The Network of Cancer Genes (NCG): a comprehensive catalogue of known and candidate cancer genes from cancer sequencing screens.

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ABSTRACT (100 words)

The Network of Cancer Genes (NCG) is a manually curated repository of 2,372 genes whose somatic modification is known or predicted to have a cancer driver role. These genes were collected from 275 publications, including two sources of known cancer genes and 273 cancer sequencing screens of 119 cancer types in 31 primary sites, for a total of 34,905 cancer donors. In addition to collecting cancer genes, NCG annotates their systems-level properties, such as duplicability, evolutionary origin, RNA and protein expression, miRNA and protein interactions, protein function and essentiality. NCG offers a comprehensive and up-to-date collection of cancer genes and is accessible at http://ncg.kcl.ac.uk/.

KEYWORDS (3-10)

Cancer genomics screens, cancer genes, cancer heterogeneity, systems level properties

BACKGROUND

One of the main goals of cancer genomics is to find the genes that, upon acquiring somatic alterations, play a role in driving cancer (cancer genes). To this end, in the last ten years hundreds of cancer sequencing screens have generated mutational data from thousands of cancer samples. These include large sequencing efforts led by international consortia such as the International Cancer Genome Consortium (ICGC) [1] and The Cancer Genome Atlas (TCGA) [2]. Cancer genomes usually acquire thousands of somatic alterations and several methods have been developed to identify cancer genes from the pool of all altered genes [3, 4]. These methods have been applied to datasets from specific cancer types and to pooled datasets from several cancer types. This is the case for the Pan-Cancer Atlas project [5] and for the recent analysis of the whole set of TCGA samples [6], which accompanied the conclusion of the TCGA sequencing phase [7]. As more and more studies contribute to our knowledge of cancer genes, it becomes increasingly challenging for the research community to maintain an up-to-date overview of cancer genes and of the cancer types to which they contribute.

Various databases have been developed to collect and analyse cancer data. Some of these databases collect the somatic alterations that are acquired in cancer including COSMIC [8], DoCM [9], DriverDB [10], the Cancer Genome Interpreter [11], and OncoKB [12] among others. Other databases report only cancer genes with a strong indication of involvement in cancer (the Cancer Gene Census, CGC [13]), analyse subsets of cancer genes (TSGene [14], ONGene [15]) or focus on specific cancer types (CoReCG [16]).

The Network of Cancer Genes (NCG) is a project launched in 2010 that aims to provide a comprehensive collection of cancer genes from cancer sequencing screens and to annotate their distinctive systems-level properties [17-20]. NCG is based on the manual curation of experts who review studies describing cancer mutational screens, extract the genes that were annotated as cancer genes and annotate the supporting evidence. Unlike other available databases, NCG does not focus on mutations, on particular groups of genes or specific cancer types. It instead compiles a comprehensive repository of mutated genes that have been proven or predicted to be the drivers of cancer. NCG is widely used by the community. Recent examples include the identification and validation of cancer genes [21-23] and

miRNA cancer biomarkers [24]. NCG has also been used to investigate the effect of long noncoding RNAs on cancer genes [25] and to find non-duplicated cancer-related transcription factors [26].

Here, we describe the sixth release of NCG, which contains 2,372 cancer genes extracted from 275 publications consisting of two sources of known cancer genes and 273 cancer sequencing screens. This represents an increase of more than 1.5-fold in the database content compared to the previous version. As well as screenings of individual cancer types, the collected publications now include four adult and two paediatric pan-cancer studies. In addition to an update of the systems-level properties of cancer genes already present in previous releases (gene duplicability, evolutionary origin, protein function, protein-protein and miRNA-target interactions, and mRNA expression in healthy tissues and cancer cell lines), NCG now also annotates the essentiality of cancer genes in human cell lines and their expression at the protein level in human tissues. Moreover, broader functional annotations of cancer genes in KEGG [27], Reactome [28] and BioCarta [29] are also provided.

The expert curation of a large number of cancer sequencing screens and the annotation of a wide variety of systems-level properties make NCG a comprehensive and unique resource to study the genes that promote cancer.

CONSTRUCTION AND CONTENT

The NCG database integrates information about genes with a known or predicted cancer driver role. To facilitate the broad use of NCG, we have developed a user-friendly, interactive and open-access web portal. The user interface has been tested for querying and visualising the annotation of cancer genes in a systematic and comprehensive manner. User queries are processed interactively to produce results in a constant time. The front-end is connected to a database, developed using relational database management system principles [30] (Figure S1). The web application for the NCG database was developed using MySQL v.5.6.38 and PHP v.7.0. Raw data for each of the systems-level properties were acquired from heterogeneous data sources and processed as described below. The entire content of NCG is freely available and can be downloaded from the database website.

Gene duplicability and evolutionary origin

Protein sequences from RefSeq v.85 [31] were aligned to the human genome assembly hg38 with BLAT [32]. From the resulting genomic alignments, 19,549 unique gene loci were identified and genes sharing at least 60% of the original protein sequence were considered to be duplicated [33] (Table S1). Orthologous genes for 18,486 human genes (including 2,348 cancer genes, Table S1) in 2,032 species were collected from EggNOG v.4.5.1 [34] and used to trace the gene evolutionary origin as previously described [35]. Genes were considered to have a pre-metazoan origin if their orthologs could be found in prokaryotes, unicellular eukaryotes or opisthokonts [35].

Gene and protein expression

RNA-Seq data from healthy human tissues for 18,984 human genes (including all 2,372 cancer genes, Table S1) were derived from the non-redundant union of Protein Atlas v.18 [36] and GTEx v.7 [37]. Protein Atlas reported the average Transcripts Per Million (TPM) values in 37 tissues, and genes were considered to be expressed in a tissue if their expression value was ≥1 TPM. GTEx reported the distribution of TPM values for individual genes in 11,688 samples across 30 tissue types. In this case, genes were considered to be expressed if they had a median expression value ≥1 TPM. Additionally, gene expression data for all 2,372 cancer genes in 1,561 cancer cell lines were taken from the Cancer Cell Line Encyclopedia (CCLE, 02/2018) [38], the COSMIC Cancer Cell Line Project v.84 (CLP) [13] and the Genentech collection (GNE, 06/2014) [39] (Table S1). Gene expression levels were derived directly from the original sources, namely Reads Per Kilobase Million (RPKM) values for CCLE and GNE, and microarray z-scores for CLP. Genes were categorised as expressed if their expression value was ≥1 RPKM in CCLE or GNE, and were annotated as over, under or normally expressed in CLP, as determined by COSMIC.

The current release of NCG also includes protein expression from immunohistochemistry assays of healthy human tissues as derived from Protein Atlas v.18. Data were available for 13,001 human proteins including 1,799 cancer proteins (Table S1). Proteins were categorised as not detected or as having low, medium or high expression in 44 tissues on the basis of staining intensity and fraction of stained cells [36]. In Protein Atlas, expression levels were reported in

multiple cell types for each tissue. We retained the highest reported value as the expression level for that tissue.

Gene essentiality

Gene essentiality was derived from two databases, PICKLES (09/2017) [40] and OGEE v.2 [41], both of which collected data from CRISPR Cas9 knockout and shRNA knockdown screens of human cell lines. In PICKLES, data from primary publications have been re-analysed and genes were considered essential in a cell line if their associated Bayes factor was >3 [42]. We therefore used this threshold to define essential genes. In OGEE, genes were labelled as “essential” or “not essential” according to their annotation in the original publications. Consistently, we retained the same annotation. From the non-redundant union of the two databases, essentiality information was available for a total of 18,833 genes (including all 2,372 cancer genes) in 178 cell lines (Table S1).

Protein-protein and miRNA-target interactions

Human protein-protein interactions were derived from four databases (BioGRID v.3.4.157 [43]; MIntAct v.4.2.10 [44]; DIP (02/2018) [45] and HPRD v.9 [46]). Only interactions between human proteins supported by at least one original publication were considered. The union of all interactions from the four sources was used to derive a human protein-protein interaction network of 16,322 proteins (including 2,203 cancer proteins, Table S1) and 289,368 binary interactions. To control for a possible higher number of studies on cancer proteins resulting in an artificially higher number of interactions, a network of 15,272 proteins and 224,258 interactions was derived from high-throughput screens reporting more than 100 interactions [20].

Data on human protein complexes for 8,080 human proteins (including 1,414 cancer proteins, Table S1) were derived from the non-redundant union of three primary sources, namely CORUM (07/2017) [47], HPRD v.9 [46] and Reactome v.63 [28]. Only human complexes supported by at least one original publication were considered [20].

Experimentally validated interactions between human genes and miRNAs were downloaded from miRTarBase v.7.0 [48] and miRecords v.4.0 [49], resulting in a total of 14,649 genes (including 2,034 cancer genes) and 1,762 unique miRNAs (Table S1). To control for the higher number of single-gene studies focussing on

cancer genes, a dataset of high-throughput screens testing ≥250 different miRNAs was also derived (Table S1).

Functional annotation

Data on functional categories (pathways) were collected from Reactome v.63 [28], KEGG v.85.1 [27] and BioCarta (02/2018) [29]. Data for BioCarta were extracted from the Cancer Genome Anatomy Project [50]. All levels of Reactome were included, and level 1 and 2 pathways from KEGG were added separately. Overall, functional annotations were available for 11,344 human proteins, including 750 cancer proteins assigned to 2,318 pathways in total.

UTILITY AND DISCUSSION

Catalogue of known and candidate cancer genes

To include new cancer genes in NCG, we applied a modified version of our well-established curation pipeline [20] (Figure 1A). We considered two main groups of cancer genes: known cancer genes whose involvement in cancer has robust experimental support, and candidate cancer genes whose somatic alterations have a predicted cancer driver role but lack further experimental support.

As sources of known cancer genes, we used 708 genes from CGC v.84 [13] and 125 genes from a manually curated list [51]. Of the resulting 711 genes, we further annotated 239 as tumour suppressor genes (TSGs) and 239 as oncogenes (OGs). The remaining 233 genes could not be unambiguously classified because either they had conflicting annotations in the two original sources (CGC and [51]) or they were defined as both OGs and TSGs.

Next, we reviewed the literature to search for studies that (1) described sequencing screens of human cancers and (2) provided a list of genes considered to be the cancer drivers. This led to 273 original papers published between 2008 and March 2018, 98 of which were published since the previous release of NCG [20] and 42 of which came from ICGC or TGCA (Table S2). Overall, these publications describe the sequencing screens of 119 cancer types from 31 primary anatomical sites as well as six pan-cancer studies (Table S2). In total, this amounts to 34,905 cancer donors. Each publication was reviewed independently by at least two experts and all studies whose annotation differed between the experts were further

discussed. Additionally, 31 randomly selected studies (11% of the total) were re-annotated blindly by a third expert to assess consistency.

The manual revision of the 273 studies led to 2,088 cancer genes, of which 427 were known cancer genes and 1,661 were candidate cancer genes (Figure 1B). Based on literature evidence [52], gene length and function [19], we labelled 49 candidates as possible false positive predictions. We also further investigated the reasons why 284 known cancer genes were not identified as drivers in any of the 273 cancer sequencing screens. We found that often these genes predispose to cancer rather than acquiring somatic alterations, are the chimeric product of gene fusions, are part of CGC Tier 2 (*i.e.* genes with lower support for their involvement in cancer) or where identified with different methods.

The annotation of a large number of studies allowed us to gain insights into how cancer genes have been identified in the last ten years. We observed an overall positive correlation between the number of cancer donors and the number of cancer genes (Figure 1C). This suggests that the approaches currently used to predict cancer genes are affected by the sample size of the analysed cohort. Of the overall 18 approaches used to predict cancer genes (Table S2), the recurrence of a gene alteration within the cohort without applying any threshold of statistical significance was the most widely used (Figure 1D). This was followed by MutSig [53], MuSiC [54] and the method described in [55]. All of these approaches estimate the tendency of a gene to mutate more than expected within a cohort and therefore they all depend on sample size. Finally, although the vast majority of analysed studies tended to apply only one prediction method, more recent publications have started to use a combination of two or three methods (Figure 1E).

Heterogeneity and specificity of cancer genes

The number of cancer genes and the relative proportion of known and candidate cancer genes vary greatly across cancer primary sites (Figure 2A). Cancer genes in the thymus, ovary, cervix, bone, retina and soft tissues are more than 80% known drivers. On the contrary, more than 70% of driver genes in cancers of the large intestine, pancreas, penis, testis and vascular system are candidate cancer genes (Figure 2A). This suggests that the molecular mechanisms of some cancer types are still poorly characterised. Although the number of cancer genes is overall positively

correlated with the number of sequenced samples (Figures 1C, 2B), there are marked differences across primary sites. For example, ovary, bone, prostate, thyroid and kidney cancers have substantially fewer cancer genes compared to cancers with similar numbers of cancer donors such as uterine, stomach, skin and hepatobiliary cancers (Figure 2B). This is likely due to variable levels of genomic instability and heterogeneity across cancer types of the same primary site. For example, in seven of the nine mutational screens of skin melanoma, a cancer with high genomic instability [56], more than 50% of cancer genes are study-specific (Figure 2C). Similarly, the 24 types of blood cancer are variable in terms of number of cancer genes and diffuse large B-cell lymphoma has many more cancer genes than other blood cancers with higher numbers of cancer donors (Figure 2D).

Cancer genes, and in particular candidates, are highly cancer specific (Figure 3A). Hemicentin 1 (*HMCN1*) is the only candidate cancer gene to be significantly mutated in six primary sites (blood, brain, oesophagus, large intestine, liver, and pancreas). A few known cancer genes are recurrently mutated across several primary sites, including *TP53* (25 sites), *PIK3CA* (21 sites) and *PTEN* (20 sites, Figure 3A). These are, however, exceptions and the large majority of known and candidate cancer genes (64% of the total) are found only in one primary site, indicating high heterogeneity in terms of cancer driver events. Similar specificity is also observed in terms of supporting publications. The majority of cancer genes are publication-specific, again with few exceptions including *TP53* (173), *PIK3CA* (87) and *KRAS* (86, Figure 3B). Of note, the best-supported candidate gene is Titin (*TTN*, predicted in nine publications), which is a well-known false positive of recurrence-based approaches [53].

The heterogeneity of the cancer driver landscape is also reflected in the pan-cancer studies. Approximately 40% of the cancer genes from pan-cancer analyses were not previously predicted as drivers (Figure 3C), despite the large majority of cancer samples having been already analysed in the corresponding cancer-specific study. This confirms that current methods depend on the sample size and that a larger cohort leads to novel predictions. Only 35 cancer genes were shared across the four pan-cancer re-analyses of adult tumours (Figure 3D), suggesting that the prediction of cancer genes is highly method- and cohort-dependent. This is further

confirmed by the poor overlap between cancer genes from adult and paediatric pan-cancer studies (Figure 3E).

Systems-level properties of cancer genes

In addition to collecting cancer genes from the literature, NCG also annotates the systems-level properties that distinguish cancer genes from other genes that are not implicated in cancer (Table S1). We also compare these properties between TSGs and OGs.

As previously reported [33], we confirm that a significantly lower fraction of cancer genes has duplicated copies in the human genome due to a high proportion of single-copied TSGs (Figure 4A). This trend is observed in both known and candidate cancer genes, and is significant for the combination of the two gene sets. Cancer genes, and in particular candidate cancer genes, originated earlier in evolution [35, 57, 58] and TSGs are older than OGs (Figure 4B). Known cancer genes tend to be ubiquitously expressed at the mRNA (Figure 4C) and protein (Figure 4D) levels and TSGs are more widely expressed than OGs (Figure 4C,D). A higher fraction of cancer genes, and in particular of known cancer genes, is essential in at least one human cell line (Figure 4E). Moreover, known cancer genes tend to be essential in a higher fraction of cell lines. Both trends are higher in TSGs as compared to OGs (Figure 4E). Proteins encoded by known and candidate cancer genes are more often involved in protein complexes (Figure 4F). They are also more connected (higher degree), central (higher betweenness) and clustered (higher clustering coefficient) in the protein-protein interaction network (Figure 4G). We verified that this trend holds true also when using data from high-throughput screens only (Table S2), thus excluding the possibility that the distinctive network properties of cancer proteins are due to their better annotation. Known and candidate cancer genes are regulated by a higher number of miRNAs (higher degree) and occupy more central positions (higher betweenness) in the miRNA-target interaction network (Figure 4H). Similarly to what we observed in the protein-protein interaction network, these results remain valid also when considering the miRNA-target network from high throughput screens only (Table S2). All groups of cancer genes are consistently enriched in functional categories such as signal transduction, chromatin reorganisation and cell cycle and depleted in others, such as metabolism and transport (Figure 4I, Table S3). Candidate cancer genes generally exhibit weaker

enrichment than the other groups, most notably in DNA repair. Interestingly, however, extracellular matrix reorganisation displays a specific enrichment for candidate cancer genes. Some functional categories are selectively enriched for OGs (*i.e.* development, immune and endocrine systems, Figure 4J) or TSGs (*i.e.* DNA repair and programmed cell death). While annotations from Reactome and KEGG generally give concordant results, they differ significantly for gene transcription. In this case, Reactome shows a strong enrichment for cancer genes, while KEGG only gives significance for a depletion in candidate cancer genes (Figure 4I,J).

Overall these analyses confirm that cancer genes are a distinctive group of human genes. Despite their heterogeneity in terms of driver potential across cancer types and donors, they share common properties. Interestingly, candidate cancer genes share some, albeit not all, of the properties of known cancer genes. For example, they originated early in evolution (Figure 4B) and encode central hubs of the protein-protein and miRNA-target interaction networks (Figure 4G,H). Finally, TSGs and OGs constitute two distinct classes of cancer genes even in terms of their systems-level properties.

Future directions

In the coming years, NCG will continue to collect new cancer genes and annotate their properties, including novel properties for which large datasets are becoming available such as genetic interactions or epigenetic status. So far, the cancer genomic community has focussed mostly on the identification of protein-coding genes with putative cancer driver activity. With the increasing availability of whole genome sequencing data and a rising interest in non-coding alterations [25, 59], NCG will expand to also collect non-coding cancer drivers. Another direction for future development will be the analysis of clinical data, including therapeutic treatments, to link them to the altered drivers. This will contribute to the expansion of our knowledge of cancer driver genes in the context of their clinical relevance.

CONCLUSIONS

The present release of NCG describes a substantial advance in annotations of known and candidate cancer driver genes as well as an update and expansion of

their systems-level properties. The extensive body of literature evidence collected in NCG enabled a systematic analysis of the methods used to identify cancer genes, highlighting their dependence on the number of cancer donors. We also confirmed the high heterogeneity of cancer genes within and across cancer types. The broad set of systems-level properties collected in NCG shows that cancer genes form a distinct group, different from the rest of human genes. For some of these properties, the differences observed for known cancer genes hold true also for candidate cancer genes and TSGs show more pronounced cancer gene properties than OGs. Interestingly, these properties are shared by all cancer genes, independently of the cancer type or gene function. Therefore, focussing on genes with similar characteristics could be used for the identification and prioritisation of new cancer driver genes [60]. In conclusion, the large-scale annotation of the systems-level properties of cancer genes in NCG is a valuable source of information not only for the study of individual genes, but also for the characterisation of cancer genes as a group.

LIST OF ABBREVIATIONS

CCLE, Cancer Cell Line Encyclopedia; CLP, Cell Line Project (COSMIC); GNE, Genentech; ICGC, International Cancer Genome Consortium; miRNA, microRNA; NCG, Network of Cancer Genes; OG, Oncogene; RPKM, Reads Per Kilobase Million; TCGA, The Cancer Genome Atlas; TPM, Transcripts Per Million; TSG, Tumour Suppressor Gene.

AVAILABILITY OF DATA AND MATERIALS

The whole content of NCG can be downloaded from the website. Original data were obtained from the following online sources:

BioCarta: https://cgap.nci.nih.gov/Pathways/BioCarta_Pathways;

BioGRID: https://thebiogrid.org/;

Cancer Cell Line Encyclopedia: https://portals.broadinstitute.org/ccle;

Cell Line Project: https://cancer.sanger.ac.uk/cell_lines;

CORUM: http://mips.helmholtz-muenchen.de/corum/;

DIP: http://dip.doe-mbi.ucla.edu/dip/Main.cgi;

EggNOG: http://eggnogdb.embl.de/#/app/home;

Genentech: https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-2706/;

GTEx: https://www.gtexportal.org/home/;

HPRD: http://www.hprd.org/;

ICGC, https://icgc.org/;

KEGG: http://www.genome.jp/kegg/pathway.html;

MIntAct: https://www.ebi.ac.uk/intact/;

miRecrods: http://c1.accurascience.com/miRecords/;

miRTarBase: http://mirtarbase.mbc.nctu.edu.tw/php/index.php;

OGEE: http://ogee.medgenius.info/browse/;

PICKLES: https://hartlab.shinyapps.io/pickles/;

Protein Atlas: https://www.proteinatlas.org/;

Reactome: https://reactome.org/;

RefSeq: https://www.ncbi.nlm.nih.gov/refseq/;

TCGA, https://cancergenome.nih.gov/

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

FDC conceived and supervised the study. SKV, DR, JN, LD, MB, AT, and FDC analysed the data. SKV analysed gene duplicability. MB processed evolutionary origins and miRNA-target interactions. LD processed protein-protein interactions, protein complexes and gene essentiality. JN processed RNA and protein expression and protein function. DR, AT, AY and TP curated the literature. SKV and JN updated the database and website. JN, LD, MB, AT, and FDC wrote the manuscript, with contributions from SKV and DR. All authors reviewed and approved the final version of the manuscript.

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Figure 1. Manual curation of cancer genes in NCG

a. Pipeline used for adding cancer genes to NCG. Two sources of known cancer genes [13, 51] were integrated leading to 711 known cancer genes. In parallel, 273 publications describing cancer sequencing screens were reviewed to extract 2,088 cancer genes. The non-redundant union of these two sets led to 2,372 cancer genes currently annotated in NCG.

b. Intersection between known and candidate cancer genes in NCG.

c. Cancer genes as a function of the number of cancer donors per study. The grey inset shows a magnification of the left bottom corner of the plot.

d. Pie chart of the methods used to identify cancer genes in the 273 publications. The total is greater than 273 because some studies used more than one method (Table S2).

e. Number of methods used to identify cancer genes over time. PanSoftware used in one of the pan-cancer studies [6] was considered as a single method but is in fact a combination of 26 prediction tools.

Figure 2. Distribution of cancer genes across primary sites and cancer donors

a. Number of total cancer genes and proportion of known and candidate cancer genes across the 31 tumour primary sites analysed in the 267 cancer-specific studies. The number of cancer donors followed by the number of cancer genes is given in brackets for each primary site.

b. Total number of cancer genes and cancer donors across the 31 tumour primary sites. The colour scale indicates the number of screens for each primary site.

c. Proportion of study-specific cancer genes reported by each of the seven skin melanoma screens.

d. Total number of cancer genes and donors across 24 cancer types of the blood. The full list of blood cancer types is reported in Table S2.

Figure 3. Recurrence of cancer across primary sites and publications

a. Number of primary sites in which each known or candidate cancer gene was reported to be a driver.

b. Number of publications in which each known or candidate cancer gene was reported to be a driver.

c. Intersection of cancer genes in the cancer-specific and pan-cancer studies.

d. Venn diagram of cancer genes across the four pan-cancer studies of adult donors. **e.** Intersection of cancer genes in pan-cancer screens of adult and paediatric donors. In **c**, **d**, and **e** the number of donors followed by the total number of cancer genes are given in brackets.

Figure 4. Systems-level properties of cancer genes

a. Percentage of genes with at least one gene duplicate covering ≥ 60% of the protein sequence. **b.** Proportion of genes that originated in pre-metazoan species. **c,d.** Distribution of number of human tissues in which genes (**c**) and proteins (**d**) are expressed. Only genes with concordant gene expression annotation between GTEx and Protein Atlas were used for comparison (Table S1). **e.** Percentage of genes that are essential in ≥1 cell line and distribution of cell lines in which each gene is essential. Only genes with concordant essentiality annotation between OGEE and PICKLES were used for comparison (Table S1). **f.** Percentage of proteins that are involved in ≥1 protein complex. **g.** Median values of betweenness (centrality), clustering coefficient (clustering) and degree (connectivity) of human proteins in the protein-protein interaction network. **h.** Median values of betweenness (centrality) and degree (connectivity) of the target genes in the miRNA-target interaction network. The clustering coefficient is zero for all nodes in this network, because the interactions occur between miRNAs and targets genes. Known, candidate and all cancer genes were compared to the rest of human genes, while TSGs were compared to OGs. Significance was calculated using a two-sided Fisher test (**a,b,e,f**) or Wilcoxon test (**c,d,g,h**). * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$.

Enrichment and depletion of cancer genes in representative functional categories taken from level 1 of Reactome (**i**) and level 2 of KEGG (**j**). Significance was calculated comparing each group of cancer genes to the rest of human genes using a two-sided Fisher test. P-values were further corrected for false discovery rate (FDR) in each set of comparisons separately. The full list of pathways is provided in Table S3.

LIST OF SUPPLEMENTARY DATA

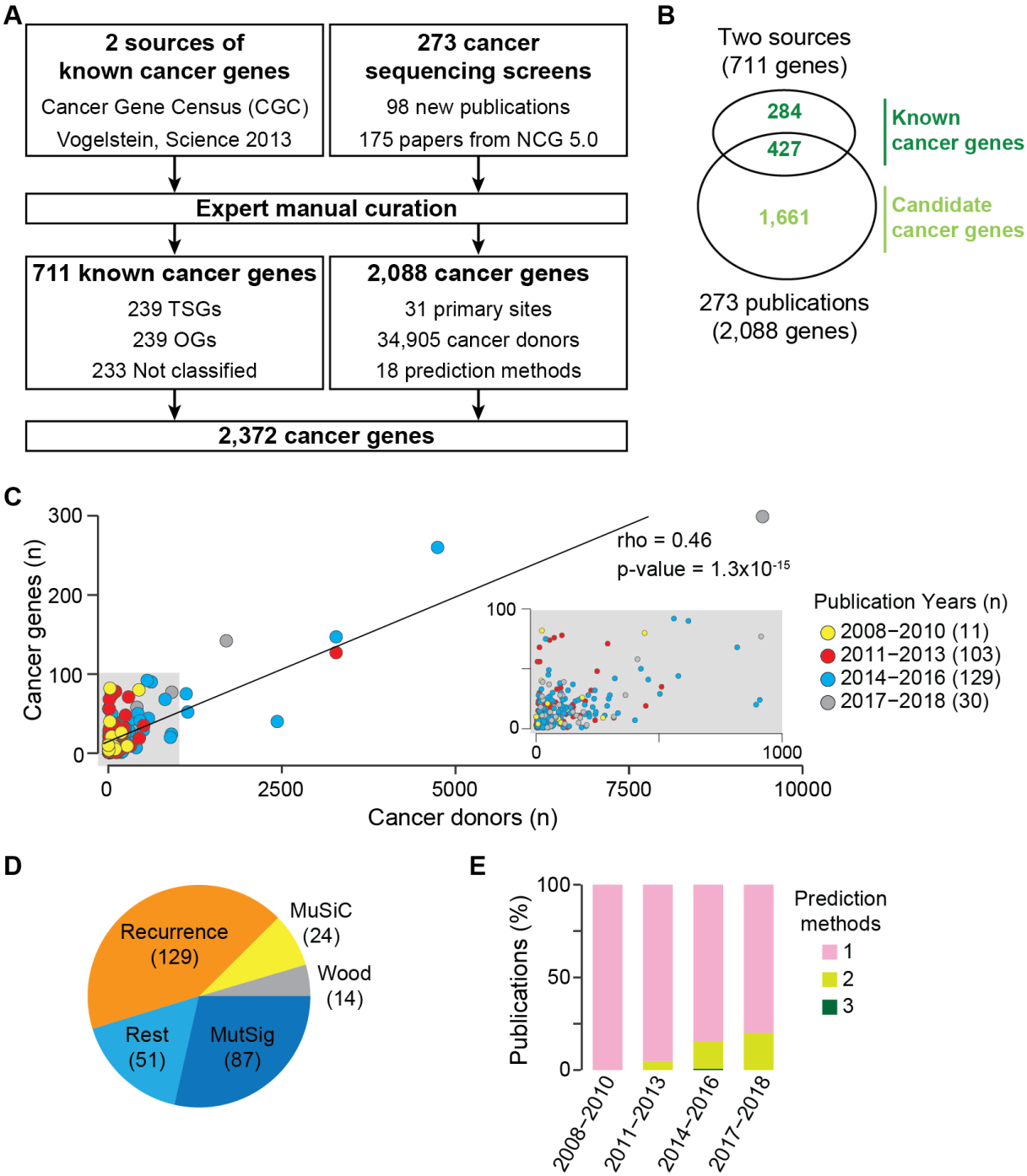
Figure S1. Schema of the NCG database

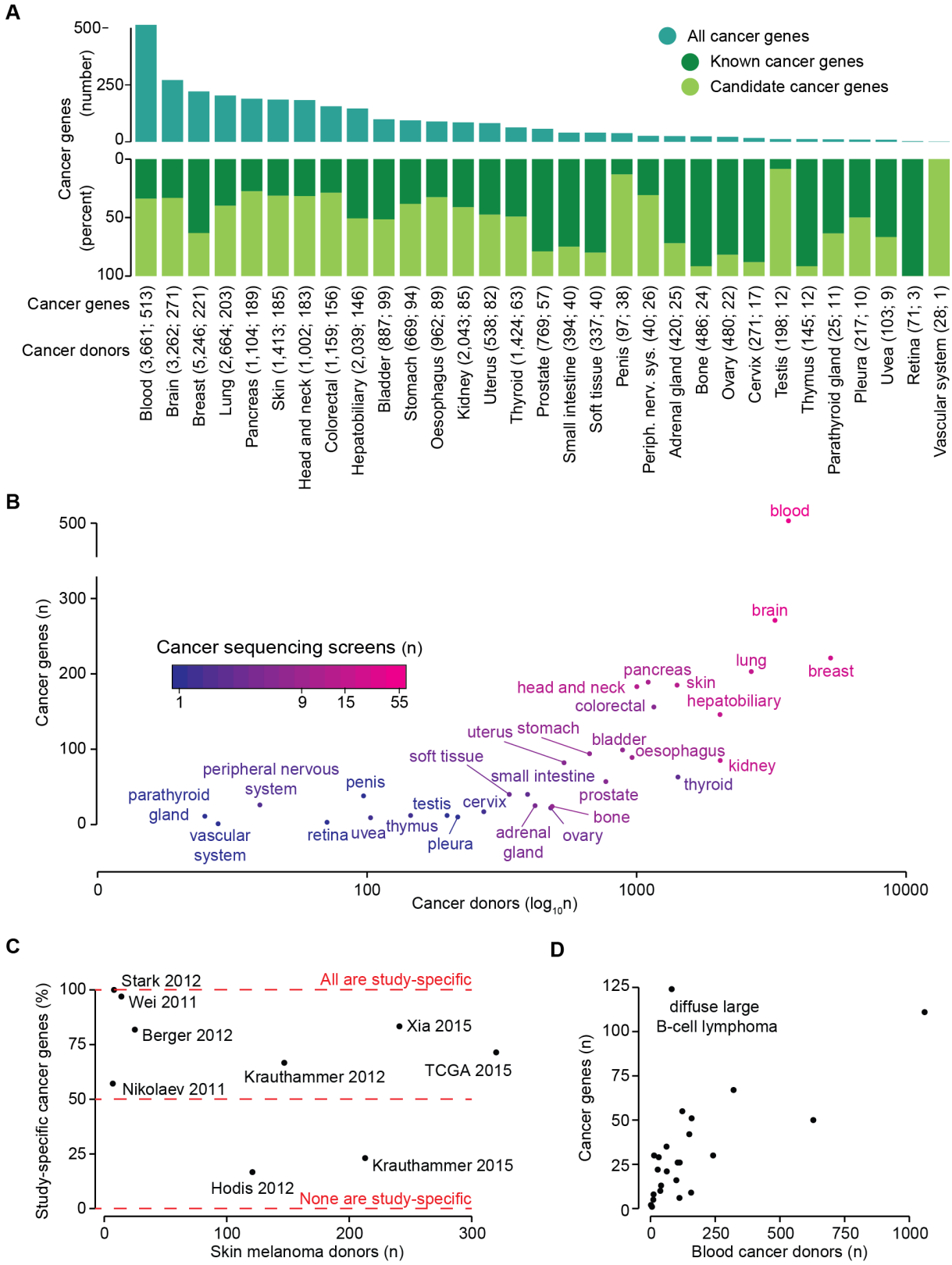
Entity-relationship diagram indicating one-to-many and many-to-many relationships between genes and other entities in the NCG database. The external source files used to generate the Genes entity are shown in grey.

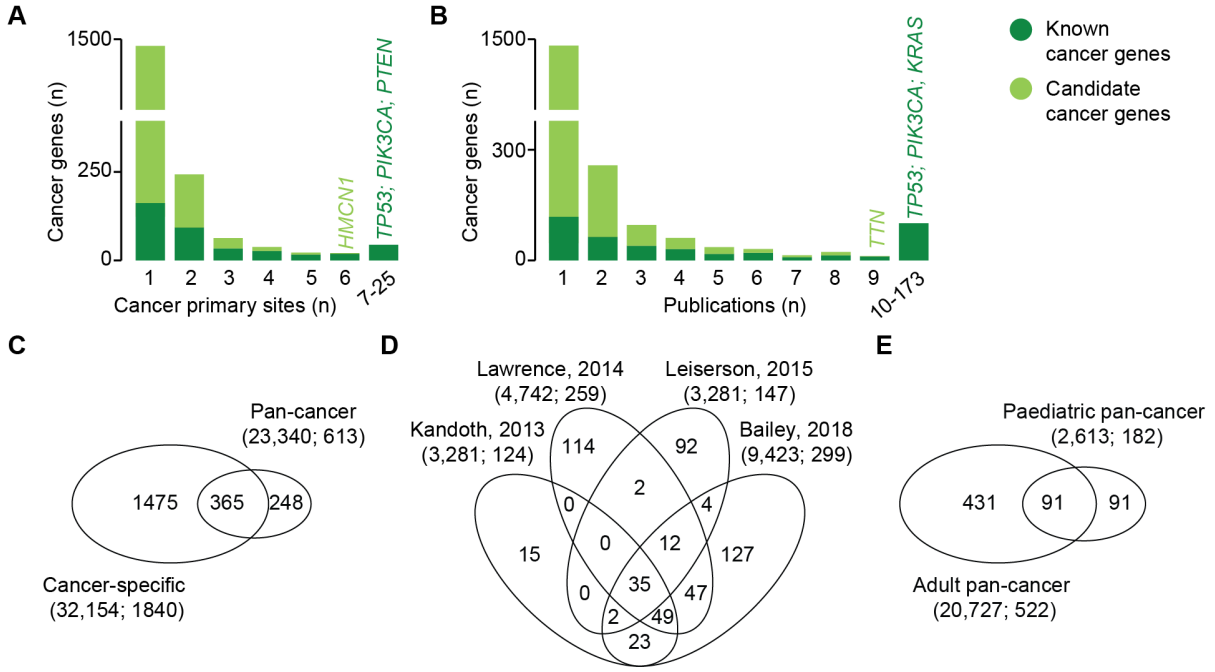
Table S1. Systems-level properties of cancer genes

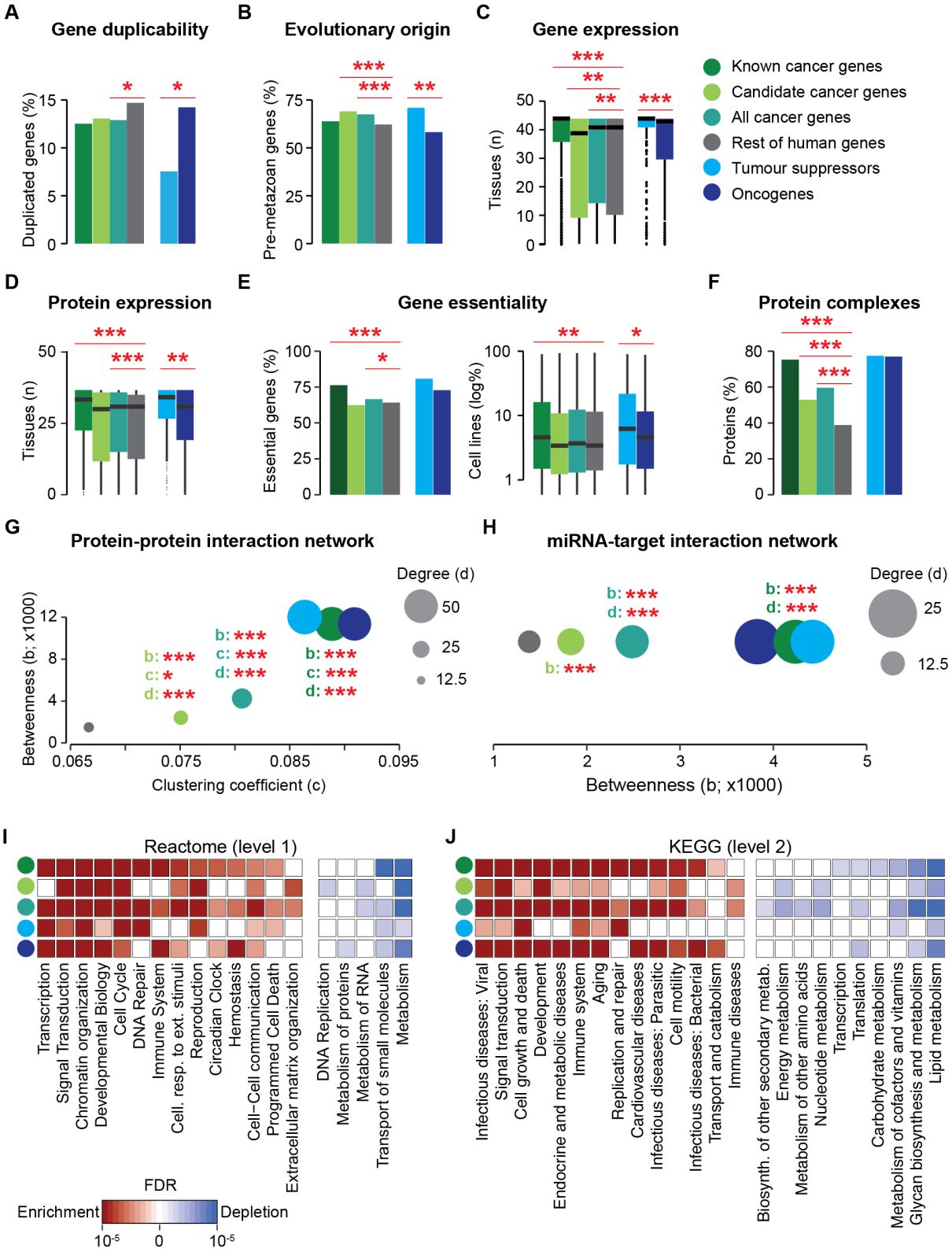
Table S2. List of 273 publications describing cancer sequencing screens in NCG

Table S3. Enrichment and depletion of cancer genes in protein functional categories


A
2 sources of known cancer genes
Cancer Gene Census (CGC)
Vogelstein, Science 2013
273 cancer sequencing screens
98 new publications
175 papers from NCG 5.0
Expert manual curation
711 known cancer genes
239 TSGs
239 OGs
233 Not classified
2,088 cancer genes
31 primary sites
34,905 cancer donors
18 prediction methods
2,372 cancer genes
B
Two sources
(711 genes)
284
427
1,661
Known cancer genes
Candidate cancer genes
273 publications
(2,088 genes)
C
Cancer genes (n)
Cancer donors (n)
rho = 0.46
p-value = 1.3x10-15
Publication Years (n)
2008–2010 (11)
2011–2013 (103)
2014–2016 (129)
2017–2018 (30)
D
Recurrence (129)
MuSiC (24)
Wood (14)
Rest (51)
MutSig (87)
E
Publications (%)
Prediction methods
1
2
3
2008–2010
2011–2013
2014–2016
2017–2018


A
All cancer genes
Known cancer genes
Candidate cancer genes
Cancer genes (number)
Cancer genes (percent)
Cancer genes
Cancer donors
Blood (3,661; 513)
Brain (3,262; 271)
Breast (5,246; 221)
Lung (2,664; 203)
Pancreas (1,104; 189)
Skin (1,413; 185)
Head and neck (1,002; 183)
Colorectal (1,159; 156)
Hepatobiliary (2,039; 146)
Bladder (887; 99)
Stomach (669; 94)
Oesophagus (962; 89)
Kidney (2,043; 85)
Uterus (538; 82)
Thyroid (1,424; 63)
Prostate (769; 57)
Small intestine (394; 40)
Soft tissue (337; 40)
Penis (97; 38)
Periph. nerv. sys. (40; 26)
Adrenal gland (420; 25)
Bone (486; 24)
Ovary (480; 22)
Cervix (271; 17)
Testis (198; 12)
Thymus (145; 12)
Parathyroid gland (25; 11)
Pleura (217; 10)
Uvea (103; 9)
Retina (71; 3)
Vascular system (28; 1)
B
Cancer genes (n)
Cancer sequencing screens (n)
Cancer donors (log10n)
blood
brain
lung
breast
pancreas
skin
head and neck
colorectal
hepatobiliary
uterus
stomach
bladder
oesophagus
kidney
soft tissue
small intestine
thyroid
peripheral nervous system
penis
prostate
parathyroid gland
testis
cervix
bone
vascular system
retina
uvea
thymus
pleura
adrenal gland
ovary
C
Study-specific cancer genes (%)
Skin melanoma donors (n)
All are study-specific
None are study-specific
Stark 2012
Wei 2011
Berger 2012
Xia 2015
Krauthammer 2012
TCGA 2015
Nikolaev 2011
Krauthammer 2015
Hodis 2012
D
Cancer genes (n)
Blood cancer donors (n)
diffuse large B-cell lymphoma


A
1500
250
0
Cancer genes (n)
1 2 3 4 5 6 7-25
Cancer primary sites (n)
HMCN1
TP53; PIK3CA; PTEN
B
1500
300
0
Cancer genes (n)
1 2 3 4 5 6 7 8 9 10-173
Publications (n)
TTN
TP53; PIK3CA; KRAS
Known cancer genes
Candidate cancer genes
C
Pan-cancer (23,340; 613)
1475
365
248
Cancer-specific (32,154; 1840)
D
Lawrence, 2014 (4,742; 259)
Leiserson, 2015 (3,281; 147)
Kandoth, 2013 (3,281; 124)
Bailey, 2018 (9,423; 299)
114
92
2
0
4
15
0
12
127
0
35
47
2
49
23
E
Paediatric pan-cancer (2,613; 182)
431
91
91
Adult pan-cancer (20,727; 522)


A
Gene duplicability
Duplicated genes (%)
B
Evolutionary origin
Pre-metazoan genes (%)
C
Gene expression
Tissues (n)
Known cancer genes
Candidate cancer genes
All cancer genes
Rest of human genes
Tumour suppressors
Oncogenes
D
Protein expression
Tissues (n)
E
Gene essentiality
Essential genes (%)
Cell lines (log%)
F
Protein complexes
Proteins (%)
G
Protein-protein interaction network
Betweenness (b; x1000)
Clustering coefficient (c)
Degree (d)
H
miRNA-target interaction network
Betweenness (b; x1000)
Degree (d)
I
Reactome (level 1)
Transcription
Signal Transduction
Chromatin organization
Developmental Biology
Cell Cycle
DNA Repair
Immune System
Cell. resp. to ext. stimuli
Reproduction
Circadian Clock
Hemostasis
Cell−Cell communication
Programmed Cell Death
Extracellular matrix organization
DNA Replication
Metabolism of proteins
Metabolism of RNA
Transport of small molecules
Metabolism
FDR
Enrichment
Depletion
J
KEGG (level 2)
Infectious diseases: Viral
Signal transduction
Cell growth and death
Development
Endocrine and metabolic diseases
Immune system
Aging
Replication and repair
Cardiovascular diseases
Infectious diseases: Parasitic
Cell motility
Infectious diseases: Bacterial
Transport and catabolism
Immune diseases
Biosynth. of other secondary metab.
Energy metabolism
Metabolism of other amino acids
Nucleotide metabolism
Transcription
Translation
Carbohydrate metabolism
Metabolism of cofactors and vitamins
Glycan biosynthesis and metabolism
Lipid metabolism