 TCP1
19 TEK
20 TEX10
21 TFAP2B
22 THSD7A
23 TMEM131
24 TMEM63B
25 TOPBP1
26 TSC2
27 TSN
28 TTC17
29 TTC7B
30 U2SURP
31 UBE2F
32 UBE3A
33 UBE3C
34 UBN1
35 UHRF1BP1L
36 USP15
37 USP19
38 USP46
39 XAB2
40 XRCC6
41 ZC3H14
42 ZDHHC17
43 ZEB1
44 ZMYND11
45 ZNF687
46 ZSWIM8
47

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1  S6
2  ,,,,,,#GO term overlap data,,
3  GO biological process complete,N,Enrich,P-value,,,GO terms,Number,Genes
4  regulation of G1/S transition of mitotic cell cycle
5  (GO:2000045),9,8.02,2.69E-02,,,16032 16570 1902494 1990234 2000045
6  51276 6325 70647 9057,1,CDK1
7  histone modification (GO:0016570),14,4.8,1.82E-02,,,16032 1902494
8  1990234 2000045 3712 51276 6325 785 8134,1,RB1
9  chromatin organization (GO:0006325),22,4.03,3.85E-04,,,16570 1902494
10 1990234 2000045 51276 6325 70647 9057,1,CUL4B
11 viral process (GO:0016032),18,3.71,2.16E-02,,,16570 1902494 1990234
12 3712 51276 6325 70647,1,ATXN7L3
13 chromosome organization (GO:0051276),30,3.68,7.56E-06,,,16570 1902494
14 1990234 51276 6325 70647 785,1,CBX8
15 protein modification by small protein conjugation or removal
16 (GO:0070647),24,3.27,3.84E-03,,,16570 1902494 1990234 51276 6325 785
17 8134,1,HDAC2
18 macromolecule catabolic process (GO:0009057),24,3.01,1.57E-02,,,16570
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20 protein localization (GO:0008104),40,2.4,1.56E-03,,,16570 1902494 3712
21 51276 6325 9057,1,TBL1XR1
22 protein-containing complex subunit organization
23 (GO:0043933),34,2.38,2.03E-02,,,16570 1902494 1990234 51276 6325
24 9057,1,CDK5
25 macromolecule localization (GO:0033036),42,2.18,1.05E-02,,,1902494 3712
26 51276 6325 785 8134,1,SMARCE1
27 nucleic acid metabolic process (GO:0090304),39,2.14,4.19E-02,,,16032
28 1902494 3712 51276 785 8134,1,DHX9
29 cellular protein modification process (GO:0006464),49,2.03,7.05E-
30 03,,,16570 2000045 51276 6325 785,1,KMT2E
31 ,,,,,,16570 51276 6325 70647 9057,1,USP15
32 ,,,,,,16570 3712 51276 6325 8134,1,MIER1
33 GO molecular function complete,N,Enrich,P-value,,,16570 1902494 51276
34 6325 8134,1,HDAC8
35 transcription coregulator activity (GO:0003712),16,3.58,3.98E-
36 02,,,16570 1902494 51276 6325 785,1,CHD5
37 transcription factor binding (GO:0008134),18,3.43,1.98E-02,,,2000045
38 51276 6325 785 8134,1,RBL2
39 ,,,,,,1902494 3712 51276 6325 785,1,SMARCD2
40 ,,,,,,16032 3712 51276 6325,1,ZMYND11
41 GO cellular component complete,N, Enrich,P-value,,,1902494 51276 6325
42 785,1,PBRM1
43 catalytic step 2 spliceosome (GO:0071013),7,10.18,1.32E-02,,,16032
44 1902494 1990234 51276,1,RAE1
45 chromatin (GO:0000785),16,3.8,9.83E-03,,,2000045 3712 8134 9057,1,CNOT7
46 catalytic complex (GO:1902494),39,3.54,6.72E-09,,,16032 1902494 70647
47 9057,1,UBE3A
48 transferase complex (GO:1990234),20,3.19,8.67E-03,,,1902494 70647 71013
49 9057,1,PRPF19
50 nucleoplasm part (GO:0044451),26,2.94,1.40E-03,,,1902494 1990234 70647
51 9057,2,RMND5A
52 chromosome (GO:0005694),22,2.69,3.96E-02,,,,,ARIH2
53 nucleoplasm (GO:0005654),73,2.65,2.72E-13,,,1902494 3712 785
54 8134,1,PHF12
55 nuclear lumen (GO:0031981),79,2.44,9.19E-13,,,16570 51276 6325,1,EYA3
56 protein-containing complex (GO:0032991),98,2.3,2.53E-16,,,16032 51276
57 6325,1,UBN1
58 nuclear part (GO:0044428),79,2.22,1.83E-10,,,16032 51276 70647,1,COPS7A

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Animal complexity and information flow

41

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1 organelle lumen (GO:0043233),87,2.1,7.51E-11,,,1902494 2000045
2 70647,1,PSME3
3 intracellular organelle lumen (GO:0070013),87,2.1,7.51E-11,,,16032
4 1902494 1990234,1,MAP3K5
5 membrane-enclosed lumen (GO:0031974),87,2.1,7.51E-11,,,1902494 70647
6 9057,1,UBE3C
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8 ,,,,,,,SENP3
9 ,,,,,,1902494 1990234 9057,1,ARMC8
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15 ,,,,,,,PDS5A
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18 ,,,,,,,AP2S1
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20 ,,,,,,70647 9057,3,HERC2
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22 ,,,,,,,USP19
23 ,,,,,,3712 8134,4,ARNT
24 ,,,,,,,SUFU
25 ,,,,,,,ZEB1
26 ,,,,,,,KCTD1
27 ,,,,,,1902494 71013,6,SNRNP200
28 ,,,,,,,HNRNPH1
29 ,,,,,,,XAB2
30 ,,,,,,,DHX8
31 ,,,,,,,SF3A1
32 ,,,,,,,CDC40
33 ,,,,,,1902494 1990234,5,REV3L
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36 ,,,,,,,DLST
37 ,,,,,,,DEPDC5
38 ,,,,,,2000045,1,PKD2
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41 ,,,,,,,TSC2
42 ,,,,,,,ABI2
43 ,,,,,,70647,6,MYCBP2
44 ,,,,,,,UBE2F
45 ,,,,,,,RNF220
46 ,,,,,,,KLHL10
47 ,,,,,,,DTX3
48 ,,,,,,,SENP5
49 ,,,,,,9057,6,BACE1
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52 ,,,,,,,DERL2
53 ,,,,,,,ERLIN1
54 ,,,,,,,RPL4
55 ,,,,,,3712,2,TFAP2B
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57 ,,,,,,8134,4,FOXP1
58 ,,,,,,,SIX1

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Animal complexity and information flow

42

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1  , , , , , , , NR4A2
2  , , , , , , , NR4A1
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4  , , , , , , , TCP1
5  , , , , , 1902494, 1, PPP2R2B
6

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S7

,,,ELEMENT,,,,,,,,,GO-TERM,,,,,,,,,
Gene,Remod,Mediator,ChromMod,Splicing,RNAexport,Translation,Transport,U
biq-related,Cell cycle,DNA
repair,STRING,2000045,16570,6325,16032,51276,70647,9057,3712,8134,71013
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49 traffic pathways./nvolved in cargo selection and vesicle formation. /
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51 lipids,10.1111/cpr.12522.
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55 formation,PMID: 7593184
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2 network.",10.1038/ng.3279.
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8 hedgehog/smoothed signaling pathway.,
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