

# sigPathway: Pathway Analysis with Microarray Data

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## 1 Introduction

*sigPathway* is an R package that performs pathway (gene set) analysis on microarray data. It calculates two gene set statistics, the  $NT_k$  (Q1) and  $NE_k$  (Q2), by permutation, ranks the pathways based on the magnitudes of the two statistical tests, and estimates q-values for each pathway (Tian et al., 2005). The program permutes the rows and columns of the expression matrix for  $NT_k$  and  $NE_k$ , respectively. In this vignette, we demonstrate how the user can use this package to identify statistically significant pathways in their data and export the results to HTML for browsing.

## 2 Data

In Tian et al. (2005), microarray data from patients with diabetes, inflammatory myopathies, and Alzheimers' data sets were analyzed. The inflammatory myopathies data set, which was collected on the Affymetrix HG-U133A microarray platform, is included with *sigPathway* as a real, example data set. Expression values and annotations for this data set are stored in the **MuscleData** workspace. This workspace contains the following R objects:

**MuscleData** a data frame consisting of expression values obtained from normal, inclusion body myositis, and dermatomyositis samples. The row and column names of the data frame correspond to Affymetrix probe set IDs and sample IDs, respectively.

**index.NORM** a numeric vector containing the indices for normal samples

**index.IBM** a numeric vector containing the indices for inclusion body myositis

**index.DM** a numeric vector containing the indices for dermatomyositis

To load this data set, type 'data(MuscleData)' after loading the **sigPathway** package.

In addition, *sigPathway* contains pathway annotations for the probe sets on the Affymetrix HG-U133A microarray platform. The pathway annotations are stored in the **GenesetsU133a** workspace. This workspace contains **G**, a list whose elements point to pathways curated from Gene Ontology, KEGG, BioCarta, BioCyc, and SuperArray. Each element within **G** is a list describing a pathway with the following sub-elements:

**src** a character vector containing either the pathway ID (for Gene Ontology) or the name of the pathway database.

**locusID** (optional) a numeric vector containing the Entrez Gene IDs linked to the pathway

**title** a character vector containing the pathway name

**probes** a character vector containing probe set IDs that are associated with the pathway (by mapping them to Entrez Gene IDs)

To load the pathway annotations, type 'data(GenesetsU133a)' after loading the **sigPathway** package. Pathway annotations for other, selected Affymetrix microarray platforms can be downloaded from

<http://www.chip.org/~ppark/Supplements/PNAS05.html>

The user can make his/her own pathway annotations and use them in **sigPathway** as long as the pathway annotations are arranged in the format as described above for **G**.

### 3 Example

In this section, we demonstrate the type of analyses possible with *sigPathway* by comparing microarray data obtained from dermatomyositis and normal samples.

First, we load *sigPathway* into memory, extract the inflammatory myopathies data set from the **MuscleData** workspace, scale each array to the same trimmed mean, and remove probe sets that have expression values less than the trimmed mean in all of the arrays. We remove probe sets because we assume that the probe sets with lower expression values across all arrays are less reliable.

```
> library(sigPathway)
> data(MuscleData)
> sf <- apply(MuscleData, 2, mean, tr = 0.025)
> temp <- sweep(MuscleData, 2, sf, FUN = "/")
> ind.pskeep <- which(rowSums(temp > 1) > 0)
> tabMD <- MuscleData[ind.pskeep, ]
> rm(temp)
```

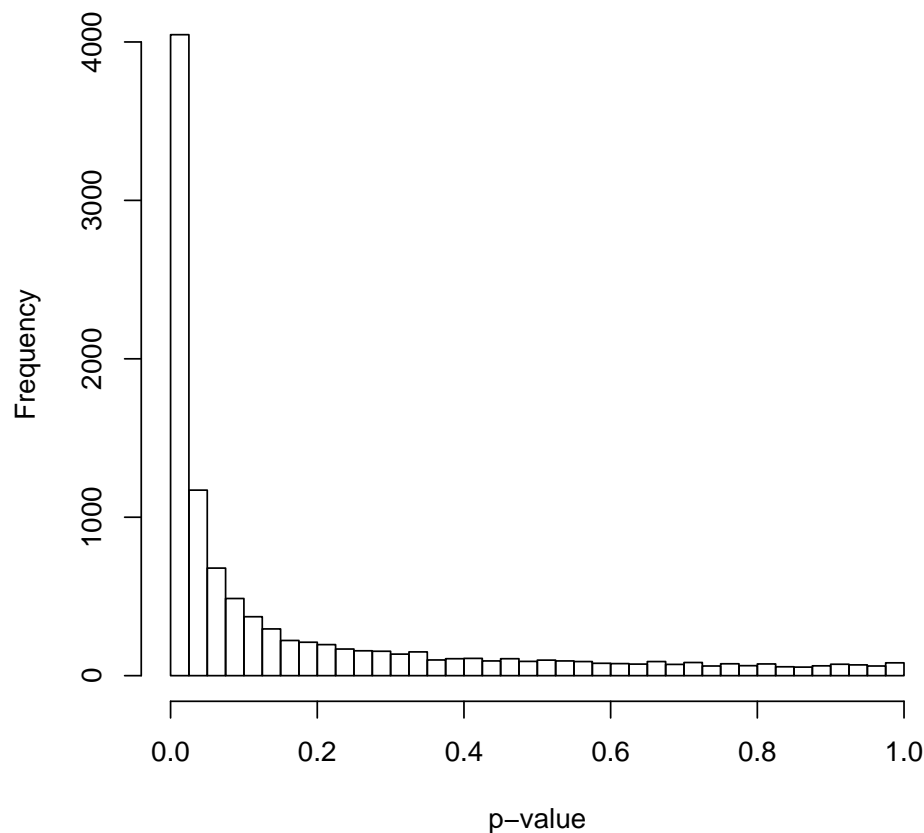
Since we are only interested in comparing dermatomyositis to normal samples in this example, we subset `tabMD`. For microarray data, the convention is to use rows and columns to represent probe sets and individual arrays, respectively. To tell the program which column in `tab` belongs to which phenotype, we create an indicator vector with 0 to represent normal and 1 to represent dermatomyositis. Note that the row names for `tab` are probe set IDs.

```
> tab <- tabMD[, c(index.NORM, index.DM)]
> phenotype <- c(rep.int(0, length(index.NORM)), rep.int(1, length(index.DM)))
> print(rownames(tab)[1001:1005])
```

```
[1] "201207_at"    "201210_at"    "201211_s_at" "201212_at"    "201214_s_at"
```

How much do the dermatomyositis and normal samples differ? Let us plot the unadjusted p-values for each probe set from the 2 group (sample) t-test, assuming unequal variances and using the Welch approximation to estimate the appropriate degrees of freedom.

```
> statList <- calcTStatFast(tab, phenotype, ngroups = 2)
> hist(statList$pval, breaks = seq(0, 1, 0.025), xlab = "p-value",
+      ylab = "Frequency", main = "")
```



The two different types of samples are certainly very different, but which pathways are driving the differences? We load the HG-U133A pathway annotations, calculate the  $NT_k$  and  $NE_k$  statistics for each gene set, and rank the top pathways based on the magnitude of the two statistics. The result is stored in a list (`res.muscle`).

```
> data(GenesetsU133a)
> set.seed(77)
> res.muscle <- runSigPathway(G, 20, 500, tab, phenotype, nsim = 1000,
+   weightType = "constant", ngroups = 2, npath = 25, verbose = FALSE,
+   allpathways = FALSE, annotpkg = "hgu133a", alwaysUseRandomPerm = FALSE)
```

```
Loading required package: hgu133a
Selecting the gene sets
Calculating NTk statistics for each selected gene set
Calculating NEk statistics for each selected gene set
Summarizing the top 25 pathways from each statistic
Done! Use the writeSigPathway() function to write results to HTML
```

Because there are many thousands of pathways represented in the pathway annotations, we have chosen to analyze pathways that contain at least 20 probe sets as represented in `tab` and have, at most, 500 probe sets. These two values were the ones used in Tian et al. (2005).

The run time of the  $NT_k$  and  $NE_k$  is approximately linearly proportional to `nsim`, or the maximum number of permutations. When `alwaysUseRandomPerm` is set to `FALSE` (the default value), the program will use a smaller `nsim` for the  $NE_k$  calculations and switch to using complete permutation if the total number of unique permutations for the phenotype is less than `nsim`.

In this example, we are setting `weightType` to 'constant' because the q-values corresponding to the  $NE_k$  statistics are very low. If the histogram of unadjusted p-values (of probe sets) is flat, and we observe high q-values (i.e., approaching 1) for the top ranked pathways, then setting `weightType` to 'variable' should lower some of the  $NE_k$  q-values. The default value for `weightType` is set to 'constant' because of the amount of additional time required to calculate variable weights for  $NE_k$ .

To rank the pathways, the program adds up the ranks of the magnitudes of  $NT_k$  and  $NE_k$ . When `npath` is set to 25 and `allpathways` to `FALSE`, the program considers the top 25 pathways for each gene set statistic before summing the individual ranks. If `allpathways` is set to `TRUE`, then all pathways are ranked for each gene set statistic before summing the individual ranks. Here, `allpathways` is set to `FALSE` because we are interested in observing pathways that are consistently highly ranked for each gene set statistic.

Also note that out of the numerous input parameters to `runSigPathway`, `annotpkg` is optional because it refers to some Bioconductor metadata package. In this case, 'hgu133a' refers to the Bioconductor metadata package which contains the accession number, Entrez Gene ID, gene symbol, and gene name associated with each probe set on the Affymetrix HG-U133A array platform. By specifying 'hgu133a' for `annotpkg`, `runSigPathway` will include such annotations for each pathway in the list of top pathways.

Printed below is a table of the top pathways, the set size, the  $NT_k$  and  $NE_k$  statistics, and the statistics' ranks and q-values. This table is accessible through the following command:

```
> print(res.muscle$df.pathways)
```

	Index	Gene Set	Category
1	6468		humanpaths

2	2936	G0:0019883
3	1313	G0:0030106
4	2943	G0:0019885
5	3460	G0:0042611
6	3462	G0:0042612
7	922	G0:0001772
8	737	G0:0030333
9	2935	G0:0019882
10	6435	humanpaths
11	3634	G0:0009451
12	3469	G0:0006399
13	5496	G0:0009615
14	6403	KEGG
15	1092	G0:0008452
16	3243	G0:0016875
17	3244	G0:0016876
18	4287	G0:0004812
19	4074	G0:0051258
20	6289	BioCyc
21	4107	G0:0006400
22	3975	G0:0006418
23	5291	G0:0043038
24	401	G0:0006986
25	5300	G0:0044419
26	4414	G0:0007517
27	477	G0:0006936
28	242	G0:0005840
29	77	G0:0030016
30	5090	G0:0003735
31	467	G0:0006941
32	4815	G0:0005386
33	6214	BioCyc
34	697	G0:0043292
35	5785	G0:0015980
36	2590	G0:0015399
37	2295	G0:0006092
38	6405	KEGG
39	975	G0:0008307
40	1711	G0:0015077
41	2870	G0:0019866
42	1712	G0:0015078
43	6317	KEGG
44	6285	BioCyc
45	6300	KEGG
46	6284	BioCyc
47	833	G0:0045333
48	2297	G0:0006096

Pathway

1 Interferon a,b Response  
 2 antigen presentation, endogenous antigen  
 3 MHC class I receptor activity  
 4 antigen processing, endogenous antigen via MHC class I  
 5 MHC protein complex  
 6 MHC class I protein complex  
 7 immunological synapse  
 8 antigen processing  
 9 antigen presentation  
 10 Stress / Toxicity PathwayFinder  
 11 RNA modification  
 12 tRNA metabolism  
 13 response to virus  
 14 Aminoacyl-tRNA\_biosynthesis  
 15 RNA ligase activity  
 16 ligase activity, forming carbon-oxygen bonds  
 17 ligase activity, forming aminoacyl-tRNA and related compounds  
 18 tRNA ligase activity  
 19 protein polymerization  
 20 tRNA charging pathway  
 21 tRNA modification  
 22 tRNA aminoacylation for protein translation  
 23 amino acid activation  
 24 response to unfolded protein  
 25 interaction between organisms  
 26 muscle development  
 27 muscle contraction  
 28 ribosome  
 29 myofibril  
 30 structural constituent of ribosome  
 31 striated muscle contraction  
 32 carrier activity  
 33 glycolysis I  
 34 contractile fiber  
 35 energy derivation by oxidation of organic compounds  
 36 primary active transporter activity  
 37 main pathways of carbohydrate metabolism  
 38 Ribosome  
 39 structural constituent of muscle  
 40 monovalent inorganic cation transporter activity  
 41 inner membrane  
 42 hydrogen ion transporter activity  
 43 Oxidative\_phosphorylation  
 44 superpathway of glycolysis, pyruvate dehydrogenase, TCA, and glyoxylate bypass  
 45 Glycolysis\_\_Gluconeogenesis  
 46 superpathway of glycolysis and TCA variant VIII  
 47 cellular respiration  
 48 glycolysis

	Set	Size	Percent Up	NTk Stat	NTk q-value	NTk Rank	NEk Stat	NEk q-value
1		108	3.70	-11.10	0.00000000	9	-4.55	0.00000000
2		27	0.00	-8.50	0.00000000	25	-4.93	0.00000000
3		25	0.00	-8.29	0.00000000	29	-5.00	0.00000000
4		30	0.00	-8.07	0.00000000	31	-4.82	0.00000000
5		23	0.00	-7.65	0.00000000	49	-4.85	0.00000000
6		23	0.00	-7.65	0.00000000	49	-4.85	0.00000000
7		32	0.00	-6.69	0.00000000	65	-4.53	0.00000000
8		55	0.00	-6.48	0.00000000	73	-3.99	0.00000000
9		55	0.00	-6.34	0.00000000	74	-3.97	0.00000000
10		106	4.72	-6.19	0.00000000	79	-3.95	0.00000000
11		47	6.38	-5.14	0.00000000	92	-3.90	0.00000000
12		52	7.69	-4.78	0.00000000	106	-3.81	0.00000000
13		49	2.04	-4.75	0.00000000	108	-3.81	0.00000000
14		32	6.25	-4.46	0.00000000	119	-3.97	0.00000000
15		33	6.06	-4.28	0.00000000	126	-3.91	0.00000000
16		33	6.06	-4.28	0.00000000	126	-3.91	0.00000000
17		33	6.06	-4.28	0.00000000	126	-3.91	0.00000000
18		33	6.06	-4.28	0.00000000	126	-3.91	0.00000000
19		40	2.50	-4.14	0.00000000	131	-3.97	0.00000000
20		35	5.71	-4.19	0.00000000	128	-3.82	0.00000000
21		39	7.69	-4.10	0.00000000	135	-3.80	0.00000000
22		35	8.57	-3.96	0.00000000	148	-3.79	0.00000000
23		35	8.57	-3.96	0.00000000	148	-3.79	0.00000000
24		57	1.75	-3.68	0.00000000	164	-3.80	0.00000000
25		21	9.52	-2.20	0.02895281	345	-3.88	0.00000000
26		168	37.50	10.10	0.00000000	12	-1.53	0.009594298
27		138	34.78	9.23	0.00000000	16	-1.47	0.010765405
28		203	37.44	10.80	0.00000000	10	-1.43	0.011561562
29		35	62.86	8.51	0.00000000	24	1.45	0.011171498
30		202	37.62	11.45	0.00000000	7	-1.30	0.014316921
31		36	58.33	8.74	0.00000000	20	1.30	0.014184397
32		243	34.98	11.42	0.00000000	8	-1.16	0.017925848
33		30	56.67	8.69	0.00000000	21	1.24	0.015759397
34		46	54.35	9.29	0.00000000	15	0.87	0.027633851
35		151	43.05	11.58	0.00000000	6	-0.72	0.033373097
36		162	41.98	11.69	0.00000000	4	-0.67	0.035463999
37		102	41.18	9.34	0.00000000	14	-0.77	0.031688935
38		154	48.05	13.39	0.00000000	1	-0.59	0.039180991
39		47	53.19	9.16	0.00000000	17	0.74	0.032838622
40		139	43.88	11.72	0.00000000	3	-0.53	0.041498994
41		117	39.32	9.67	0.00000000	13	-0.63	0.037149612
42		135	45.19	12.03	0.00000000	2	-0.40	0.047213963
43		131	47.33	11.69	0.00000000	5	-0.42	0.046618118
44		53	56.60	10.44	0.00000000	11	0.45	0.044959053
45		62	40.32	8.75	0.00000000	19	-0.53	0.041694556
46		57	49.12	9.00	0.00000000	18	-0.25	0.054734537
47		46	58.70	8.64	0.00000000	23	0.13	0.060806399

48	48	47.92	8.66	0.00000000	22	0.09	0.062946719
----	----	-------	------	------------	----	------	-------------

	NEk Rank
--	----------

1	5.0
2	2.0
3	1.0
4	4.0
5	3.0
6	3.0
7	6.0
8	7.0
9	8.0
10	11.0
11	13.0
12	16.0
13	17.0
14	9.0
15	12.0
16	12.0
17	12.0
18	12.0
19	10.0
20	15.0
21	19.0
22	20.0
23	20.0
24	18.0
25	14.0
26	825.0
27	829.0
28	837.5
29	833.0
30	852.0
31	849.5
32	863.0
33	854.0
34	875.0
35	888.0
36	892.0
37	883.0
38	897.0
39	887.0
40	902.0
41	895.0
42	913.0
43	911.0
44	909.0
45	903.5
46	919.0

```

47     923.0
48     927.0

```

As indicated in Tian et al. (2005), the interferon  $\alpha/\beta$  response pathway is not predicted by the current model of dermatomyositis. Further immunohistochemistry confirmed the role of this pathway's proteins in the disease.

Detailed information about each probe set in each pathway on the list of top pathways are stored in the `list.gPS`, an element of `res.muscle`. `list.gPS` is a list containing data frames describing the probe sets for each top pathway. Because of the size of each data frame within the list, we will summarize the contents of the top-ranking pathway with the `summary` function.

```
> summary(res.muscle$list.gPS[[1]])
```

Probes	AccNum	GeneID	Symbol
117_at : 1	NM_005561: 2	Min. : 103	STAT1 : 6
200046_at : 1	AA083478 : 1	1st Qu.: 3278	CASP1 : 4
200887_s_at: 1	AA573862 : 1	Median : 4176	VEGF : 4
201315_x_at: 1	AA747426 : 1	Mean : 6738	HLA-B : 3
201422_at : 1	AA749101 : 1	3rd Qu.: 7533	IFI16 : 3
201551_s_at: 1	AF022375 : 1	Max. : 64092	LAMP1 : 3
(Other) :102	(Other) :101		(Other):85

	Name
signal transducer and activator of transcription 1, 91kDa	: 6
caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	: 4
vascular endothelial growth factor	: 4
interferon, gamma-inducible protein 16	: 3
lysosomal-associated membrane protein 1	: 3
major histocompatibility complex, class I, B	: 3
(Other)	:85

Mean_0	Mean_1	StDev_0	StDev_1
Min. : 30.85	Min. : 181.8	Min. : 10.71	Min. : 154.6
1st Qu.: 496.71	1st Qu.: 1841.3	1st Qu.: 203.60	1st Qu.: 951.6
Median : 962.65	Median : 3328.0	Median : 351.88	Median : 1939.6
Mean : 2880.18	Mean : 8064.9	Mean : 958.42	Mean : 4102.9
3rd Qu.: 2385.85	3rd Qu.: 7403.1	3rd Qu.:1015.24	3rd Qu.: 4333.3
Max. :36083.31	Max. :63967.8	Max. :9295.45	Max. :34833.2

T-Statistic	p-value
Min. : -6.4061	Min. : 1.893e-06
1st Qu.: -4.5615	1st Qu.: 4.410e-04
Median : -3.6704	Median : 2.909e-03
Mean : -3.5411	Mean : 5.534e-02
3rd Qu.: -2.6484	3rd Qu.: 1.532e-02
Max. : 0.7338	Max. : 9.433e-01

A much more intuitive method to browse through the results is to write the results to HTML, which can then be read by an Internet browser program (e.g., Firefox, Internet Explorer). Writing the results can be achieved with the following command:

	Index	Gene Set Category	Pathway	Set Size	Percent Up	NTk Stat	NTk q-value	NTk Rank	NEk Stat	NEk q-value	NEk Rank
1	6468	humanpaths	<a href="#">Interferon a,b Response</a>	108	4	-11.10	0.0000	9.0	-4.55	0.0000	5.0
2	2936	GO:0019883	<a href="#">antigen presentation, endogenous antigen</a>	27	0	-8.50	0.0000	25.0	-4.93	0.0000	2.0
3	1313	GO:0030106	<a href="#">MHC class I receptor activity</a>	25	0	-8.29	0.0000	29.0	-5.00	0.0000	1.0
4	2943	GO:0019885	<a href="#">antigen processing, endogenous antigen via MHC class I</a>	30	0	-8.07	0.0000	31.0	-4.82	0.0000	4.0
5	3460	GO:0042611	<a href="#">MHC protein complex</a>	23	0	-7.65	0.0000	49.0	-4.85	0.0000	3.0
6	3462	GO:0042612	<a href="#">MHC class I protein complex</a>	23	0	-7.65	0.0000	49.0	-4.85	0.0000	3.0
7	922	GO:0001772	<a href="#">immunological synapse</a>	32	0	-6.69	0.0000	65.0	-4.53	0.0000	6.0
8	737	GO:0030333	<a href="#">antigen processing</a>	55	0	-6.48	0.0000	73.0	-3.99	0.0000	7.0
9	2935	GO:0019882	<a href="#">antigen presentation</a>	55	0	-6.34	0.0000	74.0	-3.97	0.0000	8.0
10	6435	humanpaths	<a href="#">Stress / Toxicity PathwayFinder</a>	106	5	-6.19	0.0000	79.0	-3.95	0.0000	11.0
11	3634	GO:0009451	<a href="#">RNA modification</a>	47	6	-5.14	0.0000	92.0	-3.90	0.0000	13.0
12	3469	GO:0006399	<a href="#">tRNA metabolism</a>	52	8	-4.78	0.0000	106.0	-3.81	0.0000	16.0
13	5496	GO:0009615	<a href="#">response to virus</a>	49	2	-4.75	0.0000	108.0	-3.81	0.0000	17.0
14	6403	KEGG	<a href="#">Aminoacyl-tRNA biosynthesis</a>	32	6	-4.46	0.0000	119.0	-3.97	0.0000	9.0
15	1092	GO:0008452	<a href="#">RNA ligase activity</a>	33	6	-4.28	0.0000	126.0	-3.91	0.0000	12.0
16	3243	GO:0016875	<a href="#">ligase activity, forming carbon-oxygen bonds</a>	33	6	-4.28	0.0000	126.0	-3.91	0.0000	12.0
17	3244	GO:0016876	<a href="#">ligase activity, forming aminoacyl-tRNA and related compounds</a>	33	6	-4.28	0.0000	126.0	-3.91	0.0000	12.0
18	4287	GO:0004812	<a href="#">tRNA ligase activity</a>	33	6	-4.28	0.0000	126.0	-3.91	0.0000	12.0
19	4074	GO:0051258	<a href="#">protein polymerization</a>	40	3	-4.14	0.0000	131.0	-3.97	0.0000	10.0
20	6289	BioCyc	<a href="#">tRNA charging pathway</a>	35	6	-4.19	0.0000	128.0	-3.82	0.0000	15.0

Figure 1: List of Top Pathways in Dermatomyositis versus Normal

```
> writeSigPathway(res.muscle, resDir = tempdir(), outputDirName = "sp_example_results",
+   topIndexFileName = "TopPathwaysTable.html")
```

The results have been saved to the following directory:

C:\DOCUME~1\wlai\LOCALS~1\Temp\RtmpwmRGpb/sp\_example\_results

Figures 1 and 2 show the HTML output in an Internet browser.

## 4 Notes

This vignette was compiled with the following settings in `sessionInfo`:

```
> print(sessionInfo())
```

R version 2.2.1, 2005-12-20, i386-pc-mingw32

Mozilla Firefox

file:///C:/Documents%20and%20Settings/wlai/My%20Documents/Work/Peter/vignette/sigPathway\_results/pathways/pa

[Back to Table of Top Pathways](#)

### Interferon a,b Response

	Probes	AccNum	GeneID	Symbol	Name	Mean_0	Mean_1	StDev_0	StDev_1	T-Statistic	p-value
1	202748_at	NM_004120	2634	GBP2	guanylate binding protein 2, interferon-inducible	1135.1	3579.0	289.2	2432.5	-3.597	0.0035
2	211368_s_at	U13700	834	CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	213.6	705.9	109.7	343.8	-4.919	0.0002
3	209970_x_at	M87507	834	CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	628.3	1741.0	242.9	1036.8	-3.767	0.0023
4	211366_x_at	U13698	834	CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	838.8	2105.1	221.8	929.9	-4.776	0.0003
5	206011_at	AI719655	834	CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	301.0	680.8	168.0	272.8	-4.274	0.0004
6	202147_s_at	NM_001550	3475	IFRD1	interferon-related developmental regulator 1	1409.8	2333.9	538.9	849.7	-3.312	0.0034
7	202146_at	AA747426	3475	IFRD1	interferon-related developmental regulator 1	2125.4	3214.0	1046.2	1567.6	-2.083	0.0497
8	204206_at	NM_020310	4335	MNT	MAX binding protein	957.8	1153.3	284.2	395.1	-1.448	0.1618
9	220330_s_at	NM_022136	64092	SAMSN1	SAM domain, SH3 domain and nuclear localisation signals, 1	73.8	371.8	35.1	291.8	-3.656	0.0031
10	218150_at	NM_012097	26225	ARL5	ADP-ribosylation factor-like 5	5944.7	8726.9	2348.7	2771.0	-2.762	0.0110
11	204533_at	NM_001565	3627	CXCL10	chemokine (C-X-C motif) ligand 10	496.5	4075.2	353.6	3743.9	-3.431	0.0049
12	210512_s_at	AF022375	7422	VEGF	vascular endothelial growth factor	6327.5	7732.9	2617.9	3426.5	-1.175	0.2522
13	210513_s_at	AF091352	7422	VEGF	vascular endothelial growth factor	1638.5	2260.4	875.8	1028.6	-1.660	0.1103
14	212171_x_at	H95344	7422	VEGF	vascular endothelial growth factor	3867.1	4605.0	756.9	1294.4	-1.774	0.0917

Done

Figure 2: Interferon a,b Response

attached base packages:

```
[1] "tools"      "methods"    "stats"      "graphics"   "grDevices"  "utils"
[7] "datasets"   "base"
```

other attached packages:

```
hgu133a sigPathway
"1.10.0"  "1.1.4"
```

## References

Lu Tian, Steven A Greenberg, Sek Won Kong, Josiah Altschuler, Isaac S Kohane, and Peter J Park.  
Discovering statistically significant pathways in expression profiling studies. *Proc Natl Acad Sci U S A*, 102(38):13544–13549, Sep 2005.