OGEE v2: an update of the online gene essentiality database with special focus on differentially essential genes in human cancer cell lines

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Received August 23, 2016; Revised October 14, 2016; Editorial Decision October 15, 2016; Accepted October 18, 2016

ABSTRACT

OGEE is an Online GEne Essentiality database. To enhance our understanding of the essentiality of genes, in OGEE we collected experimentally tested essential and non-essential genes, as well as associated gene properties known to contribute to gene essentiality. We focus on large-scale experiments, and complement our data with text-mining results. We organized tested genes into data sets according to their sources, and tagged those with variable essentiality statuses across data sets as conditionally essential genes, intending to highlight the complex interplay between gene functions and environments/experimental perturbations. Developments since the last public release include increased numbers of species and gene essentiality data sets, inclusion of non-coding essential sequences and genes with intermediate essentiality statuses. In addition, we included 16 essentiality data sets from cancer cell lines, corresponding to 9 human cancers; with OGEE, users can easily explore the shared and differentially essential genes within and between cancer types. These genes, especially those derived from cell lines that are similar to tumor samples, could reveal the oncogenic drivers, paralogous gene expression pattern and chromosomal structure of the corresponding cancer types, and can be further screened to identify targets for cancer therapy and/or new drug development. OGEE is freely available at http://ogee.medgenius.info.

INTRODUCTION

Essential genes are those genes of an organism that are critical for its survival; essential genes are of particular importance because of their theoretical and practical applications such as studying the robustness of a biological system (1), defining a minimal genome/organism (2,3) and identifying effective therapeutic targets in pathogens (4–6) and human cancers (7–11). In recent years, the technologies used for gene essentiality studies have been evolving rapidly, ranging from low-throughput single gene knockout experiment (12,13) to high-throughput mutagenesis (3), RNAi (7,8) and more recently CRISPR-based genome editing methods (14–18); recent studies showed that CRISPR technology outperformed other methods (14,19), featuring low noise and minimal off-target effects (19).

Being essential is not an intrinsic property of a gene; rather, it is highly dependent on a variety of factors including the function and expression pattern of the gene, the genetic background of the host, the environment and other settings. For example, genes coding for proteins involved in the biosynthesis of amino acids, nucleic acids and vitamins are essential for cell survival in minimal media, but not in rich media where the corresponding metabolites are supplied (20). In addition, different experimental methods may generate different results. For example, CRISPR-based methods could identify more essential genes than siRNA-based methods (21), while cell lines generate lower propor-
tion of essential genes than in vivo if the same multi-cellular organism is used (22).

Genes with variable essentiality statuses under different circumstances are referred to ‘conditionally essential genes (CEGs)’ or ‘differentially essential genes (DEGs)’ (14,22). CEG is a biologically meaningful and very important concept; e.g. genes that are essential in a cancer cell line but are non-essential in human tissues can reveal the oncogenic drivers, paralogous gene expression pattern and chromosomal structure of the corresponding cancer type (14).

In 2012, we introduced OEGE v1 (22) to promote the concept of ‘conditional essentiality’, which had not been widely adopted by existing essential gene databases at the time, and to advance our understanding on gene essentiality. We did so by including not only essential and non-essential genes, but also associated gene properties that are known to affect gene essentiality; we provided tools that allow users to compare gene essentiality among different gene groups, or compare properties of essential genes to non-essential genes. In addition, we organized experimentally tested genes into data sets according to their sources and tagged those with variable essentiality statuses across data sets as CEGs.

In this study we introduce an updated version of OEGE. In this new version we added new species and new data sets; we added genes with intermediate essentiality statuses (fitness genes) and non-coding essential genes. In addition, we re-organized the 16 gene essentiality data sets from human cancer cell lines corresponding to nine cancer types in order to help users to explore the shared and differentially essential genes within and between cancer types, because these genes, especially those derived from cell lines that are similar to tumor samples, could be further screened to identify targets for cancer therapy and/or new drug development.

**DATA GENERATION**

**Collection and organization of genes tested for essentiality**

We collected 99 large-scale gene essentiality experiments (data sets) for 48 species, including 34 data sets for 9 eukaryotes and 65 data sets for 39 prokaryotes. We added 1609 noncoding genes and 122 non-transcribed genomic regions from 10 species. In addition to essential and nonessential genes, we also included 1911 fitness genes from 10 species, and 37 growth-advanced genes from two species. Fitness genes are defined as those whose removal is not lethal but could result in significantly decreased fitness, while growth-advanced genes are defined as genes whose removal lead to significantly increased fitness. In the statistics below, fitness genes are counted as non-essential genes.

In sum, our database contains 167 799 genes tested for essentiality from 48 species, increased significantly from the 91 436 genes and 24 species respectively from the last version (22). In total 43 961 genes are covered by multiple data sets (in each species the text-mining results are considered as a data set), representing ~26.2% of all collected genes; among which 13 397 genes are CEGs, accounting for ~30.5% of those covered by multiple data sets. The proportion of conditionally essential genes (\(P_{CEG}\)) in species having more than 200 genes covered by two or more data sets ranges from 9.2% in *Staphylococcus aureus subsp. aureus NCTC 8325* to 41.6% in *Salmonella enterica subsp. enterica serovar Typhimurium str. SL1344*, as shown in Table 1. The number of data sets does not seem to contribute significantly to \(P_{CEG}\) (Pearson’s correlation coefficient = −0.24, P-value = 0.36).
Collection of gene properties influencing gene essentiality

We also collected several gene properties that are known to influence gene essentiality, including duplication status (23), the number of homologous genes (family size) in the same genome, connectivity in protein–protein interaction (PPI) networks (defined as the number of direct neighbors) (24), functional category of a gene (25) and the earliest expression stage during embryonic development. We used the BLAST tool (26) to search for duplicated genes within each genome using parameters and cutoffs described previously (27), and calculated the family size for each duplicated genes accordingly. We also calculated evolutionary measurements for each duplicated gene and its best BLAST hit, including Ka, Ks and Ka/Ks ratio using KaKs_Calculator (v2.0) (28). We obtained the PPI data from STRING v10.0 (29), the functional category data from Gene Ontology (30) and the expression data (for multi-cellular organisms only) from NCBI UniGene database (31). For more information, please consult the ‘Help’ page of the database.

BUILT-IN TOOLS FOR ANALYZING COLLECTED GENE PROPERTIES

We also provided integrated tools in the ‘Analyze’ page for users to analyze the impact of the collected gene properties on gene essentiality: users can divide genes into distinct groups according to one of the available properties, calculate the proportion of essential genes (P_E) in each group, and then plot the results as bar-chart. To illustrate this feature, we plotted in Figure 1 the P_E values of different groups of mouse genes as functions of their involvement in development (Figure 1A) and duplication status (Figure 1B). These results showed that that developmental genes are more essential than non-developmental genes, while singletons are more essential than duplicated genes, consisting to previous results (23,25); these trends are generally true in other species.

RE-ORGANIZATION OF ESSENTIAL GENES FROM HUMAN CANCER CELL LINES

In recent years, ‘conditional essentiality’ or ‘differential essentiality’ has been increasingly used as a tool for researchers to interrogate genes that are essential under specific conditions and search for genes required by the survival of human cancer cell lines (7,9–11,14,16). In OGGE we collected in total 16 such data sets and re-organized them into 9 groups according to their cancers of origin, including breast cancer, Burkitt’s lymphoma, chronic myelogenous leukemia (CML), colon cancer, esophageal squamous carcinoma, glioblastoma (GBM), non-small cell lung cancer (NSCLC), ovarian cancer and pancreatic cancer. Shared and differentially essential genes within and between cancer types were pre-calculated. Shown in Table 2 are the brief summary on the nine cancers, including the number of data sets for each cancer, the number of total essential genes and the number of uniquely essential genes. Here, the ‘uniquely essential genes’ are defined as those that are non-essential in any other human data sets available in OGGE. An up-to-date version of this table and additional results can be found in the ‘Cancer’ page of our website.

Lineage-specific essential genes, i.e. those that are essential only in a particular cancer type, are important targets for cancer therapies; because they are likely the results of the unique mutational profile and subsequent functional consequences of the cell line, targeting these genes in cancer therapies will achieve high efficiency and specificity. Cancer cell lines are often used as models for cancer research. However, recent studies suggest that although some cell lines are indeed good models for cancers, some other cancer cell lines could have pronounced differences as compared to tumor samples of the same origin in terms of copy number changes, key mutations and mRNA expression profiles, due in part to ambiguity in classification and annotation (32,33). Thus, in the future, we will exclude cell lines that are remarkably different from cancers of the same origin, and keep only the good ones, should such information are reliable and easily accessible.

DATA ACCESS

All data are freely accessible to all academic users. This work is licensed under a Creative Commons Attribution 3.0 Unported License (CC BY 3.0). Users can download combined data from the ‘Downloads’ page. Users can also download individual data sets or combined data sets for individual species in the ‘Browse’ page.
CONCLUSIONS

In this article, we introduced OGEE v2, an online gene essentiality database. Updates since the last updated version include increased numbers of species and gene essentiality data sets, inclusion of non-coding essential sequences and fitness genes. We also re-organize the essentiality data sets from nine human cancers so that our users can easily explore the shared and differentially essential genes within and between cancer types. As compared with existing gene essentiality databases such as DEG (34), OGEE provides several unique features. For example, (i) OGEE provides both essential and non-essential genes from large-scale as well as small-scale studies; (ii) OGEE introduces ‘conditional essentiality’ to reflect the complexity of biological systems and the interplay between gene functions, genetic backgrounds and environments; (iii) OGEE lists a variety of gene properties known to influence gene essentiality; (iv) OGEE provides a set of online tools to explore and analyze the data and to visualize the results. We thus believe that OGEE should be highly useful to biologists and bioinformaticians studying gene essentiality, whether focusing on individual genes or on genome-wide analyses. In the future, we aim to update OGEE regularly in order to provide up-to-date contents to our users.

FUNDING

Funding for open access charge: startup funding for Chen’s lab at the Huazhong University of Science and Technology, China

Conflict of interest statement. None declared.

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