

PosMed (Positional Medline): prioritizing genes with an artificial neural network comprising medical documents to accelerate positional cloning

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ABSTRACT

PosMed (<http://omicspace.riken.jp/>) prioritizes candidate genes for positional cloning by employing our original database search engine GRASE, which uses an inferential process similar to an artificial neural network comprising documental neurons (or 'documentrons') that represent each document contained in databases such as MEDLINE and OMIM. Given a user-specified query, PosMed initially performs a full-text search of each documentron in the first-layer artificial neurons and then calculates the statistical significance of the connections between the hit documentrons and the second-layer artificial neurons representing each gene. When a chromosomal interval(s) is specified, PosMed explores the second-layer and third-layer artificial neurons representing genes within the chromosomal interval by evaluating the combined significance of the connections from the hit documentrons to the genes. PosMed is, therefore, a powerful tool that immediately ranks the candidate genes by connecting phenotypic keywords to the genes through connections representing not only gene–gene interactions but also other biological interactions (e.g. metabolite–gene, mutant mouse–gene, drug–gene, disease–gene and protein–protein interactions) and ortholog data. By utilizing orthologous connections, PosMed facilitates the ranking of human genes based on evidence found in other model species such as mouse. Currently, PosMed, an artificial superbrain that has learned a vast amount of biological knowledge

ranging from genomes to phenomes (or 'omic space'), supports the prioritization of positional candidate genes in humans, mouse, rat and *Arabidopsis thaliana*.

INTRODUCTION

Linkage analysis is used for identifying genes with a certain phenotype or genetic defect, and can suggest chromosomal intervals containing several tens to hundreds of candidate genes for positional cloning. Before performing further experiments, it is necessary to prioritize the candidate genes by using as much biological knowledge as possible. For this purpose, it is an ambitious challenge to create an artificial superbrain that has learned a vast knowledge of omic space (1).

To develop a web-based tool that can immediately suggest genes related to a certain phenotype, we initially developed a search engine named GRASE (General and Rapid Association Study Engine), and then defined its query language named GRASQL (General and Rapid Association Study Query Language) (2). GRASQL is a powerful language for expressing the statistical analysis of data retrievable by the RDF query language SPARQL (3) in a Semantic Web manner (4). The current implementation of GRASE is optimized to efficiently calculate the statistical prioritization of candidate genes based on more than 17 million medical and biological documents, and to facilitate quick return of the results within a few seconds of computational time.

Several software tools that have been developed for prioritizing positional candidate genes are based on functional annotation, gene expression patterns, protein–protein interaction and/or sequence-based features (5–10).

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The evaluation of three of these software tools using their data set has demonstrated the effectiveness of PosMed, which showed an accuracy of 88.7%, the highest of the three tools (11).

The documents searched by PosMed contain references, genome annotations, phenome information, protein–protein interactions, co-expressions, orthologous genes, drugs and metabolite information. Using this biological knowledge, PosMed executes a full-text search of documents when a query word is input and ranks the genes based on direct and indirect inference of the hit documents. Currently, PosMed supports prioritization of candidate genes for positional cloning in humans, mouse, rat and *Arabidopsis thaliana*.

OVERVIEW

A neural network representation of the statistical algorithm for searching complex Semantic Web data

PosMed network searches are performed by GRASE, a search engine that retrieves data items over a highly connected network with semantic links by statistical evaluation. First, to identify genes associated with a user's keyword, GRASE performs a full-text search using the keyword and graph pattern matching over the semantic network containing the semantic link *gene*→*document* between a document and a gene. In other words, GRASE identifies documents having the keyword and generates the semantic link *keyword*→*document*. Then, for each gene, a 2 × 2 contingency table is generated by performing graph pattern matching over the semantic links *keyword*→*document* and *document*→*gene* (see 'PosMed RANKING' section for details). For each contingency table, a *P*-value is computed using a statistical test such as Fisher's exact test. Since this *P*-value becomes smaller when the relevance between the keyword and the gene becomes higher, this value is used for the evaluation of relevance between genes and keywords.

To identify genes further related to the genes initially found, GRASE performs an inference search between gene1 and gene2. In this search, a 2 × 2 contingency table is generated for each gene by performing graph pattern matching over the semantic link *document*→*gene* (see 'PosMed RANKING' section for details), and a *P*-value is computed. This *P*-value also becomes smaller when the relevance between the two genes becomes higher based on the number of documents co-cited. This value is used for the evaluation of relevance between two genes for a gene–gene inference. A total *P*-value is computed by combining these two *P*-values (see 'PosMed RANKING' section for details), which is used to indicate statistical significance between the keyword and gene2 via gene1. A *P*-value is also computed to show the significance between the keyword and the genes in the first search step. Finally, GRASE generates a list of genes ranked using the computed *P*-values.

Although the search algorithm can be described using the above-mentioned GRASQL, a graphical representation of the search algorithm is also helpful in understanding the power of the system. Analogous to a network of

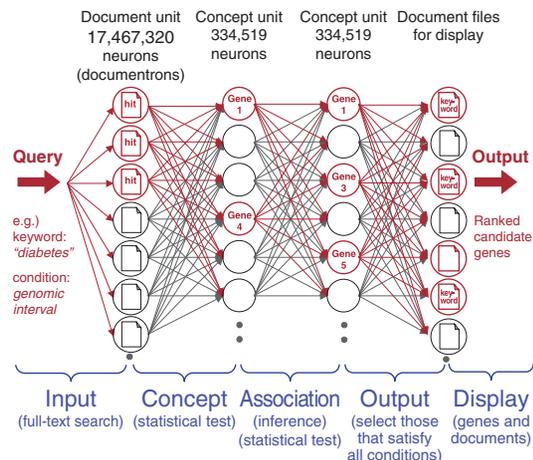


Figure 1. Neural network model for the PosMed gene search algorithm. As an example, the user's keyword 'diabetes' can be found in several documents, including MEDLINE (Input). These documents are mapped to genes that are supported by manual curation (Concept). Using biological knowledge (e.g. protein–protein interaction, co-expression and co-citation of document sets), PosMed can also suggest genes that do not have the user's keyword 'diabetes' in their associated documents (Association). PosMed then returns the candidate genes that are located within the user's specified genomic interval (Output). Thereafter, the user's keyword will be highlighted in the documents (Display).

neurons receiving signals from other neurons through connections, each document is regarded as a neuron (or 'documentron') that fires a signal when a keyword matches the document contents (Figure 1, Input). The signal fired from each documentron is statistically evaluated at the neurons in the next layer by calculating the significance of the associations between the keyword and the genes cited in the hit documents (Figure 1, Concept). Only the neurons (genes) showing *P*-values < 1% (default) fire signals to the next neural layer, according to the strength of the gene–gene relationships or co-citations (Figure 1, Association), wherein various relationships such as protein–protein interactions, co-expressions and ortholog genes are potential additional associations. Only significant genes located within the user-specified genome interval are then displayed together with the most appropriate documents containing the supporting evidence (Figure 1, Output). The keywords are highlighted in the documents (Figure 1, Display).

General usage of PosMed

PosMed is a simple and user-friendly system for prioritizing positional candidate genes. To use this system, users need to input species, a keyword and genome version and additionally select the genomic interval. For example, a search using the keyword 'diabetes OR insulin' in the 90–140M bp genome interval on chromosome 1 in mouse retrieves 114 candidate genes ordered by their statistical significance (Figure 2). Users can download these genes together with the relevant gene annotation information using the 'download rank list' button (Figure 2D). Users can also select the 'expert mode' in the 'All Hits' tab to enable detailed retrieval. With this expert mode, users can check all the direct and inferential paths of

(A)Query Pos Med

search condition species

Select Interval with OmicBrowse chromosome position from to clear version

keyword gene name clear recent 4 years show

(B)Search documents

Total Hits: 116 (3.305 sec)

mouse mutant HsPPI human gene record MEDLINE (sentence)
 mouse gene record OMIM REACTOME rat gene record

Associate the keyword with
 Further associate the entities with

(C)Output (candidate genes) Page 1 display mode:

1. **Insig2 , insulin induced gene 2**
 Insig2 ← 31 docs Position: [Mm:1:123200934-123224363](#) Link to: [MGI](#)
 ← 26 hits
 diabetes OR insulin
2. **Il10 , interleukin 10**
 Il10 ← 21808 docs P value: 9.53E-3563 Position: [Mm:1:132916422-132921547](#) Link to: [MGI](#)
 ← 9305 docs P value: 9.53E-3563
 Tnf ← 97937 docs Position: [Mm:17:35336326-35338952](#) Link to: [MGI](#)
 ← 3994 hits P value: 3.81E-4214
 diabetes OR insulin
3. **Serpib2 , serine (or cysteine) peptidase inhibitor, clade B, member 2**
 Serpib2 ← 833 docs P value: 2.18E-1149 Position: [Mm:1:109408000-109422169](#) Link to: [MGI](#)
 ← 714 docs P value: 2.18E-1149
 Serpine1 ← 6056 docs Position: [Mm:5:137537378-137548129](#) Link to: [MGI](#)
 ← 1258 hits P value: 6.22E-1328
 diabetes OR insulin
4. **Adora1 , adenosine A1 receptor**
 Adora1 ← 2803 docs P value: 3.63E-1096 Position: [Mm:1:136095800-136132004](#) Link to: [MGI](#)
 ← 1344 docs P value: 3.63E-1096
 Adenosine ← 120136 docs Link to: [Original](#)
 ← 1290 hits P value: 1.12E-1361
 diabetes OR insulin
5. **Ptprc , protein tyrosine phosphatase, receptor type, C**
 Ptprc ← 8265 docs P value: 7.60E-694 Position: [Mm:1:139959992-140071843](#) Link to: [MGI](#)
 ← 1519 docs P value: 7.60E-694
 Cd4 ← 73297 docs Position: [Mm:6:124814711-124838227](#) Link to: [MGI](#)
 ← 710 hits P value: 5.43E-750
 diabetes OR insulin
6. **Adipor1 , adiponectin receptor 1** Click to figure 3
 Adipor1 ← 205 docs P value: 1.73E-603 Position: [Mm:1:136312033-136329925](#) Link to: [MGI](#)
 ← 298 docs P value: 1.73E-603
 Adipoq ← 4246 docs Position: [Mm:16:23146692-23157813](#) Link to: [MGI](#)
 ← 4787 hits P value: 4.66E-5052
 diabetes OR insulin

(D)list of candidates

download annotation
download rank list
set as target
add comment
 check all

1. Insig2
2. Il10
3. Serpib2
4. Adora1
5. Ptprc
6. Adipor1
7. Mapkapk2
8. Capn10
9. Bcl2
10. Ramp1
11. Pigr
12. Lct
13. Dbi
14. Pdccl1
15. Il19
16. Cxcr4
17. Tnni2
18. Myog
19. Gpc1
20. Ctse
21. Sox13
22. Ugt1a1
23. Sctr
24. Pam
25. Nr5a2
26. Ugt1a6a
27. Bok
28. Kiss1
29. Acmsd
30. Ren2
31. Avpr1b
32. Trpm8

Figure 2. Output display on PosMed Search. Example search result for mouse genes against the keyword ‘diabetes OR insulin’ between 90M and 140M bp on Chr 1 in the NCBI36 genome. Users can apply their queries at the top of the output display (A). To select genomic interval visually, PosMed cooperates with the Flash-based genomic browser OmicBrowse (12). The tab labeled ‘All Hits’ (B) shows a list of selectable document sets to be included in the search. As a default parameter, PosMed sets ‘Associate the keyword with entities co-cited within the same sentences’. If the total number of the candidate genes is below 20, PosMed will automatically change this parameter to ‘Associate the keyword with entities co-cited within the same document’ to show more candidates (B). PosMed search results are ranked in (C). Users can download at most 300 candidate genes and their annotations from (D).

search condition species

Select Interval with OmicBrowse chromosome position from to clear version

keyword gene name search clear recent 4 years show

All Hits **Adipor1** **Relation** Adipoq

download annotation
download rank list
set as target
add comment
check all
1. Insig2
2. Il10
3. Serpinb2
4. Adora1
5. Ptpcr
6. >> **Adipor1**
7. Mapkapk2
8. Capn10
9. Bcl2
10. Ramp1
11. Pigr
12. Lct
13. Dbi
14. Pdc1
15. Il19
16. Cxcr4
17. Tnnt2
18. Myog
19. Gpc1
20. Ctse
21. Sox13
22. Ugt1a1
23. Sctr
24. Pam
25. Nr5a2
26. Ugt1a6a
27. Bok
28. Kiss1
29. Acmsd
30. Ren2
31. Avpr1b

Symbol: **Adipor1**
Name: adiponectin receptor 1
ID: MGI:1919924
Link to: [MGI](#)
Position: [Mm:1:136312033-136329925](#)

P value: 1.73E-603
182 mouse mutant: 0
HsPPI: 0
MEDLINE: 182
mouse gene record: 0
REACTOME: 0

Symbol: **Adipoq**
Name: adiponectin, C1Q and collagen domain containing
Other aliases: adipoQ, adiponectin, GBP28, apM1, adipo, Acrp30, Acdd
ID: MGI:106675
Link to: [MGI](#)
Position: [Mm:16:23146692-23157813](#)

all (139/182) mouse mutant (0/0) HsPPI (0/0) MEDLINE (139/182) mouse gene record (0/0) REACTOME (0/0)

Adipor1 related entities (A)
any
check all
set as target
download
Find
Adipoq
Adipor2
non-insulin-dependent dia...
ADIPOR1
Adipor1
Deltagen and Lexicon Knoc...
Mapk8
Sirt1
Map2k1
Nr3c1
Mapk14
Map2k2
Prkaca
Gad1
Cd44
Crebbp
Irs1
Mc4r
Akt1
Pik3r1
Omp
Ppara
Dgat1
Fpli
Nfkbia
Trglyd
Npy
Kitl
Il6
Pparg

keyword year Find

documents
50
40
30
20
10
0
unknown 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
with keyword
without keyword
publication year

show order by download

1-20 of 182 Page 1 next (B)

1: **Polymorphisms in adiponectin receptor genes ADIPOR1 and ADIPOR2 and insulin resistance.**
[PMID:17716299](#)
Obesity reviews : an official journal of the International Association for the Study of Obesity 2007 Sep
Adiponectin plays an important role in **insulin** sensitivity via **adiponectin receptor 1 and 2** signalling.
? **Adipor1**, adiponectin receptor 1 ([references](#), [MGI:1919924](#), [Mm:1:136312033-136329925](#))
? **Adipoq**, adiponectin, C1Q and collagen domain containing ([references](#), [MGI:106675](#), [Mm:16:23146692-23157813](#))

2: **Dietary corosolic acid ameliorates obesity and hepatic steatosis in KK-Ay mice.**
[PMID:18379057](#)
Biological & pharmaceutical bulletin 2008 Apr
The improved **insulin** sensitivity in CRA-treated mice may be due on part to the increased plasma **adiponectin** and white adipose tissue (WAT) **AdipoR1** levels.
Adipor1, adiponectin receptor 1 ([references](#), [MGI:1919924](#), [Mm:1:136312033-136329925](#))
Adipoq, adiponectin, C1Q and collagen domain containing ([references](#), [MGI:106675](#), [Mm:16:23146692-23157813](#))

3: **Relationships of plasma adiponectin level and adiponectin receptors 1 and 2 gene expression to insulin sensitivity and glucose and fat metabolism in monozygotic and dizygotic twins.**
[PMID:17426101](#)
The Journal of clinical endocrinology and metabolism 2007 Jul
DESIGN AND PARTICIPANTS: Plasma **adiponectin** and muscle gene expression of **AdipoR1/R2** were measured before and during **insulin** infusion in 89 young and 69 elderly monozygotic and dizygotic twins.

Figure 3. Detail page showing supporting documents of the inference-type search. Adipor1 related genes are listed in (A). The supporting documents for Adipor1 and Adipoq are ranked in (B).

Table 1. Document sets implemented in PosMed

Document	Display name on PosMed	No of documents	Reference
MEDLINE	MEDLINE	17 132 801	(17)
BRMM	mouse mutant	12 911	Original data ^a
OMIM	OMIM	19 891	(18)
HsPPI ^b	HsPPI	35 731	(19)
AtPID	AtPID	44 082	(20)
ATTED-II	At co-expression	24 418	(21)
REACTOME	REACTOME	10 761	(22)
MouseGeneRecord	mouse gene record	58 768	(23)
RatGeneRecord	rat gene record	36 634	(24)
HumanGeneRecord	human gene record	31 459	(25)
ArabidopsisGeneRecord	arabidopsis gene record	32 041	(26)
MetaboliteRecord	metabolite record	18 045	(27)
DrugRecord	drug record	1015	Original data ^a
DiseaseRecord	disease record	1911	Original data ^a
RIKENResearcherRecord	researcher record	6852	Original data ^a
Total		17 467 320	

^aOur original data was created from several data sources. The main data sources are listed at <http://omicspace.riken.jp/acknwldgmnt.htm>

^bHsPPI data is derived from the Genome Network Platform (<http://genomenetwork.nig.ac.jp/public/sys/gnppub/>).

the PosMed search as well as the number of hit genes. Moreover, users can change the threshold of the P -value to increase or decrease the number of genes shown.

Clicking on the gene name reveals supporting evidence for each candidate gene. As an example, the supporting documents for the sixth gene (Adipor1) presented in Figure 2 are shown in Figure 3. Typically, two genes are connected based on co-citations in a document, protein-protein interaction, or co-expression. The bar chart in Figure 3 shows the number of references in MEDLINE. It is important to make correct connections between each gene and references to ensure the accuracy of PosMed. This is, however, very costly to perform manually and thus we applied logical operations with synonyms and functionally important words of genes. For example, to detect all MEDLINE documents for the AT1G03880 gene in *A. thaliana*, we applied the following logical operation: ('AT1G03880' OR 'CRU2' OR 'CRB' OR 'CRUCIFERIN 2' OR 'CRUCIFERIN B') AND ('Arabidopsis') NOT ('chloroplast RNA binding'). Curators refine the logical operations in mouse and *A. thaliana*. For human and rat genes, we use mouse curation results via ortholog genes.

More advanced usage of PosMed is explained in the PosMed tutorial available at: http://omicspace.riken.jp/tutorial/HowToUseGPS_Eng.pdf

DATA SOURCES

Currently, PosMed uses more than 17 million documents. For inference-type searches, we employ document sets including MEDLINE (title, abstract and MeSH term), genome annotation, phenome information, protein-protein interaction, co-expression, drugs and metabolite records (Table 1).

PosMed RANKING

In order to prioritize the positional candidate genes, PosMed first calculates the statistical significance between the user's keyword and each gene. Then, a 2×2 contingency table $\begin{bmatrix} a & b \\ c & d \end{bmatrix}$ is generated and this consists of the following:

- the number of documents that match with both the keyword and the gene;
- the number of documents that match the keyword but not the gene;
- the number of documents that match the gene but not the keyword;
- the number of documents that match neither the keyword nor the gene.

The P -value is then computed using Fisher's exact test.

For an inference search, we statistically evaluate the relevance between gene1 and gene2 using the above-mentioned Fisher's exact test. Thereafter, we compute the total P -value as $P = 1 - (1 - P_s)(1 - P_r)$, where P_s is the P -value of the first association search between the user's keyword and each gene, and P_r is the P -value of the gene-gene relationship applied in the second association search.

To treat biological data such as protein-protein interaction using this method, all biological data are described as sentences (e.g. protein A interacts with protein B) and they are stored as document sets in PosMed.

EXAMPLE RESULTS

In RIKEN's large-scale mouse ENU mutagenesis project, PosMed was used to prioritize genes and has contributed to the successful identification of more than 65 responsible genes (14). PosMed is also used by researchers worldwide and has successfully narrowed down the candidate genes responsible for a specific function after QTL analysis (15,16).

FURTHER USAGE

In this manuscript, we introduced PosMed as a web tool for assisting in the prioritization of candidate genes for positional cloning. Using the search engine GRASE, we also implemented inference-type full text search functions for metabolites, drugs, mutants, diseases, researchers, document sets and databases. For cross-searching, users can select 'any' for the search items at the top right of the PosMed web page. Since this system can search various omics data, we named it OmicScan. In addition to English, GRASE accepts Japanese and French language in the query.

IMPLEMENTATION

PosMed was developed as a web-oriented tool using Java Servlet, and web browser plug-in need not be installed. However, we recommend using Microsoft Internet Explorer7 or later or Firefox2 or later for Windows, and Safari2 or later or Firefox2 or later for Macintosh.

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