MetaFun: Unveiling Sex-based Differences in Multiple Transcriptomic Studies through Comprehensive Functional Meta-analysis

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Abstract

While sex-based differences in various health scenarios have been thoroughly acknowledged in the literature, we lack a deep analysis of sex as a variable in this context. To fill this knowledge gap, we created MetaFun as an easy-to-use web-based tool to meta-analyze multiple transcriptomic datasets with a sex-based perspective to gain major statistical power and biological soundness. Furthermore, MetaFun can be used to perform case-control meta-analyses, allowing researchers with basic programming skills to access this methodology.

Availability and implementation: MetaFun is freely available at http://bioinfo.cipf.es/metafun
The back end was implemented in R and Java, and the front end was developed using Angular
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Supplementary information: R code available at https://gitlab.com/ubb-cipf/metafunr

1 Introduction

Sex-based differences in different health scenarios have been thoroughly acknowledged in the literature [1,2]; however, this variable remains incompletely analyzed in many cases. Studies often neglect sex as a variable when considering the experimental design of studies, leading to experiments with samples of just one sex in extreme cases. As a result, the underlying mechanisms behind sex-based differences in many diseases and disorders remain incompletely established.

Fortunately, the scientific community has worked to significantly improve this situation in recent times, and researchers have begun to include the sex perspective in their research; however, a vast amount of generated data currently stored in public databases (such as Gene Expression Omnibus (GEO) [3] or NCI's Genomic Data Commons (GDC) [4]) remains unanalyzed from this perspective. The information in these databases represents a powerful resource that must be considered.

When exploiting these resources with a particular objective, multiple studies dealing with similar scientific questions can provide different and often contradictory results. No one study is likely to provide a definitive answer; therefore, integrating all datasets into a single analysis may provide the means to understand the results. Defined for this purpose, meta-analysis is a statistical methodology that considers the relative importance of multiple studies upon combining them into a single integrated analysis and extracts results based on the entirety of the evidence/samples [5,6,7]. Unfortunately, applying advanced statistical techniques such as meta-analysis often remains out of reach for biomedical researchers aiming to analyze their data in a straightforward manner.

We designed the "MetaFun" tool to simplify the analytical process and facilitate the application of functional meta-analysis to researchers working with multiple transcriptomic datasets. Meta-analysis approaches can analyze datasets from perspectives such as sex and combine datasets to gain significant statistical power and soundness. MetaFun is a complete suite that allows the analysis of transcriptomics data and the exploration of the results at all levels, performing single-dataset exploratory analysis, differential gene expression, gene set functional enrichment, and finally, combining results in a functional meta-analysis.

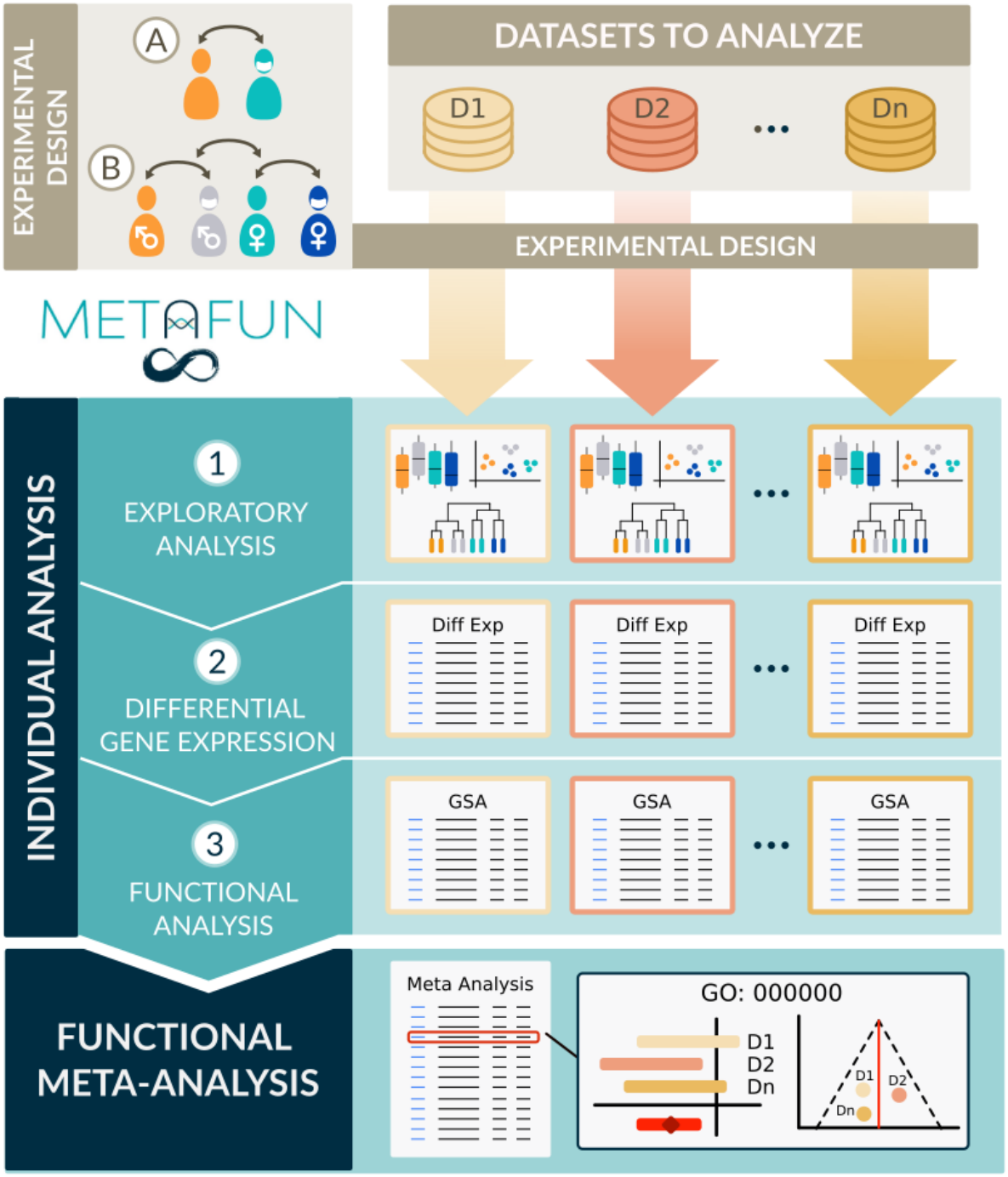

Figure 1: MetaFun pipeline. First, datasets and experimental designs are uploaded as CSV and TSV files. Available comparisons include (**A**) a classical comparison - *Case vs. Control* - and (**B**) a sex-perspective comparison - (*Female case* vs. *Female control*) vs. (*Male case* vs. *Male control*). Single experiment analyses include 1) exploratory analysis, 2) differential gene expression, and 3) functional analysis performed on each dataset. Finally, the results are integrated into a functional meta-analysis. The MetaFun tool allows users to explore all results generated during the process.

2 Methods

The MetaFun tool is available at https://bioinfo.cipf.es/metafun while additional help can be found at https://gitlab.com/ubb-cipf/metafunweb/-/wikis/Summary.

2.1 Input Data and Experimental Design

MetaFun takes a set of at least two CSV expression files and two TSV experimental design files as inputs. CSV expression files must include normalized transcriptomics data from comparable studies with assimilable experimental groups. Columns must contain the study samples, while rows must contain analyzed genes as their Entrez Gene ID. The first row contains sample names. TSV experimental files define the class to which each sample of the study belongs by including at least two columns: sample names and the class to which they belong. Column names in the CSV expression files must match row names in the corresponding TSV experimental file. Accepted reference organisms are (for the moment) humans (*Homo sapiens*), mice (*Mus musculus*), and rats (*Rattus norvegicus*). Analyses can be made with respect to a comparison that must apply to all datasets. Options include the classical comparison - *Case* vs. *Control* (**Fig. 1A**) - or a sex-perspective comparison - (*Male case* vs. *Male control*) vs. (*Female case* vs. *Female control*) (**Fig. 1B**) - in which the effect under study is compared between sexes.

2.2 Single Dataset Analyses

After the selection of the studies and experimental design, MetaFun analyzes each dataset separately with an individual analysis consisting of:

- an exploratory analysis including boxplots, PCA, and cluster plots using the *plotly* library [8]
- a differential gene expression analysis using the *limma* package [9]
- a gene set enrichment analysis (GSEA) [10] based on gene ontology (GO) [11] from the *mdgsa* package [12].

Figures and tables from these analyses can be explored and downloaded from the *Results* area once the job has been completed. Links to NCBI [13] and QuickGO [14] databases are present to detail the results.

2.3 Functional Meta-analysis

MetaFun combines the gene set functional enrichments from all datasets into a meta-analysis with the same experimental design using the *metafor* package [15]. Forest and funnel plots are generated utilizing the *plot.lyJS* library [8]. Figures and tables from this meta-analysis are interactive and may be explored and downloaded from the *Results* area once the job has been completed.

2.4 Implementation

The MetaFun back end was written using Java and R and is supported by the non-relational database *MongoDB* [16], which stores the files, users, and job information. The front end was developed using the *Angular* framework [17]. All graphics generated in this web tool were implemented with *Plot.ly* [8] except for the exploratory analysis cluster plot, which uses the *ggplot2* R package [18].

2.5 Study Cases

As an example, MetaFun includes two sets of pre-selected study cases, one for each accepted species: human and rat. The study cases can be executed directly from the web tool, allowing the tool's functionalities to be easily explored. The human study case includes nine studies from lung cancer patients [6].

Acknowledgments

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Conflict of Interest: none declared.

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Supplementary Material

MetaFun: Unveiling Sex-based Differences in Multiple Transcriptomic Studies through Comprehensive Functional Meta-analysis

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S1. Web Tool Overview

The web tool can be used with registered or anonymous users. Registered users will keep their data and jobs stored from one session to the other, while data and jobs from anonymous users will not be saved after leaving the session. The general design of the web tool includes an upper right menu with basic tool functionalities, a left side panel with specific submenus, and a central panel from which to interact with the web. Users are directed to a form launching a new job after logging in, which can be otherwise accessed through the *New Analysis* button in the top right menu. The *New Analysis* form passes through a series of steps, asking for information that must be completed (see **Supplementary Section S2** for details) and allows for a new meta-analysis. After the launch and execution, the job will be listed in the jobs area, which can be accessed through the *My jobs* button located in the top right menu. All created jobs are listed and can be accessed through the left side submenu to visualize results. Users can access their personal area through the top right panel using a button carrying their username. Each user's personal area includes a browser for folders and information regarding all launched jobs. The user's personal area submenu supports a series of actions related to personal settings and deleting options. The top right panel also includes an exit icon button that logs users out and a question mark icon that opens documentation pertinent to the web tool (accessible through https://gitlab.com/ubb-cipf/metafunweb/-/wikis/Summary).

S2. Input Data

All datasets in the same meta-analysis should be comparable, including similar experimental designs and individuals with similar conditions. At least two datasets must be included in a meta-analysis. Input data consists of one expression matrix and one experimental design file for each dataset in the meta-analysis. The expression matrix must have been normalized, with samples in columns and Entrez ID genes in rows. The experimental design file must indicate the original group to which each sample belongs, with samples in rows and groupings in columns. More than one grouping per file is accepted, placing each grouping in a different column (for instance, the first column could be sex, the second column experimental conditions, and the third column disease grade). However, only one grouping at a time will be used in a meta-analysis.

S3. Launching a Meta-analysis

The *New Analysis* button in the top right menu directs users to a form that launches a new meta-analysis. The first tab of the form - labeled *Files* - includes a browser for user files and allows users to upload and manage the datasets to analyze. The *Options* tab allows users to specify the *Effect Model* to *random* or *fixed*, to select the reference organism among *Homo*

sapiens, and *Rattus norvegicus*, to define the GO ontologies to analyze (*Biological Process*, *Molecular Function*, and *Cellular Component*), and whether to propagate the annotation. A brief description accompanies each option to help users in their decisions. The *Studies* tab is used to select the studies to meta-analyze and the experimental design. Depending on the case, selections are made by dragging files from the right panel entitled *My Files* to the columns *Expression* or *Experimental Design*. Matched studies and experimental designs must be placed in the same row, verifying their compatibility by checking sample names in the expression and experimental design files. Users can specify the comparison to perform in the *Comparison* tab. Two different options are currently available: the classical *Case vs. Control*, which compares the effect of a variable, and a sex-based comparison - *(Case Female vs. Control Female) vs. (Case Male vs. Control Male)* - which compares the effect of a variable in females with respect to the effect in males. In the second case, significant results refer to differential effects between males and females and may not coincide with results from the first comparison. After selecting the comparison, users must indicate which study samples are included in each canonical compared group (*Case*, *Control*, *Case Female*, etc.) by assigning one of the classes in the experimental design of each study to these canonical groups. Finally, the *Launch* tab contains a summary of the defined meta-analysis, which may be launched through the *Launch job* button after the name assignment.

S4. Analysis Summary

After the execution of the job and its selection in the left side panel of the *My Jobs* panel, the *Analysis summary* tab will show a summary of the main results, which include:

- selected analysis options - name, comparison, effect model, functional profile, and reference organism
- a table and an interactive barplot describing the number of samples per dataset and per group
- a table describing the number of differentially expressed genes in each dataset - per column, the studies, total number of analyzed genes, total number of significantly affected genes, number of significantly upregulated genes, and number of significantly downregulated genes
- a table including the same columns describing the number of significant functional profile items in each dataset - either enriched functions or differentially activated subpathways, depending on the selected functional profile
- a table including the same columns describing the number of significant functional terms in each ontology - BP for Biological Process, MF for Molecular Functional, and CC for Cellular Component - of the meta-analysis

S5. Exploratory Analysis

The *Exploratory analysis* tab contains the figures from the unsupervised exploratory analysis performed on each dataset in the meta-analysis. This analysis includes a boxplot representation of the expression of the samples, a clustering of the samples, and a principal components analysis (PCA) plot representing the first two components of the PCA. All samples are colored by the experimental design selected in the meta-analysis.

S6. Differential Expression

The differential expression analysis is performed with the *limma* library [9], applying *lmFit, contrast.fit,* and *eBayes* functions while considering whether samples are paired or unpaired. Results will be displayed as a table in the *Differential expression* tab of the job. The table shows the Entrez ID, Gene Name, the logarithm of the fold-change (logFC), test statistic, raw p-value, and Bonferroni-Holm [19] adjusted p-value of each analyzed feature. The raw p-value initially orders the table, but buttons on column names allow users to order the table differently. Links from the Entrez ID column direct to the NCBI gene database of the specific gene. Different tools allow users to search, download, and filter the table by a maximum p-value.

S7. Gene Set Enrichment Analysis

The functional analysis consists of a GSEA [10] based on the BP, MF, and CC ontologies from GO [11] defined by users. The pipeline, performed with the *mdgsa* library [12], splits the ontologies, propagates the annotation (if indicated), filters too generic (more than 500 annotated genes) or too specific (less than ten annotated genes) annotations, transforms the p-value into an index, and performs the corresponding comparisons. Results will be displayed as a table in the *GSA* tab of the job. Three subtabs on the top right of the table separately show the results for the three different ontologies. For each ontology, the table shows the GO ID, GO term, the logarithm of the odds-ratio (LOR), raw p-value, Bonferroni-Holm adjusted p-value, and the number of genes included in each analyzed feature. The raw p-value initially orders the table, and buttons on column names allow users to order the table differently. Links from the GO ID column direct to the QuickGO [14] entry of the specific term. Different tools allow users to search, download, and filter the table by a maximum p-value.

S8. Meta-analysis

The functional meta-analysis integrates the functional analysis results and is performed using the *rma* function of the *metafor* package [15]. For each function, a meta-analysis combines the level of overrepresentation (LOR) of that function in different studies. Two methods have been implemented to perform meta-analyses: the fixed effects models (FE) and the random effects models (DL DerSimonian & Laird; HS Schmidt & Hunter; Hedges, HE) [15]. The fixed effect model has been designed for similar studies (i.e., with the same technology, platform, and at similar times), while the random effect model allows for more significant variability. Results will be displayed as a table in the *Meta-analysis* tab of the job. The table shows the GO ID, GO term, LOR, confidence interval of the LOR, raw p-value, and Bonferroni-Holm [19] adjusted p-value of each analyzed feature. The raw p-value initially orders the table, and buttons on column names allow users to order the table differently. Links from the GO ID column direct to the QuickGO [14] entry of the specific term. Different tools allow users to search, download, and filter the table by a maximum p-value.

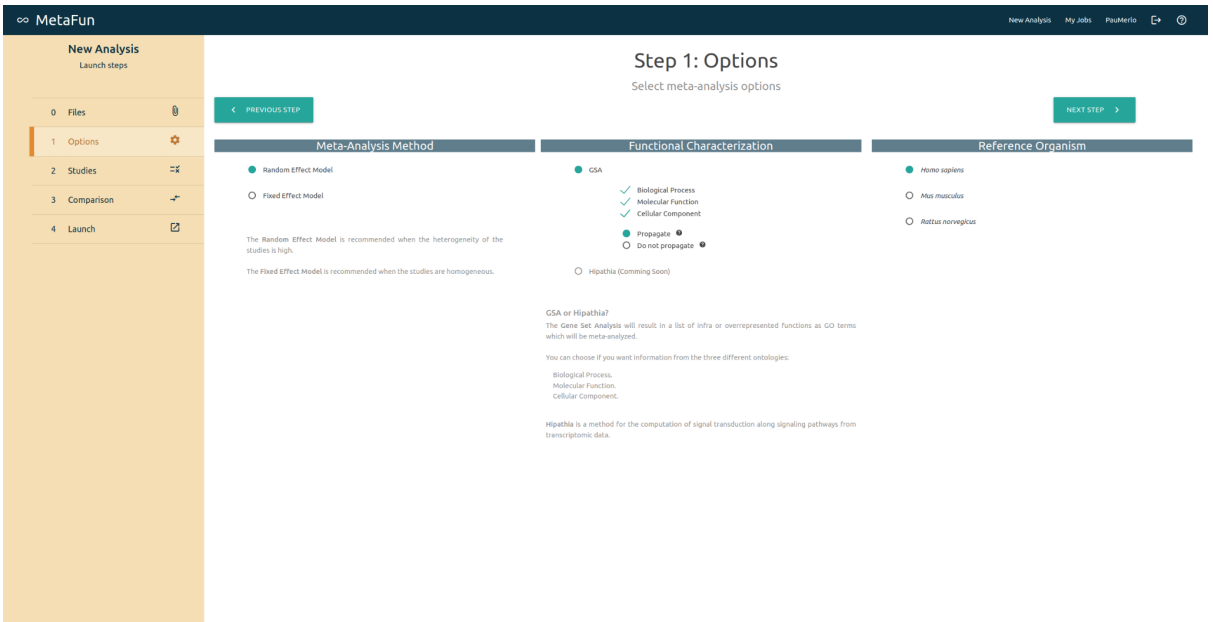
S9. Study Case

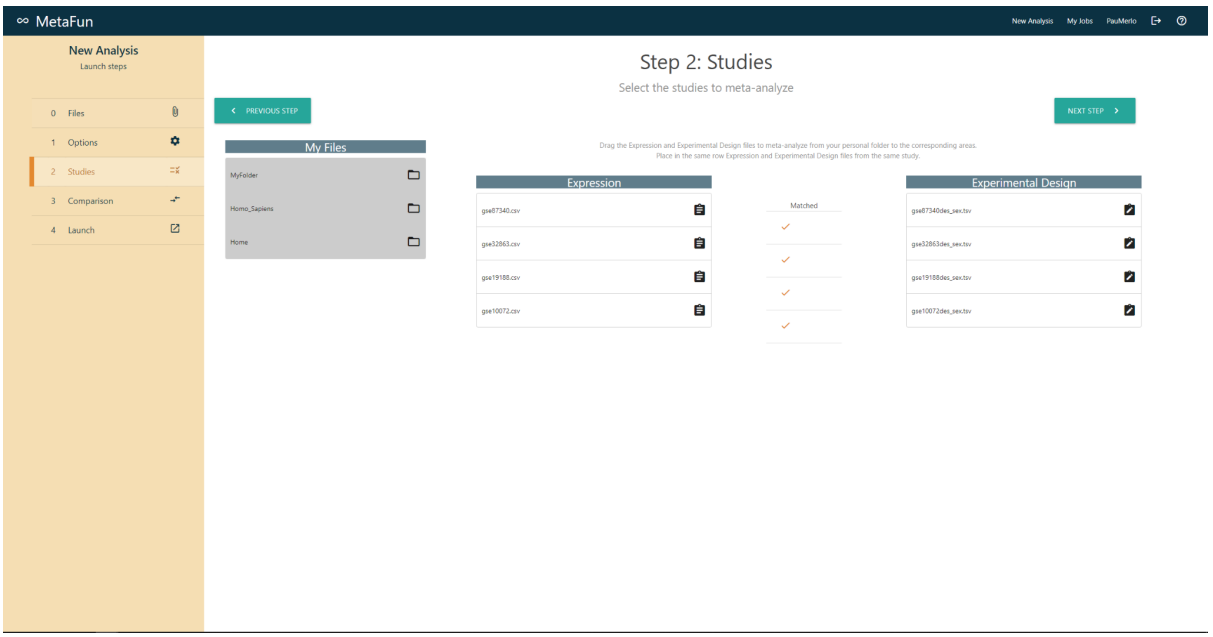
The following case describes the potential use of MetaFun in characterizing sex-based differences in lung adenocarcinoma. The results obtained were published in [20].

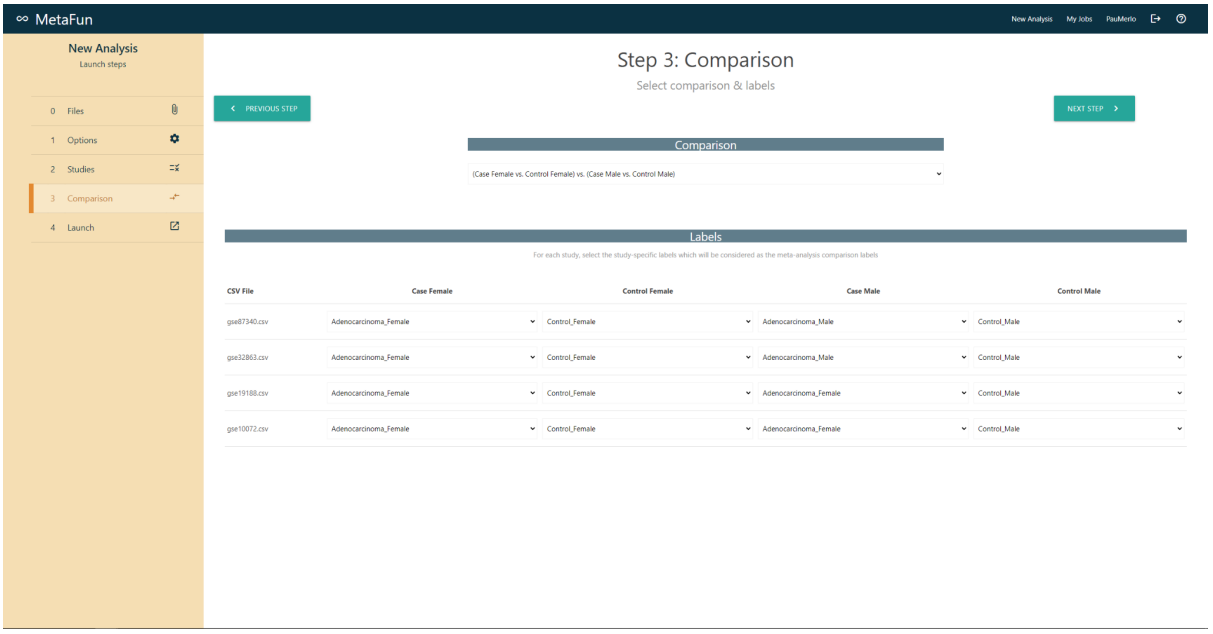
Input data:

Each study requires two files: one with expression data and a second with the description of the experimental groups to which each sample belongs, indicating the sex of the participant. The files corresponding to this use case can be downloaded at the following link - https://gitlab.com/ubb-cipf/metafunpipeline/-/blob/master/Homo%20Sapiens%20(Adenocarcinoma).zip

Four Simple Steps to Launch the Meta-analysis Job:




MetaFun
New Analysis
My Jobs
PauMerlo
New Analysis
Launch steps
0 Files
1 Options
2 Studies
3 Comparison
4 Launch
Step 2: Studies
Select the studies to meta-analyze
PREVIOUS STEP
NEXT STEP
My Files
MyFolder
Homo_Sapiens
Home
Drag the Expression and Experimental Design files to meta-analyze from your personal folder to the corresponding areas.
Place in the same row Expression and Experimental Design files from the same study.
Expression
gse87340.csv
gse32863.csv
gse19188.csv
gse10072.csv
Matched
Experimental Design
gse87340des_sex.tsv
gse32863des_sex.tsv
gse19188des_sex.tsv
gse10072des_sex.tsv


MetaFun
New Analysis
My Jobs
PauMerlo
New Analysis
Launch steps
0 Files
1 Options
2 Studies
3 Comparison
4 Launch
Step 3: Comparison
Select comparison & labels
PREVIOUS STEP
NEXT STEP
Comparison
(Case Female vs. Control Female) vs. (Case Male vs. Control Male)
Labels
For each study, select the study-specific labels which will be considered as the meta-analysis comparison labels
CSV File
Case Female
Control Female
Case Male
Control Male
gse87340.csv
Adenocarcinoma_Female
Control_Female
Adenocarcinoma_Male
Control_Male
gse32863.csv
Adenocarcinoma_Female
Control_Female
Adenocarcinoma_Male
Control_Male
gse19188.csv
Adenocarcinoma_Female
Control_Female
Adenocarcinoma_Female
Control_Male
gse10072.csv
Adenocarcinoma_Female
Control_Female
Adenocarcinoma_Female
Control_Male

MetaFun

New Analysis | My Jobs | PauMerlo

New Analysis
Launch steps

0 Files
1 Options
2 Studies
3 Comparison
4 Launch

Step 4: Launch

Check meta-analysis summary & launch job

PREVIOUS STEP

Selected Options

Meta-Analysis method:	Random Effect Model
Functional Characterization:	GSA
Ontologies:	Biological Process, Molecular Functions, Cellular Components
Propagate:	YES
Reference Organism:	*Homo Sapiens*

Selected Studies

Expression File	Experiment Design File
gse87340.csv	gse87340des_sex.tsv
gse32863.csv	gse32863des_sex.tsv
gse19188.csv	gse19188des_sex.tsv
gse10072.csv	gse10072des_sex.tsv

Selected Comparison

You have selected **Sex Difference** contrast

Study	Case Female	Control Female	Case Male	Control Male
gse87340.csv	Adenocarcinoma_Female	Control_Female	Adenocarcinoma_Male	Control_Male
gse32863.csv	Adenocarcinoma_Female	Control_Female	Adenocarcinoma_Male	Control_Male
gse19188.csv	Adenocarcinoma_Female	Control_Female	Adenocarcinoma_Female	Control_Male
gse10072.csv	Adenocarcinoma_Female	Control_Female	Adenocarcinoma_Female	Control_Male

Select Job's Name

SexDiff Adeno

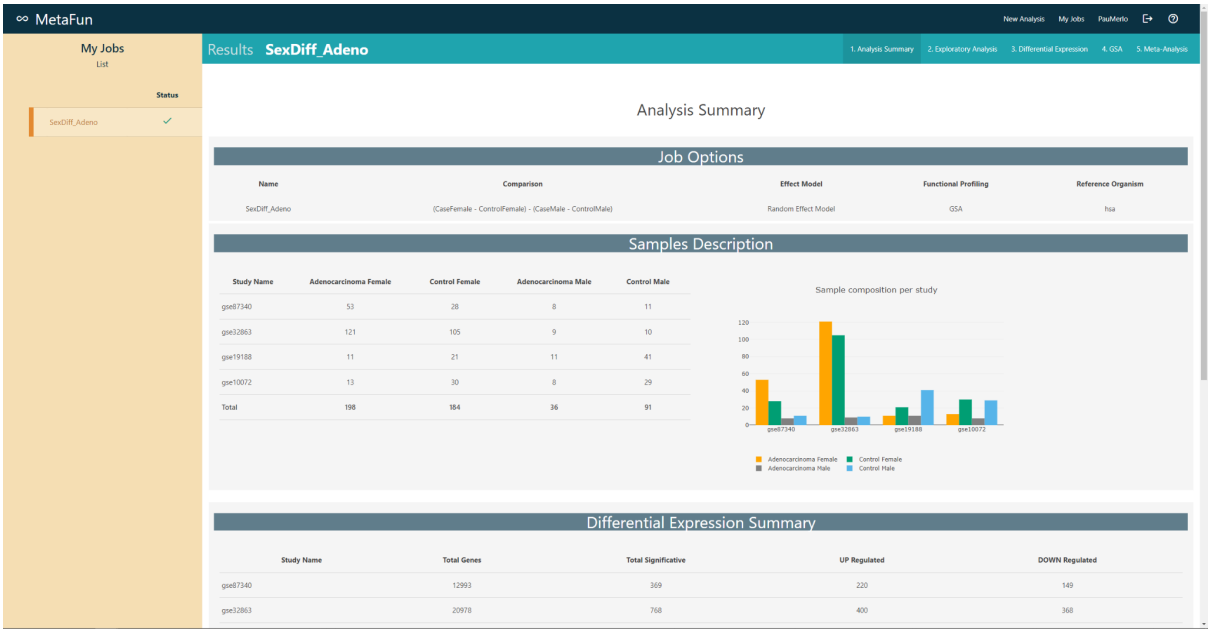
LAUNCH JOB

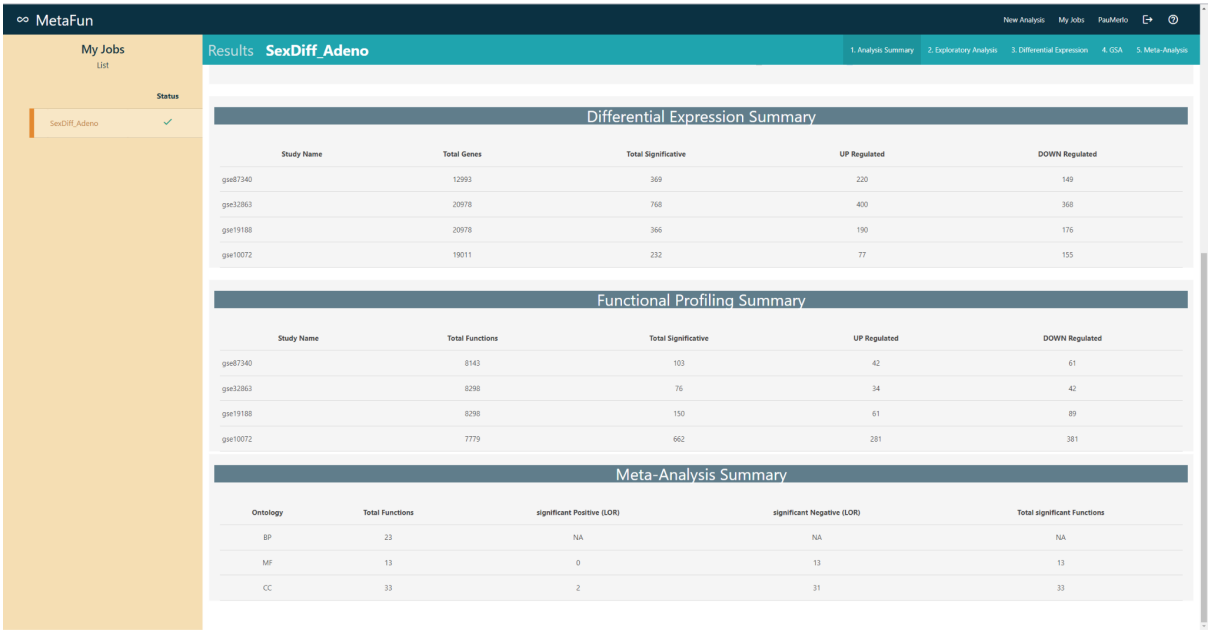
Results:

Below, we display the results generated by MetaFun in this use case for each of the sections described above (1. Analysis Summary, 2. Exploratory Analysis, 3. Differential Expression, 4. Gene Set Analysis, 5. Meta-analysis),

1. Analysis Summary

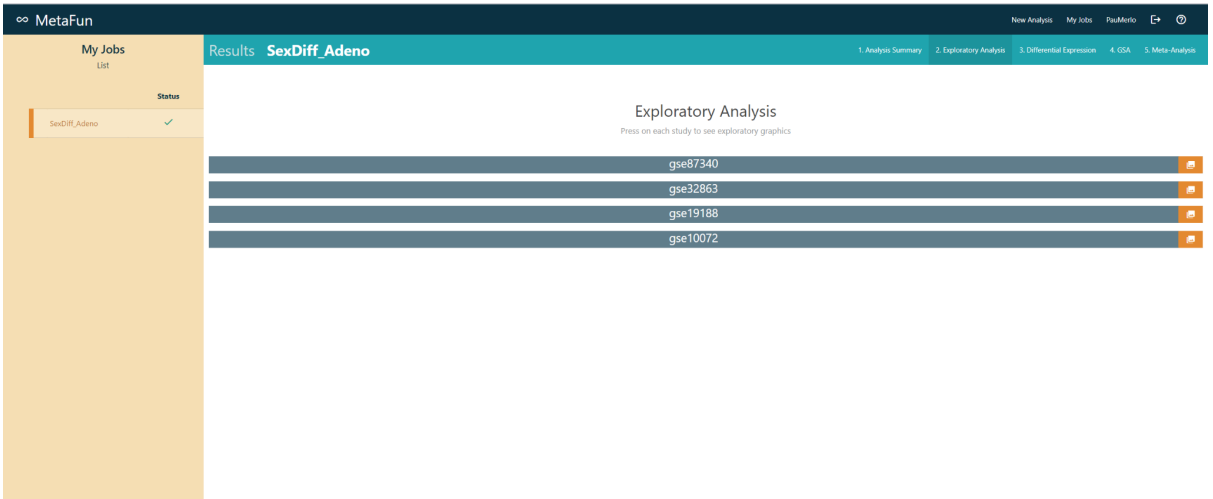
A summary of the results at the distinct stages of the bioinformatics analysis strategy:





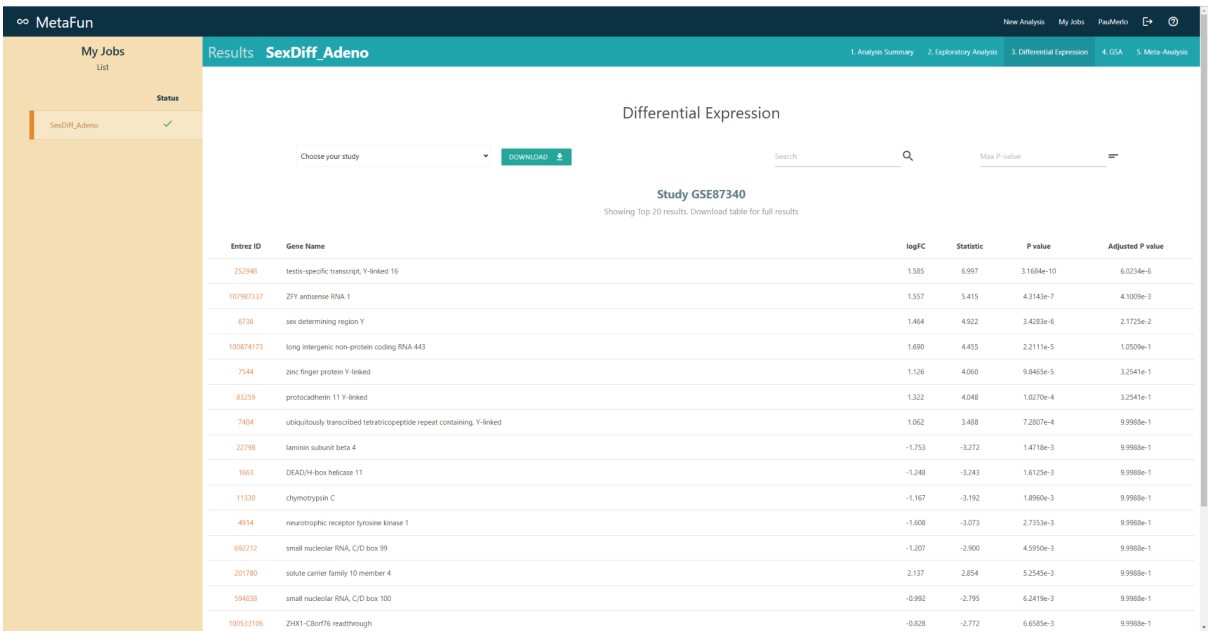
2. Exploratory Analysis

PCA, clustering, and boxplots are used to explore the expression levels of each of the samples in the selected studies:



3. Differential Expression

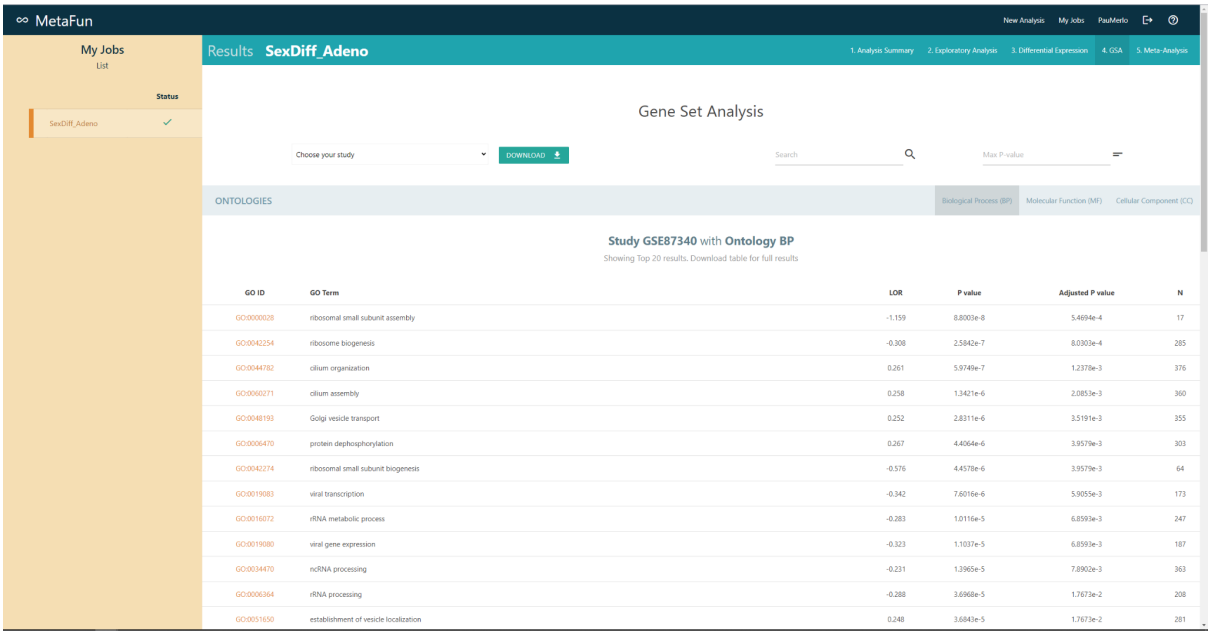
The identification of genes showing differential expression by sex in affected patients for each study (Clicking on each link to the gene identifiers expands their biological information):



Entrez ID	Gene Name	logFC	Statistic	P value	Adjusted P value
252948	testis-specific transcript, Y-linked 16	1.585	6.997	3.1684e-10	6.0234e-6
107987337	ZFY antisense RNA 1	1.557	5.415	4.3143e-7	4.1009e-3
6736	sex determining region Y	1.464	4.922	3.4283e-6	2.1725e-2
100874173	long intergenic non-protein coding RNA 443	1.690	4.455	2.2111e-5	1.0509e-1
7544	zinc finger protein Y-linked	1.126	4.060	9.8465e-5	3.2541e-1
83259	protocadherin 11 Y-linked	1.322	4.048	1.0270e-4	3.2541e-1
7404	ubiquitously transcribed tetratricopeptide repeat containing, Y-linked	1.062	3.488	7.2807e-4	9.9988e-1
22798	laminin subunit beta 4	-1.753	-3.272	1.4718e-3	9.9988e-1
1663	DEAD/H-box helicase 11	-1.248	-3.243	1.6125e-3	9.9988e-1
11330	chymotrypsin C	-1.167	-3.192	1.8960e-3	9.9988e-1
4914	neurotrophic receptor tyrosine kinase 1	-1.608	-3.073	2.7353e-3	9.9988e-1
692212	small nucleolar RNA, C/D box 99	-1.207	-2.900	4.5950e-3	9.9988e-1
201780	solute carrier family 10 member 4	2.137	2.854	5.2545e-3	9.9988e-1
594838	small nucleolar RNA, C/D box 100	-0.992	-2.795	6.2419e-3	9.9988e-1
100533106	ZHX1-C8orf76 readthrough	-0.828	-2.772	6.6585e-3	9.9988e-1

4. Gene Set Analysis (GSA)

Functional characterization of the differential expression results identifies those functions more active in males and females (Clicking on each link to the identifiers expands the information for each significant function):



GO ID	GO Term	LOR	P value	Adjusted P value	N
GO:0000028	ribosomal small subunit assembly	-1.159	8.8003e-8	5.4694e-4	17
GO:0042254	ribosome biogenesis	-0.308	2.5842e-7	8.0303e-4	285
GO:0044782	cilium organization	0.261	5.9749e-7	1.2378e-3	376
GO:0060271	cilium assembly	0.258	1.3421e-6	2.0853e-3	360
GO:0048193	Golgi vesicle transport	0.252	2.8311e-6	3.5191e-3	355
GO:0006470	protein dephosphorylation	0.267	4.4064e-6	3.9579e-3	303
GO:0042274	ribosomal small subunit biogenesis	-0.576	4.4578e-6	3.9579e-3	64
GO:0019083	viral transcription	-0.342	7.6016e-6	5.9055e-3	173
GO:0016072	rRNA metabolic process	-0.283	1.0116e-5	6.8593e-3	247
GO:0019080	viral gene expression	-0.323	1.1037e-5	6.8593e-3	187
GO:0034470	ncRNA processing	-0.231	1.3965e-5	7.8902e-3	363
GO:0006364	rRNA processing	-0.288	3.6968e-5	1.7673e-2	208
GO:0051650	establishment of vesicle localization	0.248	3.6843e-5	1.7673e-2	281

5. Meta-analysis

Demonstration of MetaFun functions and the pathways activated in evaluated studies (Clicking on the information icon leads to detailed information on these significant functions):

MetaFun

New Analysis | My Jobs | PauMerlo

My Jobs
List

Status

SexDiff_Adeno ✓

Results **SexDiff_Adeno**

1. Analysis Summary | 2. Exploratory Analysis | 3. Differential Expression | 4. GSA | 5. Meta-Analysis

Meta-Analysis

Showing Top 20 results. Download table for full results.

DOWNLOAD

All Results | 20 First Results

GO ID	GO Term	LOR	Confidence Interval	P value	Adjusted P value
GO:0000070	mitotic sister chromatid segregation	-0.405	[-0.605 , -0.206]	0.0000e+0	0.0000e+0
GO:0000280	nuclear division	-0.281	[-0.37 , -0.192]	0.0000e+0	0.0000e+0
GO:0000819	sister chromatid segregation	-0.383	[-0.559 , -0.207]	0.0000e+0	0.0000e+0
GO:0006261	DNA-dependent DNA replication	-0.288	[-0.401 , -0.175]	0.0000e+0	0.0000e+0
GO:0006364	rRNA processing	-0.339	[-0.438 , -0.24]	0.0000e+0	0.0000e+0
GO:0007059	chromosome segregation	-0.355	[-0.529 , -0.18]	0.0000e+0	0.0000e+0
GO:0016072	rRNA metabolic process	-0.324	[-0.413 , -0.235]	0.0000e+0	0.0000e+0
GO:0022613	ribonucleoprotein complex biogenesis	-0.188	[-0.254 , -0.122]	0.0000e+0	0.0000e+0
GO:0030198	extracellular matrix organization	-0.257	[-0.383 , -0.13]	0.0000e+0	0.0000e+0
GO:0034470	ncRNA processing	-0.236	[-0.309 , -0.163]	0.0000e+0	0.0000e+0
GO:0042254	ribosome biogenesis	-0.317	[-0.4 , -0.235]	0.0000e+0	0.0000e+0
GO:0043062	extracellular structure organization	-0.204	[-0.261 , -0.148]	0.0000e+0	0.0000e+0
GO:0048285	organelle fission	-0.262	[-0.344 , -0.18]	0.0000e+0	0.0000e+0

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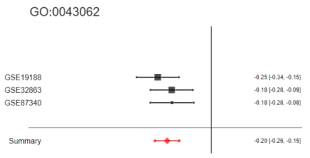
Status

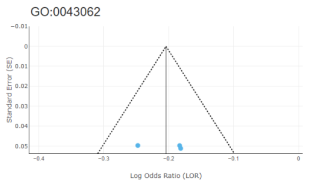
SexDiff_Adeno ✓

Results **SexDiff_Adeno**

1. Analysis Summary | 2. Exploratory Analysis | 3. Differential Expression | 4. GSA | 5. Meta-Analysis

GO:0034470	ncRNA processing	-0.236	[-0.309 , -0.163]	0.0000e+0	0.0000e+0
GO:0042254	ribosome biogenesis	-0.317	[-0.4 , -0.235]	0.0000e+0	0.0000e+0
GO:0043062	extracellular structure organization	-0.204	[-0.261 , -0.148]	0.0000e+0	0.0000e+0





GO:0048285	organelle fission	-0.262	[-0.344 , -0.18]	0.0000e+0	0.0000e+0

GO:0051983	regulation of chromosome segregation	-0.472	[-0.688 , -0.257]	0.0000e+0	0.0000e+0
GO:0098813	nuclear chromosome segregation	-0.362	[-0.526 , -0.199]	0.0000e+0	0.0000e+0
GO:0004386	helicase activity	-0.288	[-0.404 , -0.173]	0.0000e+0	0.0000e+0
GO:0005201	extracellular matrix structural constituent	-0.458	[-0.743 , -0.173]	2.0000e-3	2.0000e-3
GO:0008234	cysteine-type peptidase activity	0.228	[0.117 , 0.339]	0.0000e+0	0.0000e+0
GO:0016706	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, 2-oxoglutarate as one donor, and incorporation of one atom each of oxygen into both donors	-0.482	[-0.687 , -0.277]	0.0000e+0	0.0000e+0