GEOsearch: Extendable Search Engine for Gene Expression Omnibus

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1 Introductions

As the largest and most used public repositories for genomics data, the NCBI Gene Expression Omnibus (GEO [1], http://www.ncbi.nlm.nih.gov/geo/) is an indispensable tool for researchers to search and explore various kind of genomics data. However, the default search function of GEO is not comprehensive and powerful enough. For example, if the search term contains gene name such as Oct4, GEO will ignore samples or experiments related to its alias Pou5f1, which makes the search results incomprehensive. In addition, GEO does not provide second-round search functions for users to further narrow down the experiments or samples of interest after an initial search. For example, users may want to focus on experiments related to specific biological contexts such as
different cell types, tissues and diseases. It is tedious and inefficient for users to perform such second-round search with default search functions provided by GEO. GEOmetadb [2] was previously proposed as an alternative search engine for GEO to facilitate the query of GEO metadata. However, GEOmetadb does not provide the function of searching gene alias or performing second-round search. In addition, GEOmetadb depends on a static GEO metadata database which requires frequent updating and prevents it from obtaining the most up-to-dated results. To address these problems, we developed GEOsearch which is an expandable search engine available online. GEOsearch can provide more comprehensive search results by automatically searching all alias of the gene names contained in the search term. The search results are then integrated and displayed in a compact and editable table. After an initial search, GEOsearch summarize the biological contexts of the search results and allows users to perform second-round search to further narrow down the search results. Unlike GEOmetadb, GEOsearch takes advantage of the programmatic search portal provided by GEO and does not depend on any external database. As a result GEOsearch does not require routine updating and maintaining. GEOsearch can be primarily accessed by directly visiting the online user interface https://zhiji.shinyapps.io/GEOsearch. In this way GEOsearch can be used as an alternative of NCBI GEO’s default search engine. GEOsearch can also be used programmatically by running R commands.

## 2 Find Term Alias

The function termalias first picks gene names from the search term. It then searches alias for all the gene names contained in the search term. It next queries GEO and retain alias that appear frequently enough in GEO database. Finally it returns a combinatorial results of retained alias.

```r
##
## Warning: Package 'GEOsearch' is deprecated and will be removed from Bioconductor version 3.6
## Loading required package: AnnotationDbi
## Loading required package: stats4
## Loading required package: BiocGenerics
## Loading required package: parallel
##
## Attaching package: 'BiocGenerics'
## The following objects are masked from 'package:parallel':
##
##   clusterApply, clusterApplyLB, clusterCall, clusterEvalQ, clusterExport, clusterMap, parApply, parCapply, parLapply, parLapplyLB, parRapply, parSapply, parSapplyLB
```
In this example, termalias picks the gene name (Oct4) and finds all its alias (e.g. Pou5f1). It returns the combinatory results of all alias.

### 3 Perform Searching

The function GEOsearchterm searches the input terms one by one in NCBI GEO database and returns an integrated table of search results. The returned results
should contain exactly the same information as the results returned by directly searching in http://www.ncbi.nlm.nih.gov/geo/. The input of GEOsearchterm is typically the direct output of the function termalias.

```r
Oct4searchres <- GEOSearchTerm(Oct4alias)
head(Oct4searchres)
```

<table>
<thead>
<tr>
<th>Series</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSE79636</td>
<td>Homo sapiens</td>
</tr>
<tr>
<td>GSE85854</td>
<td>Homo sapiens</td>
</tr>
<tr>
<td>GSE86790</td>
<td>Mus musculus</td>
</tr>
<tr>
<td>GSE56568</td>
<td>Homo sapiens</td>
</tr>
<tr>
<td>GSE45338</td>
<td>Mus musculus</td>
</tr>
<tr>
<td>GSE70713</td>
<td>Mus musculus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>NextGen Consortium: GENESiPS Study: Identifying the Gene Networks of Insulin Resistance</td>
</tr>
<tr>
<td>Transcriptome analysis of alternative splicing events in WT and P-KO H9 cells</td>
</tr>
<tr>
<td>Three-dimensional retinal organoids from mouse pluripotent stem cells mimic in vivo development</td>
</tr>
<tr>
<td>Critical role of transient activation of human endogenous retroviruses during reprogramming (RNA-Seq)</td>
</tr>
<tr>
<td>Role of SMARCAD1 and H3R26Cit in Maintenance of the Naïve Pluripotent State</td>
</tr>
<tr>
<td>Single-cell analysis reveals lineage segregation in early post-implantation mouse embryos</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expression profiling by high throughput sequencing</td>
</tr>
<tr>
<td>Expression profiling by high throughput sequencing</td>
</tr>
<tr>
<td>Expression profiling by high throughput sequencing</td>
</tr>
<tr>
<td>Non-coding RNA profiling by high throughput sequencing</td>
</tr>
<tr>
<td>Genome binding/occupancy profiling by high throughput sequencing; Expression profiling</td>
</tr>
<tr>
<td>Genome binding/occupancy profiling by high throughput sequencing; Expression profiling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platform</th>
<th>Sample.Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPL16791</td>
<td>317</td>
</tr>
<tr>
<td>GPL11154</td>
<td>4</td>
</tr>
<tr>
<td>GPL17021</td>
<td>16</td>
</tr>
<tr>
<td>GPL11154</td>
<td>15</td>
</tr>
<tr>
<td>4 related Platforms</td>
<td>13</td>
</tr>
<tr>
<td>GPL17021 GPL13112</td>
<td>236</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>oct3 rna-seq;oct4 rna-seq</td>
</tr>
<tr>
<td>oct3 rna-seq</td>
</tr>
<tr>
<td>oct3 rna-seq</td>
</tr>
</tbody>
</table>
The example above lists not only search results for the term "Oct4 RNA-seq" but also results for the term "Pou5f1 RNA-seq". The combined results are more comprehensive than the results of searching either one of the term. In principal the search results returned by GEOsearch should always be as or more comprehensive than the search results returned by GEO default search functions.

4 Frequencies of Common Biology Keywords

The function keywordfreq calculates the frequencies of each common biology keyword appearing in the given search table. The list of common biology keywords is compiled from http://www.atcc.org/. The list contains three categories: cell types, diseases and tissues. Users can specify which category to be used. The function also returns log fold change and FDR of fisher test to check whether each keyword has significantly more appearance compared to base frequency. The base frequency is defined as the number of appearance of the keyword in all samples (roughly 40000 samples) included in GEO database.

```r
Oct4keywordfreq <- KeyWordFreq(Oct4searchres)
head(Oct4keywordfreq)
```

<table>
<thead>
<tr>
<th>term</th>
<th>frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>pluripotent</td>
<td>26</td>
</tr>
<tr>
<td>embryonic</td>
<td>32</td>
</tr>
<tr>
<td>stem cell</td>
<td>15</td>
</tr>
<tr>
<td>embryonic stem cell</td>
<td>8</td>
</tr>
<tr>
<td>pluripotent embryonic stem cell</td>
<td>1</td>
</tr>
<tr>
<td>inner cell mass</td>
<td>2</td>
</tr>
</tbody>
</table>

In this example embryonic stem cell is among the most frequently appeared biology keyword, which is consistent with known biology [3]. This function allows users to quickly explore the cell types, tissues or organs strongly related to the search term. Users can easily perform second-round search to filter out unrelated records using the online user interface.
5 Details of GSM Samples Given GSE Accession ID.

The function sampleDetail returns an integrated table containing details of all GSM samples for a list of GSE accession ID. This function is especially useful if users want to compare samples from different experiments (GSE).

```
SampleDetail(c("GSE69322","GSE64008"))
```
## 1 Mouse embryonic stem cell line1 Mus musculus
## 2 Mouse embryonic stem cell line1 Mus musculus
## 3 Mouse embryonic stem cell line2 Mus musculus
## 4 Mouse embryonic stem cell line2 Mus musculus
## 5 Extraembryonic endoderm stem cell line1 Mus musculus
## 6 Extraembryonic endoderm stem cell line1 Mus musculus
## 7 Extraembryonic endoderm stem cell line2 Mus musculus
## 8 Extraembryonic endoderm stem cell line2 Mus musculus
## 9 Human embryonic stem cells Homo sapiens
## 10 Human embryonic stem cells Homo sapiens
## 11 Human embryonic stem cells Homo sapiens
## 12 Human embryonic stem cells Homo sapiens
## 13 Human embryonic stem cells Homo sapiens
## 14 Human embryonic stem cells Homo sapiens
## 15 Human embryonic stem cells Homo sapiens
## 16 Human embryonic stem cells Homo sapiens
## 17 mouse embryonic stem cells E14 Mus musculus
## 18 mouse embryonic stem cells E14 Mus musculus
## 19 mouse embryonic stem cells E14 Mus musculus
## 20 mouse embryonic stem cells E14 Mus musculus
## 21 mouse embryonic stem cells E14 Mus musculus
## 22 mouse embryonic stem cells E14 Mus musculus
## 23 mouse embryonic stem cells E14 Mus musculus
## 24 mouse embryonic stem cells E14 Mus musculus
## 25 mouse embryonic stem cells E14 Mus musculus
## 26 mouse embryonic stem cells E14 Mus musculus
## 27 mouse embryonic stem cells E14 Mus musculus
## 28 Neural progenitor cells Mus musculus
## 29 mouse embryonic stem cells E14 Mus musculus
## 30 mouse embryonic stem cells E14 Mus musculus
## 31 mouse embryonic stem cells E14 Mus musculus
## 32 mouse embryonic stem cells E14 Mus musculus
## 33 mouse embryonic stem cells E14 Mus musculus
## 34 Neural progenitor cells Mus musculus
## 35 Neural progenitor cells Mus musculus
##
## 1 cell type: embryonic stem cell; treatment: ChIP for FLAG-tagged Gata6 in embryonic stem cell line1; antibody: anti-FLAG (Sigma, catalog number F1804)
## 2 cell type: embryonic stem cell; treatment: Input control in embryonic stem cell line1
## 3 cell type: embryonic stem cell; treatment: ChIP for FLAG-tagged Gata6 in embryonic stem cell line2; antibody: anti-FLAG (Sigma, catalog number F1804)
## 4 cell type: embryonic stem cell; treatment: Input control FLAG-tagged Gata6 in embryonic stem cell line2
## 5 cell type: extraembryonic endoderm stem cell; treatment: Gata6 ChIP XEN cell line1 in standard maintenance media; antibody: anti-Gata6 (R&D, catalog number AF1700)
## 6 cell type: extraembryonic endoderm stem cell; treatment: Input control XEN cell line1 in standard maintenance media
## 7 cell type: extraembryonic endoderm stem cell; treatment: Gata6 ChIP XEN cell line2 in standard maintenance media; antibody: anti-Gata6 (R&D, catalog number AF1700)
## 8 cell type: extraembryonic endoderm stem cell; treatment: Input control XEN cell line2 in standard maintenance media
## 9 cell type: embryonic stem cell; treatment: Gata6 overexpressing hESC line1 in KSR media
10 cell type: embryonic stem cell; treatment: Gata6 overexpressing hESC line2 in KSR media
11 cell type: embryonic stem cell; treatment: Gata6 overexpressing hESC line1 in mTeSR media
12 cell type: embryonic stem cell; treatment: Gata6 overexpressing hESC line2 in mTeSR media
13 cell type: embryonic stem cell; treatment: hESC line1 in KSR media
14 cell type: embryonic stem cell; treatment: hESC line2 in KSR media
15 cell type: embryonic stem cell; treatment: hESC line1 in mTeSR media
16 cell type: embryonic stem cell; treatment: hESC line2 in mTeSR media
17 cell type: mouse embryonic stem cells E14; shRNA: none; cell line: E14; damid tagged factor: Nup153; antibody: none
18 cell type: mouse embryonic stem cells E14; shRNA: none; cell line: E14; damid tagged factor: Nup153; antibody: none
19 cell type: mouse embryonic stem cells E14; shRNA: none; cell line: E14; damid tagged factor: Oct4; antibody: none
20 cell type: mouse embryonic stem cells E14; shRNA: none; cell line: E14; damid tagged factor: Oct4; antibody: none
21 cell type: mouse embryonic stem cells E14; shRNA: shCtrl (Scramble); cell line: E14; damid tagged factor: none; antibody: sc-5279, Santa Cruz
22 cell type: mouse embryonic stem cells E14; shRNA: shNup153 #2; cell line: E14; damid tagged factor: none; antibody: sc-5279, Santa Cruz
23 cell type: mouse embryonic stem cells E14; shRNA: shCtrl (Scramble); cell line: E14; damid tagged factor: none; antibody: 39663, Active Motif
24 cell type: mouse embryonic stem cells E14; shRNA: shNup153 #2; cell line: E14; damid tagged factor: none; antibody: 39663, Active Motif
25 cell type: mouse embryonic stem cells E14; shRNA: shNup153 #4; cell line: E14; damid tagged factor: none; antibody: 39663, Active Motif
26 cell type: neural progenitor cells; shRNA: none; damid tagged factor: none; antibody: 39663, Active Motif
27 cell type: neural progenitor cells; shRNA: none; damid tagged factor: none; antibody: none
28 cell type: neural progenitor cells; shRNA: none; damid tagged factor: none; antibody: none
29 cell type: mouse embryonic stem cells E14; shRNA: shCtrl (Scramble); cell line: E14; damid tagged factor: none; antibody: ab21873, Abcam
30 cell type: mouse embryonic stem cells E14; shRNA: none; cell line: E14; damid tagged factor: none; antibody: none
31 cell type: mouse embryonic stem cells E14; shRNA: shCtrl (Scramble); cell line: E14; damid tagged factor: none; antibody: none
32 cell type: mouse embryonic stem cells E14; shRNA: shNup153 #2; cell line: E14; damid tagged factor: none; antibody: none
33 cell type: mouse embryonic stem cells E14; shRNA: shNup153 #4; cell line: E14; damid tagged factor: none; antibody: none
34 cell type: neural progenitor cells; shRNA: none; damid tagged factor: none; antibody: none
35 cell type: neural progenitor cells; shRNA: none; damid tagged factor: none; antibody: none

Description
1 processed data file: Gata6_ChIP-seq_peaks_36h_post_dox.xls
2 processed data file: Gata6_ChIP-seq_peaks_36h_post_dox.xls
3 processed data file: Gata6_ChIP-seq_peaks_36h_post_dox.xls
4 processed data file: Gata6_ChIP-seq_peaks_36h_post_dox.xls
5 processed data file: Gata6_ChIP-seq_peaks_XEN_cells.xlsx
6 processed data file: Gata6_ChIP-seq_peaks_XEN_cells.xlsx
7 processed data file: Gata6_ChIP-seq_peaks_XEN_cells2.xlsx
8 processed data file: Gata6_ChIP-seq_peaks_XEN_cells2.xlsx
9 processed data file: RNA-seq_analysis_GATA6_induction_hESCs.xlsx
10 processed data file: RNA-seq_analysis_GATA6_induction_hESCs.xlsx
11 processed data file: RNA-seq_analysis_GATA6_induction_hESCs.xlsx
12 processed data file: RNA-seq_analysis_GATA6_induction_hESCs.xlsx
13 processed data file: RNA-seq_analysis_GATA6_induction_hESCs.xlsx
14 processed data file: RNA-seq_analysis_GATA6_induction_hESCs.xlsx
15 processed data file: RNA-seq_analysis_GATA6_induction_hESCs.xlsx
16 processed data file: RNA-seq_analysis_GATA6_induction_hESCs.xlsx
17 DamID-Seq localization of Nup153 replicate 1; Nup153 DamID.bed
18 DamID-Seq localization of Nup153 replicate 2; Nup153 DamID.bed
## 19 DamID-Seq localization of Oct4 (positive control) replicate 1; Oct4.DamID.bed
## 20 DamID-Seq localization of Oct4 (positive control) replicate 2; Oct4.DamID.bed
## 21 DamID-Seq localization of GFP (negative control) replicate 1; Nup153.DamID.bed
## 22 DamID-Seq localization of GFP (negative control) replicate 2; Nup153.DamID.bed
## 23 ChIP-Seq localization of Oct4 with shCtrl; Oct4.ctrl.bed
## 24 ChIP-Seq localization of Oct4 with shNup153 #2; Oct4.shNup153.bed
## 25 ChIP-Seq localization of Ring1B with shCtrl; Ring1B.shCtrl.bed
## 26 ChIP-Seq localization of Ring1B with shNup153 #2; Ring1B.shNup153-2.bed
## 27 ChIP-Seq localization of Ring1B with shNup153 #4; Ring1B.shNup153-4.bed
## 28 ChIP-Seq localization of Ring1B in NeuP; Ring1B.NeuP.bed
## 29 ChIP-Seq localization of Cbx7 with shCtrl; Cbx7.shCtrl.bed
## 30 ChIP-Seq input control; Oct4.ctrl.bed
## 31 strand specific polyA+ RNA; RNA-Seq of mESC with shCtrl; fpkm.txt
## 32 strand specific polyA+ RNA; RNA-Seq of mESC with shNup153 #2; fpkm.txt
## 33 strand specific polyA+ RNA; RNA-Seq of mESC with shNup153 #4; fpkm.txt
## 34 strand specific polyA+ RNA; RNA-Seq of NeuP; fpkm.txt
## 35 strand specific polyA+ RNA; RNA-Seq of NeuP; fpkm.txt

6 SEPA GUI

In addition to the basic command lines tools discussed above, SEPA provides a powerful which provides more comprehensive and convenient functions for gene expression pattern analysis. For example, users can easily transform raw gene expression data and convert gene identifiers before the analysis; save the result tables and plots of publication quality; identify genes with different expression patterns on true time and pseudo-time axis. Users are encouraged to use SEPA GUI.

7 Reference