

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/metafun>

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.

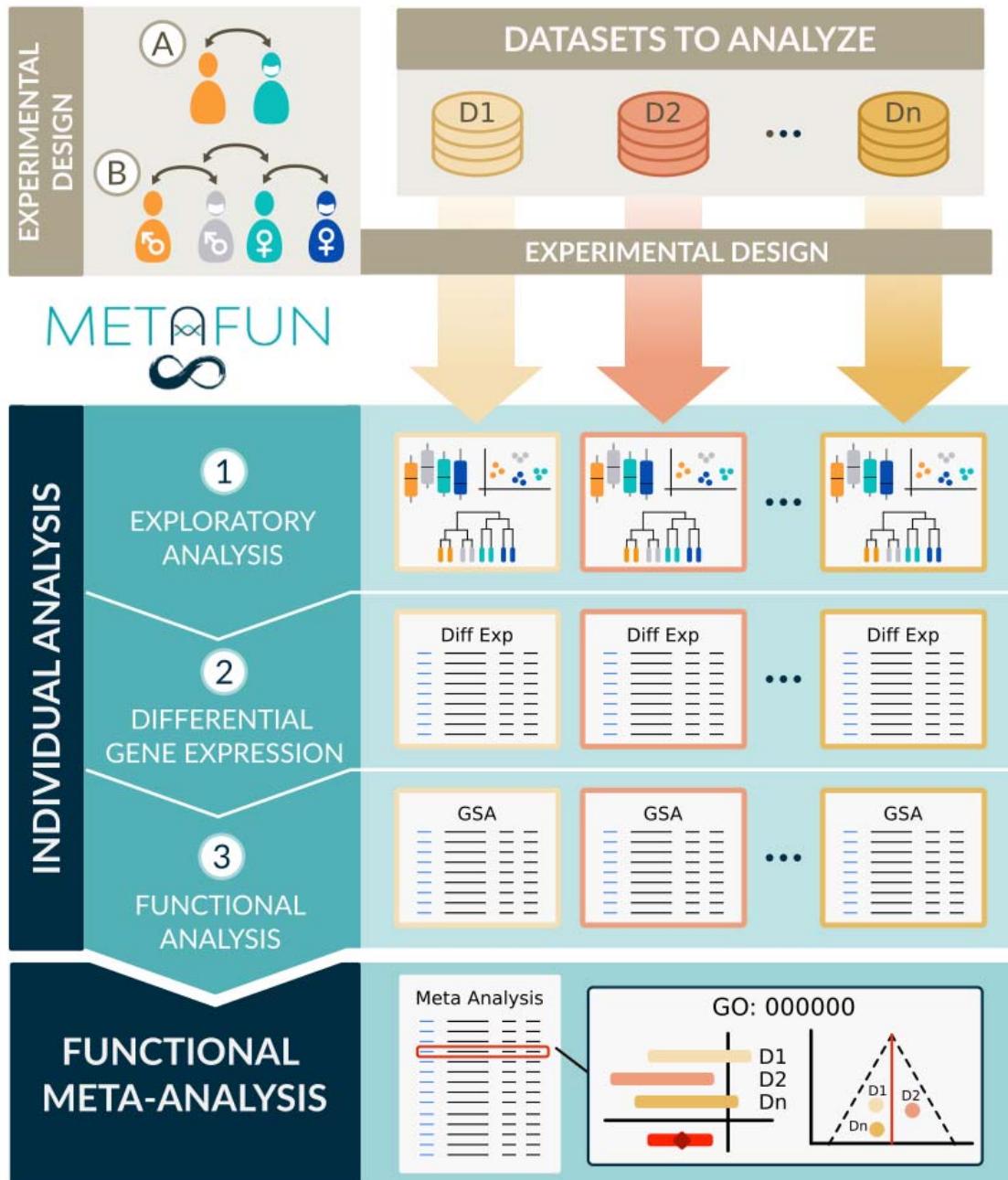


Figure 1: MetaFun pipeline. First, datasets and experimental designs are uploaded as CSV and TSV files. Available comparisons include (A) a classical comparison - *Case vs. Control* - and (B) a sex-perspective comparison - *(Female case vs. Female control)* vs. *(Male case vs. Male control)*. Single 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].

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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](https://gitlab.com/ubb-cipf/metafunpipeline/-/blob/master/Homo%20Sapiens%20(Adenocarcinoma).zip)

Four Simple Steps to Launch the Meta-analysis Job:

New Analysis

Step 1: Options

Select meta-analysis options

Meta-Analysis Method

Random Effect Model

Fixed Effect Model

The Random Effect Model is recommended when the heterogeneity of the studies is high.

The Fixed Effect Model is recommended when the studies are homogeneous.

Functional Characterization

GSA

Biological Process

Molecular Function

Cellular Component

Propagate

Do not propagate

Reference Organism

Homo sapiens

Mac musculus

Rattus norvegicus

GSA or Hepatia?

The Gene Set Analysis will result in a list of info or overrepresented functions as GO items which will be meta-analyzed.

You can choose if you want information from the three different ontologies:

Biological Process, Molecular Function, Cellular Component.

Hepatia is a method for the computation of signal transduction along signaling pathways from transcriptomic data.

New Analysis

My Jobs

Visualizer

PREVIOUS STEP

NEXT STEP

1 Options

2 Studies

3 Comparison

4 Launch

Homo sapiens (Coming Soon)

oo MetaFun

New Analysis

Launch steps

0 Files

1 Options

2 Studies

3 Comparison

4 Launch

PREVIOUS STEP

Step 2: Studies

Select the studies to meta-analyze

Drag the Expression and Experimental Design files to meta-analyze from your personal folder to the corresponding areas.
Place at the same time Expression and Experimental Design files from the same study.

NEXT STEP

My Files

MyFolder

Home_Samples

Home

Expression

gse87540.csv

gse32963.csv

gse19188.csv

gse10071.csv

Matched

gse87540.csv,rec.txt

gse32963.csv,rec.txt

gse19188.csv,rec.txt

gse10071.csv,rec.txt

Experimental Design

oo MetaFun

New Analysis

Launch steps

0 Files

1 Options

2 Studies

3 Comparison

4 Launch

PREVIOUS STEP

Step 3: Comparison

Select comparison & labels

Comparison

(Case Female vs. Control Female) vs. (Case Male vs. Control Male)

NEXT STEP

Labels

For each study, select the study-specific labels which will be (consistently) as the meta-analysis comparison labels.

CSV File	Case Female	Control Female	Case Male	Control Male
gse87540.csv	Adenocarcinoma_Female	Control_Female	Adenocarcinoma_Male	Control_Male
gse32963.csv	Adenocarcinoma_Female	Control_Female	Adenocarcinoma_Male	Control_Male
gse19188.csv	Adenocarcinoma_Female	Control_Female	Adenocarcinoma_Female	Control_Male
gse10071.csv	Adenocarcinoma_Female	Control_Female	Adenocarcinoma_Female	Control_Male

oo MetaFun

New Analysis

Launch steps

0 Files

1 Options

2 Studies

3 Comparison

4 Launch

PREVIOUS STEP

Step 4: Launch

Check meta-analysis summary & launch job

Selected Options

Meta-Analysis method: Random Effect Model

Functional Characterization: GSA

Ontologies: Biological Process, Molecular Functions, Cellular Components

Preprint: YES

Reference Organism: Homo Sapiens

Selected Studies

Expression File Experiment Design File

gse87340.csv gse87340des.csv

gse13861.csv gse13861des.csv

gse19188.csv gse19188des.csv

gse10072.csv gse10072des.csv

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
gse13861.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:

The screenshot shows the 'Analysis Summary' section of the MetaFun interface. It includes a 'Job Options' table with columns for Name, Comparison, Effect Model, Functional Profiling, and Reference Organism. Below this is a 'Samples Description' section with a table of study names, sample counts, and a bar chart showing sample composition per study. The 'Differential Expression Summary' section shows a table of study names, total genes, total significant, UP Regulated, and DOWN Regulated counts.

Name	Comparison	Effect Model	Functional Profiling	Reference Organism
SexDiff_Adeno	(Female-Female) (Female-Male) (Female-Male)	Random Forest Model	GOA	hsa

Study Name	Adenocarcinoma Female	Control Female	Adenocarcinoma Male	Control Male
gse3710	55	25	8	15
gse32653	571	305	4	11
gse30058	11	41	31	41
gse30077	15	39	8	24
gse3134	190	182	49	49

Sample composition per study

Study Name	Total Genes	Total Significant	UP Regulated	DOWN Regulated
gse3710	17605	368	230	148
gse32653	204670	716	400	316

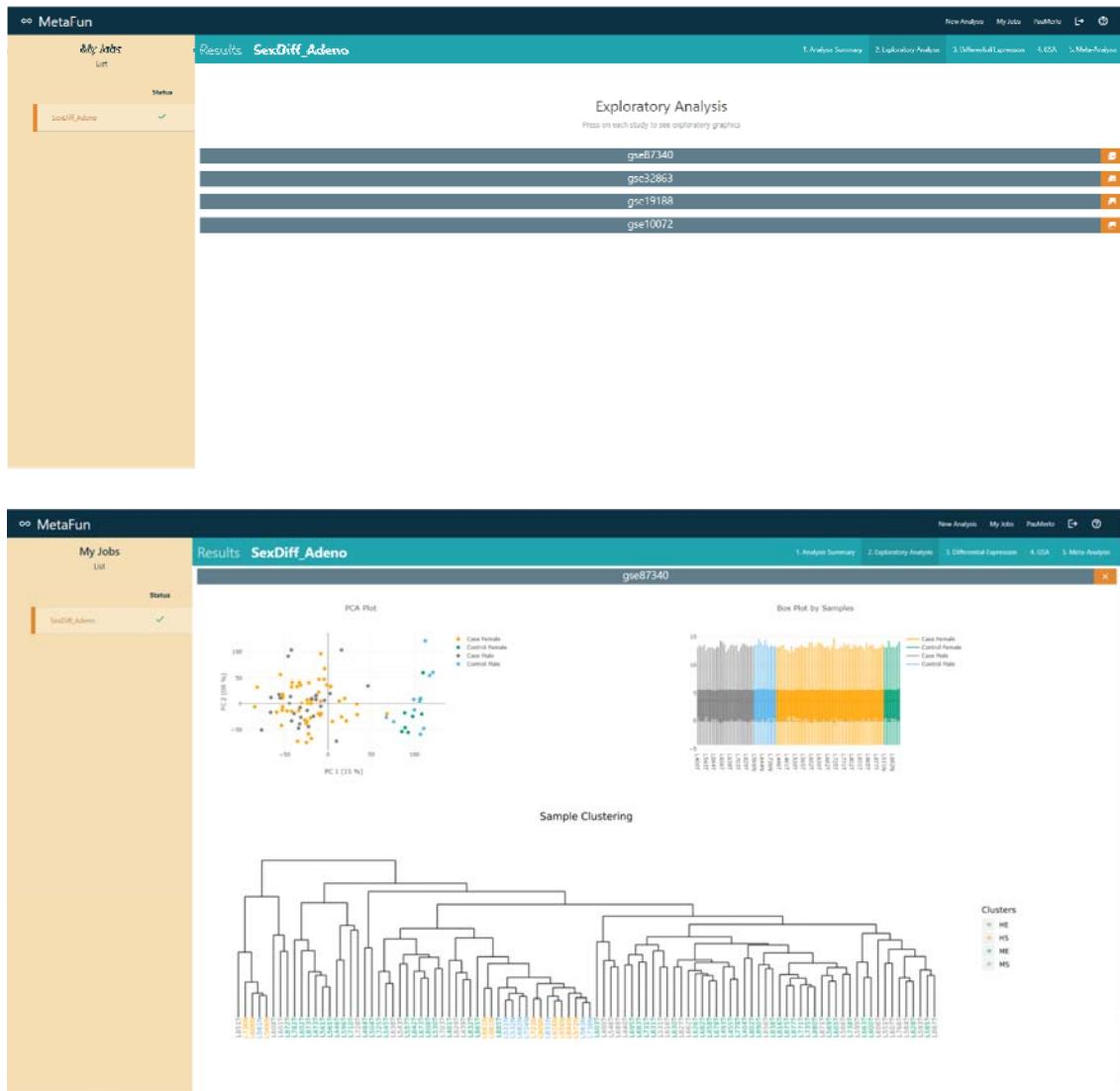
The screenshot shows the 'Differential Expression Summary', 'Functional Profiling Summary', and 'Meta-Analysis Summary' sections of the MetaFun interface. The 'Differential Expression Summary' section is identical to the one in the previous screenshot. The 'Functional Profiling Summary' section shows a table of study names, total functions, total significant, UP Regulated, and DOWN Regulated counts. The 'Meta-Analysis Summary' section shows a table of ontologies, total functions, significant Positive (Z>0), significant Negative (Z<0), and total significant functions.

Study Name	Total Genes	Total Significant	UP Regulated	DOWN Regulated
gse3710	17605	368	230	148
gse32653	204670	716	400	316
gse30058	22070	266	159	107
gse30077	19011	332	77	155

Ontology	Total Functions	Significant Positive (Z>0)	Significant Negative (Z<0)	Total Significant Functions
BP	11	na	na	na
MF	12	0	12	12
CC	44	7	41	44

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):

oo MetaFun

My Jobs List Status

Results SexDiff_Adeno

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

Differential Expression

Choose your study DOWNLOAD

Study GSE87340

Showing top 20 results. Download table for full results

Entrez ID	Gene Name	logFC	Statistic	P value	Adjusted P value
212740	testis-specific transcript, Y-linked 10	1.305	0.997	3.1630e-10	6.0234e-6
10706120	ZFY antisense RNA 1	1.357	5.415	4.2130e-7	4.9309e-3
6736	sex determining region Y	1.468	4.932	3.4203e-6	2.1725e-2
100074175	long intergenic non-protein coding RNA 442	1.600	4.455	2.2111e-5	1.2509e-1
7544	zinc finger protein Y-linked	1.138	4.060	9.8405e-5	3.2541e-1
83259	pre-microRNA 11 Y-linked	1.322	4.048	1.0270e-4	3.2541e-1
7404	ultraconserved transcribed tetranucleotide repeat containing, Y-linked	1.262	3.488	7.2057e-4	9.9900e-1
22738	semimbrinosa beta 4	-1.753	-0.272	5.4710e-1	9.9900e-1
1063	DEAD214-box helicase 11	-1.248	-5.243	1.6125e-3	9.9900e-1
11330	chymotrypsin C	-1.167	-3.192	1.8900e-3	9.9900e-1
40514	neurotrophin receptor tyrosine kinase 1	-1.008	-3.071	2.7130e-3	9.9900e-1
100074171	small nuclear RNA, C/D box 9	-1.207	-2.300	4.5910e-3	9.9900e-1
201190	adult carmine red member 4	2.137	2.854	5.2500e-3	9.9900e-1
104400	small nuclear RNA, C/D box 100	-0.932	-2.795	8.2410e-3	9.9900e-1
100074176	ZFAT-ObnR76 transloch	-0.829	-0.772	6.4505e-3	9.9900e-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):

oo MetaFun

My Jobs List Status

Results SexDiff_Adeno

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

Gene Set Analysis

Choose your study DOWNLOAD

Study GSE87340 with Ontology BP

Showing top 20 results. Download table for full results

GO ID	GO Term	LR	P value	Adjusted P value	N
GO:000602	ribosome small ribosomal subunit	-1.729	8.8000e-8	2.3893e-1	57
GO:0006761	ribosome biogenesis	0.208	7.5800e-7	2.0200e-4	745
GO:0044762	ribonucleoprotein complex	0.761	5.9300e-7	1.3578e-3	376
GO:0006271	ribonucleoprotein	0.258	1.2401e-6	2.0200e-3	302
GO:0044140	ribonucleoprotein complex	0.270	7.8110e-6	2.3191e-3	325
GO:0006470	ribonucleoprotein complex	0.747	4.4050e-6	1.5579e-3	301
GO:0044274	ribonucleic acid nucleic acid metabolism	-0.101	4.1510e-6	1.4521e-3	61
GO:0019982	ribonucleoprotein	-0.242	7.8770e-6	2.0200e-2	172
GO:0019872	ribonucleoprotein complex	-0.303	1.0110e-5	6.5591e-3	147
GO:0019868	ribonucleoprotein	-0.521	1.1510e-5	6.8591e-3	187
GO:0024410	ribonucleic acid processing	-0.221	1.2900e-5	1.0952e-2	262
GO:0026294	ribonucleic acid processing	-0.208	1.3090e-2	1.7979e-2	209
GO:0001626	establishment of nucleic acid localization	0.240	3.5040e-5	1.7073e-2	201

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):

My Jobs		Results		SexDiff_Adeno		1. Analysis Summary				2. Exploratory Analysis		3. Differential Expression		4. GSA		5. Meta Analysis																	
List		Status																															
SexDiff_Adeno		✓																															
Meta-Analysis																																	
Showing Top 20 results. Download table for full results																																	
Download																																	
All Results		100% Done																															
GO ID	GO Term	LDR	Confidence Interval	P value	Adjusted P value																												
GO0000000	mitotic sister chromatid segregation	-0.403 (7)	[-0.405, -0.200]	0.0000e+0	0.0000e+0																												
GO0000000	nuclear division	-0.281 (7)	[-0.337, -0.191]	0.0000e+0	0.0000e+0																												
GO0000000	sister chromatid segregation	-0.363 (7)	[-0.358, -0.207]	0.0000e+0	0.0000e+0																												
GO0000000	DNA-dependent DNA replication	-0.288 (7)	[-0.401, -0.170]	0.0000e+0	0.0000e+0																												
GO0000004	ncRNA processing	-0.339 (7)	[-0.438, -0.240]	0.0000e+0	0.0000e+0																												
GO0000000	chromosome segregation	-0.353 (7)	[-0.327, -0.181]	0.0000e+0	0.0000e+0																												
GO0000002	ribosome biogenesis	-0.334 (7)	[-0.412, -0.255]	0.0000e+0	0.0000e+0																												
GO0000000	ribonucleoprotein complex biogenesis	-0.188 (7)	[-0.254, -0.122]	0.0000e+0	0.0000e+0																												
GO0000000	extracellular matrix organization	-0.297 (7)	[-0.381, -0.113]	0.0000e+0	0.0000e+0																												
GO0000000	ncRNA processing	-0.236 (7)	[-0.309, -0.163]	0.0000e+0	0.0000e+0																												
GO0000002	ribosome biogenesis	-0.317 (7)	[-0.4, -0.230]	0.0000e+0	0.0000e+0																												
GO0000002	extracellular structure organization	-0.204 (7)	[-0.281, -0.148]	0.0000e+0	0.0000e+0																												
GO0000000	organelle biogenesis	0.262 (7)	[0.344, 0.181]	0.0000e+0	0.0000e+0																												